2023 Free, Live Streamed Webinar
Highlights of the 2023 International Invasive Lobular Carcinoma (ILC) Symposium

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Executive Director
Lobular Breast Cancer Alliance (LBCA)

Claire Turner - Moderator
Chair
Lobular Breast Cancer UK

Jason Mouabbi, MD
University of Texas, MD Anderson
Chair, LBCA Scientific Advisory Board

Patrick Derksen, PhD
LBCA Scientific Advisor and ELBCC
UMC Utrecht

Peter Simpson, PhD
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The James at The Ohio State University

Priscilla McAuliffe, MD, PhD
UPMC Hillman Cancer Center
University of Pittsburgh School of Medicine

Matt Covington
University of Utah and
Huntsman Cancer Institute

European Lobular Breast Cancer Consortium

LBCA® Lobular Breast Cancer Alliance

ILC 2023 Pittsburgh, PA

Today's Agenda

Welcome and Agenda Review – Laurie and Claire
Basic Science - Patrick Derksen, PhD and Peter Simpson, PhD
Translational Science - Bhuvaneswari Ramaswamy, MD
Imaging Science - Matthew Covington, MD
Clinical Science - Priscilla McAuliffe, MD, PhD
Moderated Q&A – All panelists

Our Panelists

Patrick Derksen, PhD

Peter Simpson, PhD

Bhuvaneswari Ramaswamy, MD

Matt Covington, MD

Priscilla McAuliffe, MD, PhD

Jason Mouabbi, MD

European Lobular Breast Cancer Consortium

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ILC 2023 Pittsburgh, PA

Basic (Foundational) Science

Session 1: Pathology, Diagnosis, ILC Variants and Lobular Neoplasia

Session 2: E-cadherin and the ILC Tumor Microenvironment

Session 3: Modelling ILC

Patrick WB Derksen, PhD
Professor of Experimental & Preclinical Oncology
UMC Utrecht

Peter Simpson, PhD
A/Professor of Cancer Genomics
The University Of Queensland
AUSTRALIA

Recap of Session 1: Pathology, Diagnosis, ILC Variants and Lobular Neoplasia

Stuart Schnitt, MD (Dana-Farber Cancer Institute, Boston, MA)
– The Leigh Pate Memorial Lectureship on Lobular Breast Cancer
Invasive Lobular Carcinoma: Where Have We Been and Where Are We Going?

Tari King, MD (Dana-Farber Cancer Institute, Boston, MA)
Lobular Carcinoma In Situ – Current Concepts and Challenges

Maxim De Schepper, MD, PhD (KU Leuven, Belgium)
Homogenization of Pathological Diagnosis of ILC

Lounes Djerroudi, MD (Institut Curie, Paris)
E-cadherin inactivation shapes tumor microenvironment specificities in ILC

Osama Shah, PhD (UPMC Hillman Cancer Center)
Spatial profiling of mixed invasive ductal-lobular carcinoma reveals intrinsic molecular subtype and oncogenic signaling heterogeneity

NATURAL HISTORY OF ILC

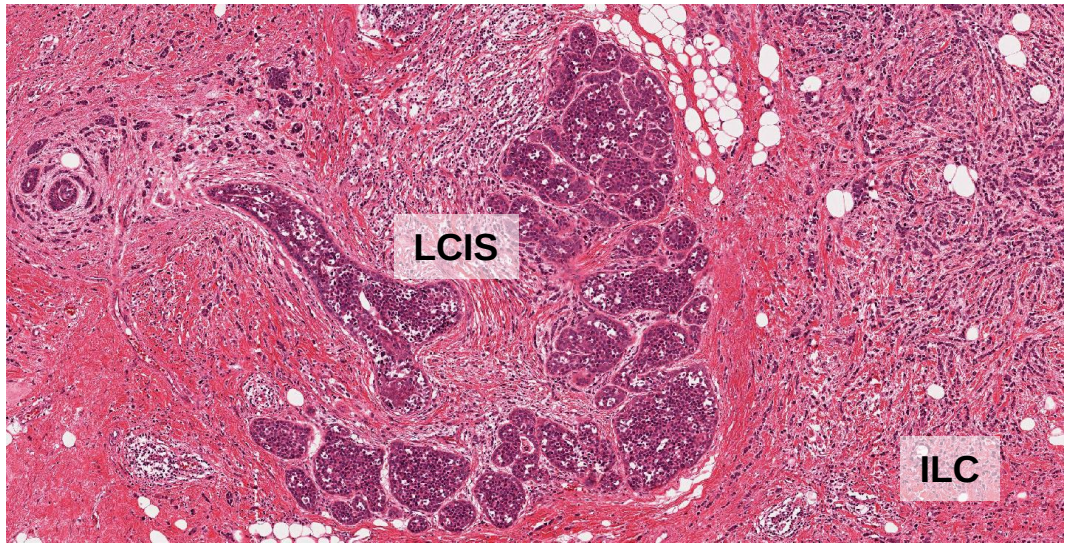
Stuart Schnitt
- history of ILC
- 'Rogue' variants

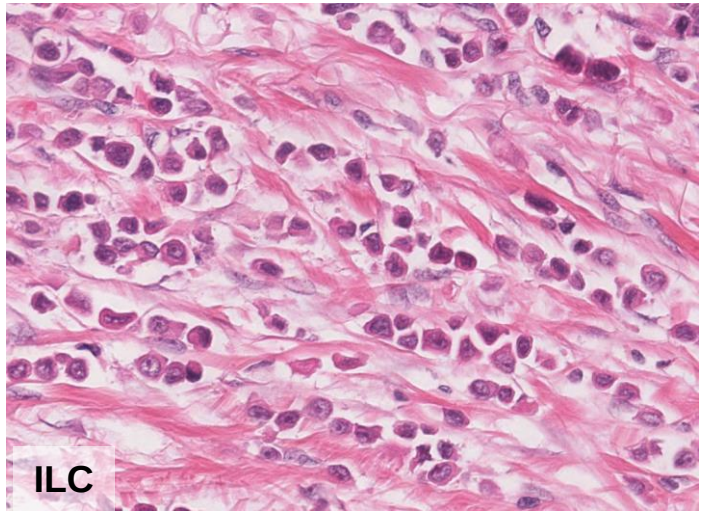
Tari King
- LCIS

Maxim De Schepper
- classification/diagnosis

Normal → (- E-Cadherin; -16q +1q; *PIK3CA/AKT1/PTEN*) → Atypical Lobular Hyperplasia (ALH) → Lobular carcinoma in situ (LCIS) → Classic ILC
- Grade 2
- ER+
- HER2-
- Low Ki67

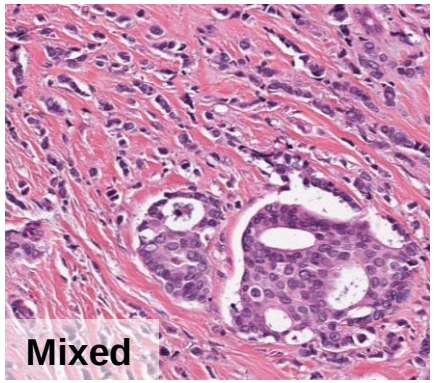
Default





Lounes Djerroudi
- biology of 'stroma'

Osama Shah
- biology of mixed ductal-lobular carcinomas



NATURAL HISTORY OF ILC

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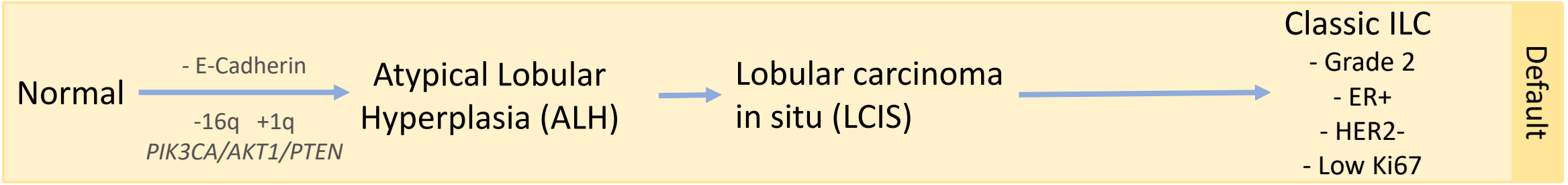


More complex than this:

- Not all LCIS progress to ILC – how to predict? How to manage?
- Some LCIS have variable morphological features – how to manage them?

- ILC can be difficult to classify at diagnosis – what tools can help?
- Not all ILC are 'classic' type – what are 'Rogue' variants, how do we define/identify them?

TARI KING: LCIS – CURRENT CONCEPTS AND CHALLENGES

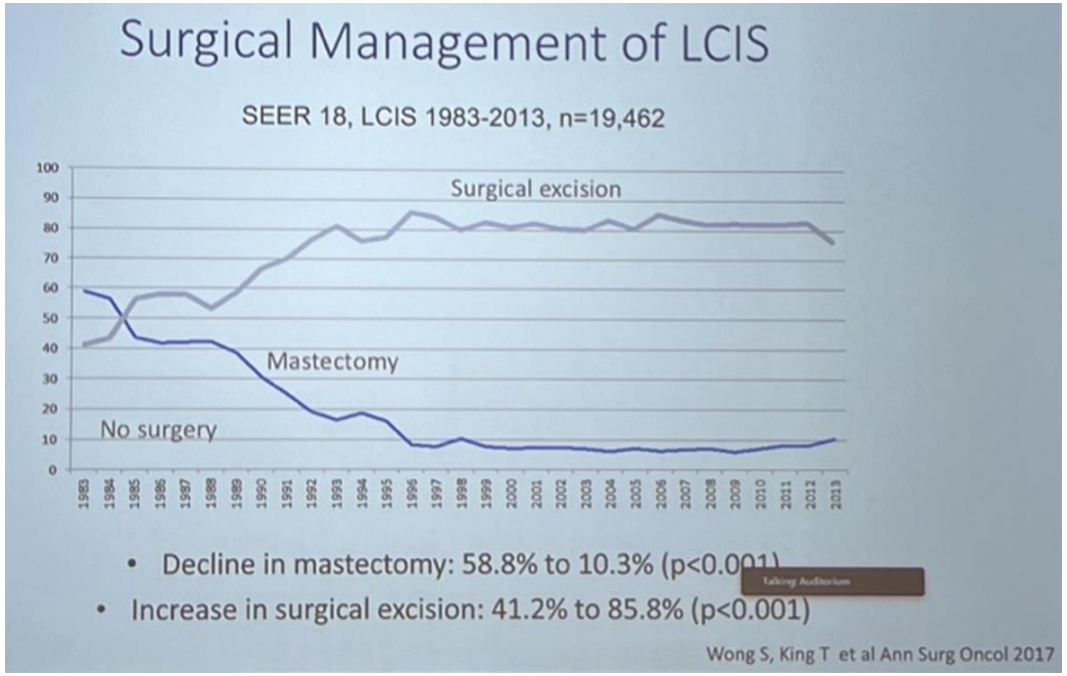
- Risk of upgrade / progression to inv ca ~2%/yr
- Risk is for lobular and ductal types (ILC and DCIS/IDC)
- Risk for ipsilateral but also contralateral breast
  -> LCIS is a risk lesion for both breasts

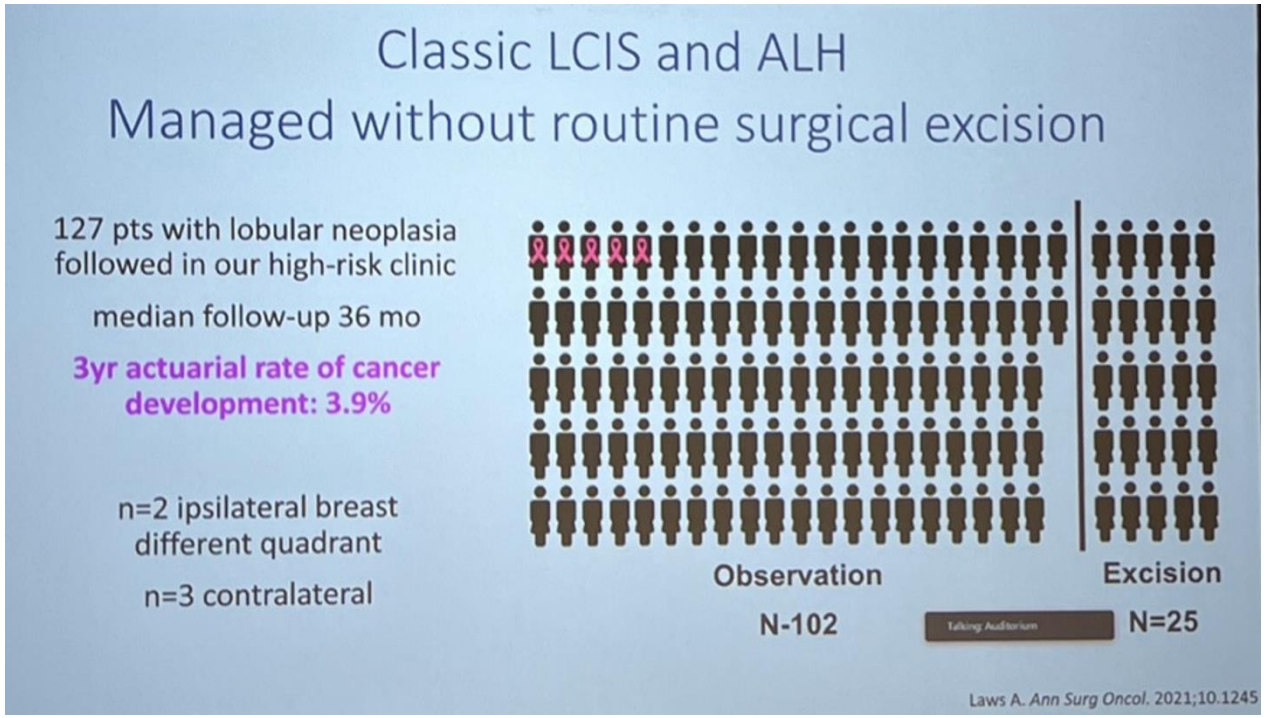
- LCIS and ILC are genetically v similar
  -> LCIS is a non-obligate precursor to cancer

- **Challenge** - what to do if LCIS identified in a biopsy
  – bilateral mastectomy, mastectomy, wide local excision or observe??!!

- **cLCIS**
  - **selective excision only**
  - **observation with imaging**
  - **chemoprevention possible**

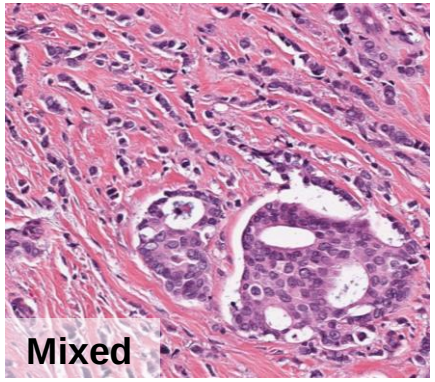
- **PLCIS**
  - **natural history less clear, but upgrade rate higher**
  - **excision and clear margins**
  - **ie treat like DCIS**

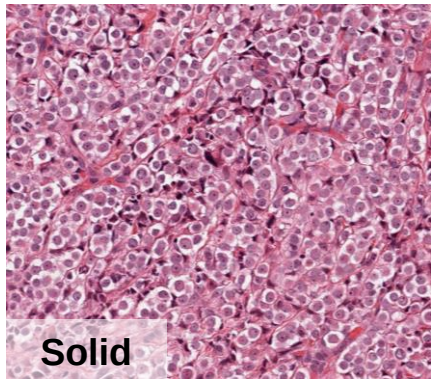


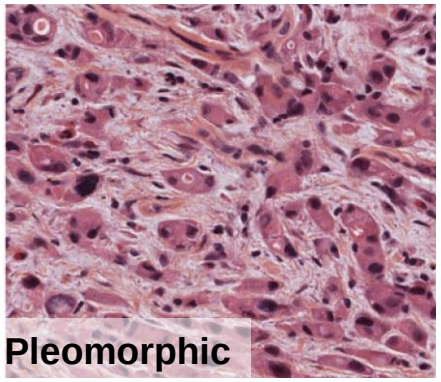


Stuart Schnitt / Maxim De Schepper: ILC – Classification

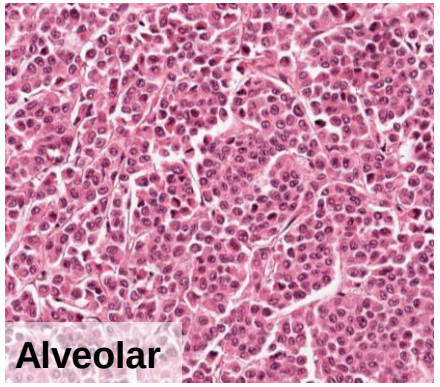
- ILC is a pathological diagnosis, made based on the morphological appearance under the microscope.
- Correct classification is critical – for clinical management, epidemiological and biology studies
- Diagnosis is challenging, despite guidelines from the WHO
- There is a large variability in practice between pathologists worldwide for the diagnosis of ILC.
- Helpful tools – recognizing **morphological variants**, and using **Immunohistochemistry** & **Artificial Intelligence**

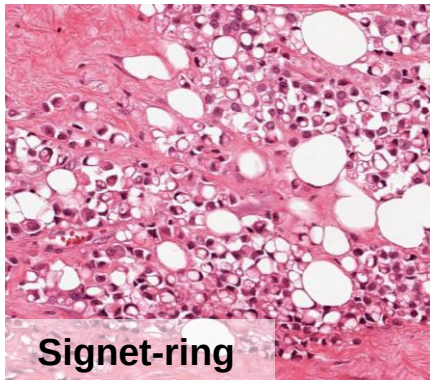




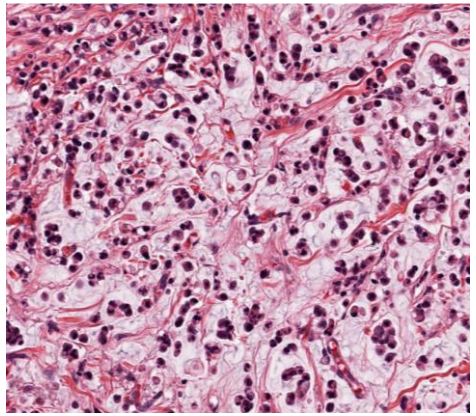


Collectively the morphological variants have worse prognosis to classic ILC
But not enough data to treatment differently





ILC with extracellular mucin

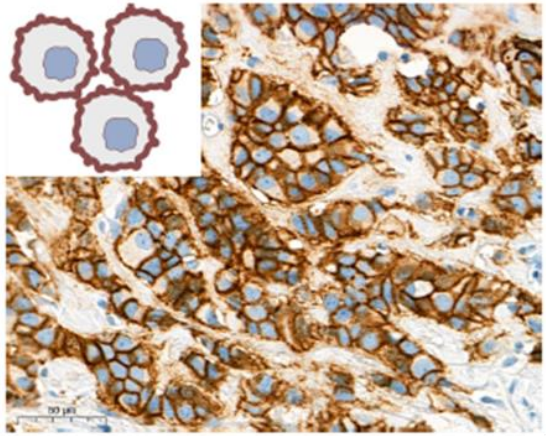


Other '**rogue**' variants:
- grade 3
- ER and/or PR -ve
- TN 2-9%
- HER2+ve <5%
- HER2-low 40-65%

[HER2 mutations]

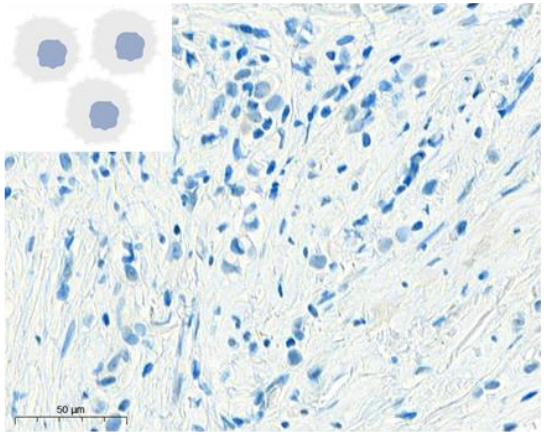
STUART SCHNITT / MAXIM DE SCHEPPER: ILC – CLASSIFICATION

- Helpful tools – recognizing **morphological variants**, and using **Immunohistochemistry** & **Artificial Intelligence**



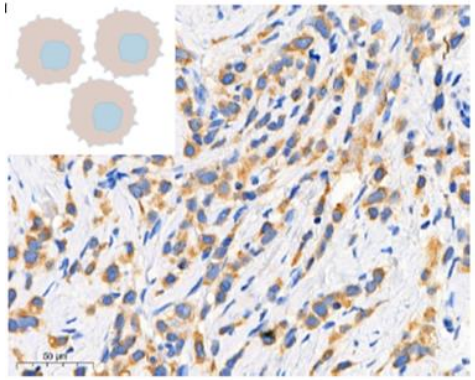
Complete membranous staining

Aberrant

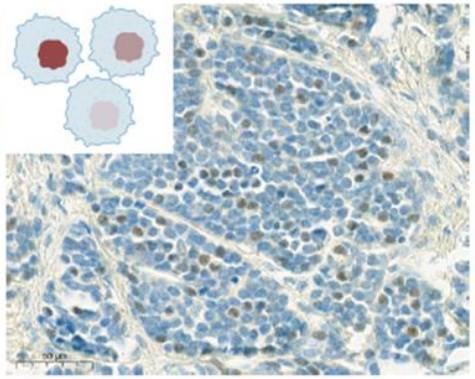


Absent

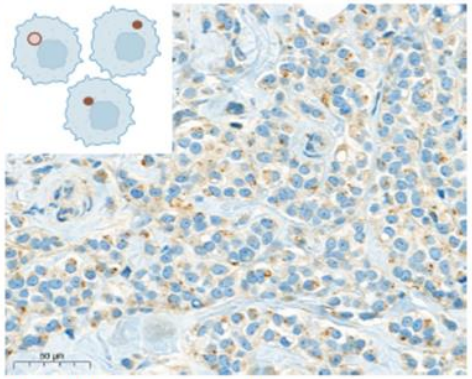
Maxim De Schepper, on behalf of the ELBCC pathology working group



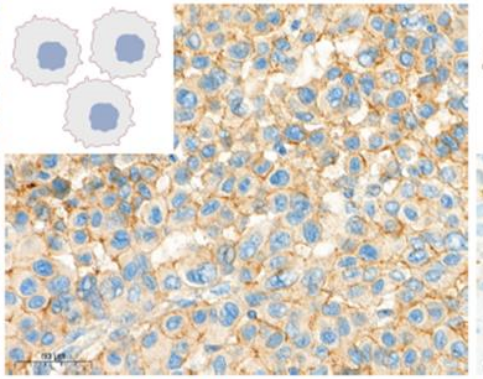
Cytoplasmic



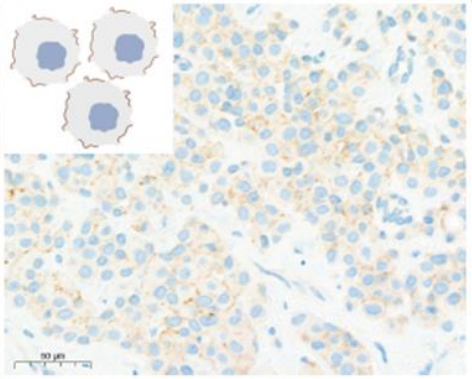
Nuclear



Dot-like perinuclear



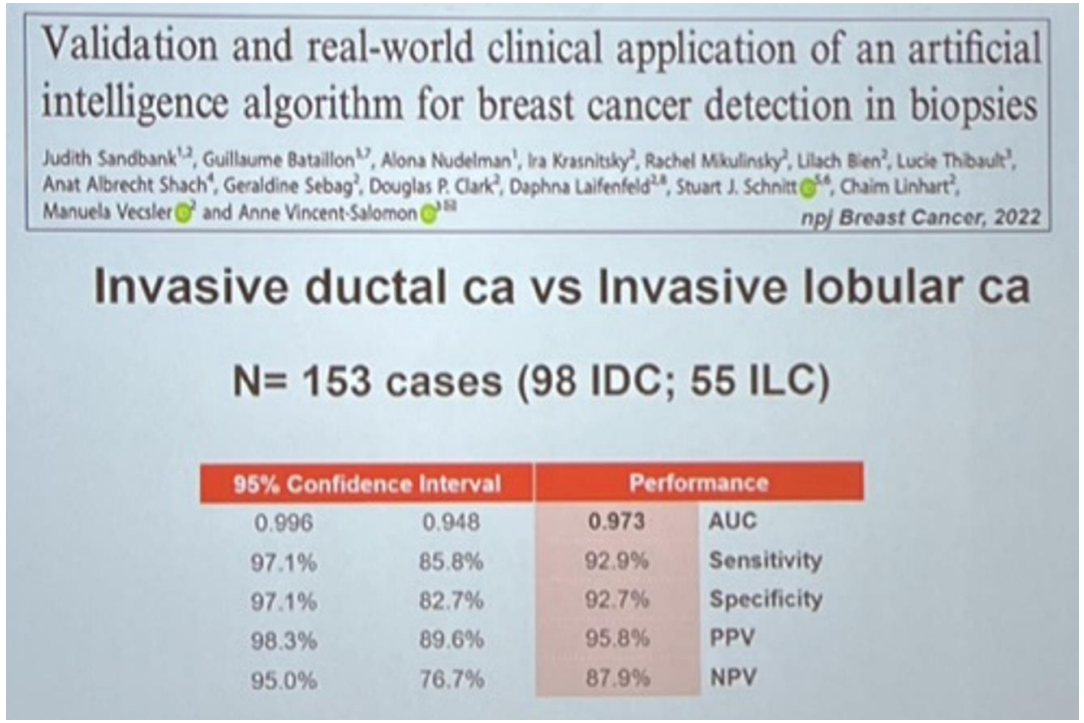
Complete, but weak membranous staining

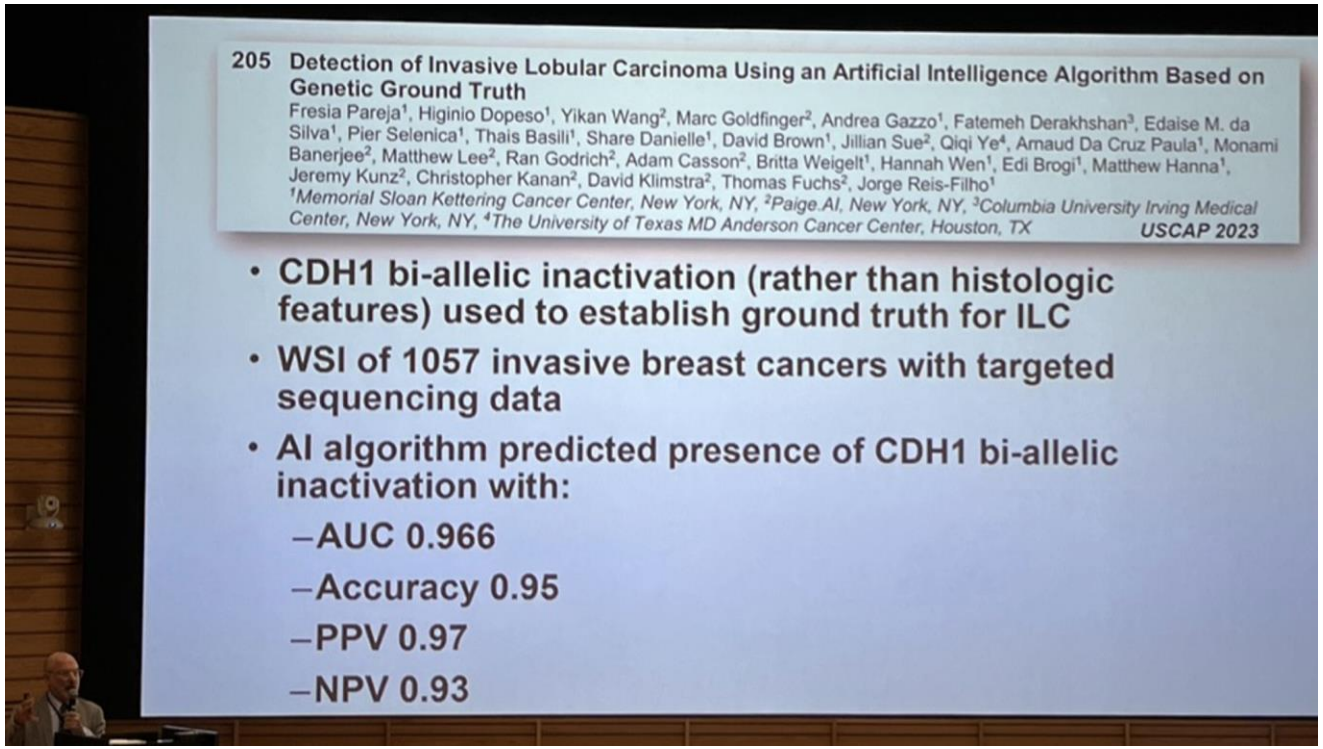


Fragmented, focal or beaded membranous

STUART SCHNITT / MAXIM DE SCHEPPER: ILC – CLASSIFICATION

- Helpful tools – recognizing **morphological variants**, and using **Immunohistochemistry** & **Artificial Intelligence**





Osama Shah, PhD (UPMC Hillman Cancer Center)

Spatial profiling of mixed invasive ductal-lobular carcinoma reveals intrinsic molecular subtype and oncogenic signaling heterogeneity

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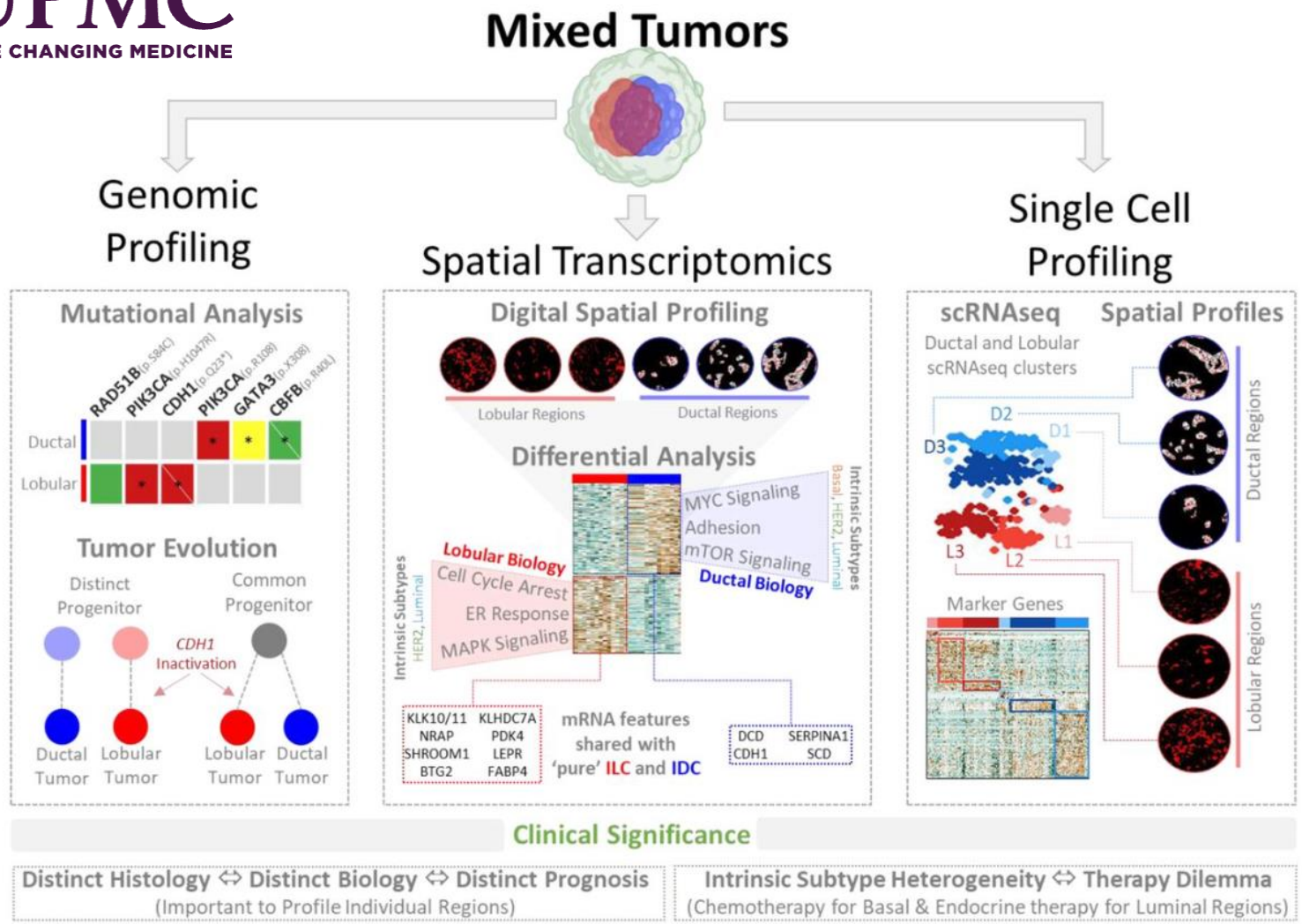
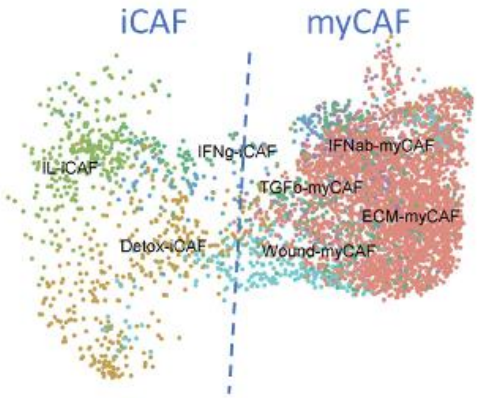
E-cadherin inactivation shapes tumor microenvironment specificities in ILC

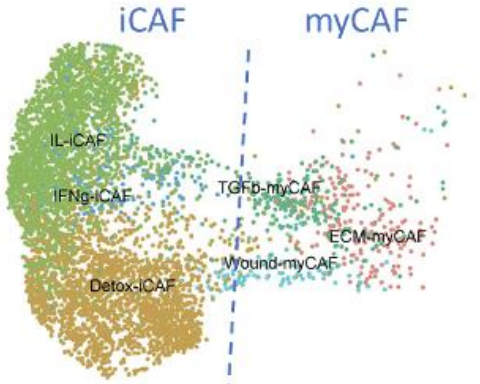




ER+ IDC

(N=15, from public data*)

*Croizer et al. SUBMITTED



ILC (N=6)

https://www.biorxiv.org/content/10.1101/2023.09.09.557013v1.full.pdf+html

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RECAP OF SESSION 2:

E-CADHERIN, GROWTH FACTORS, AND THE ILC TUMOR MICROENVIRONMENT

Patrick WB Derksen, PhD

UMC Utrecht

Professor of Experimental & Preclinical Oncology

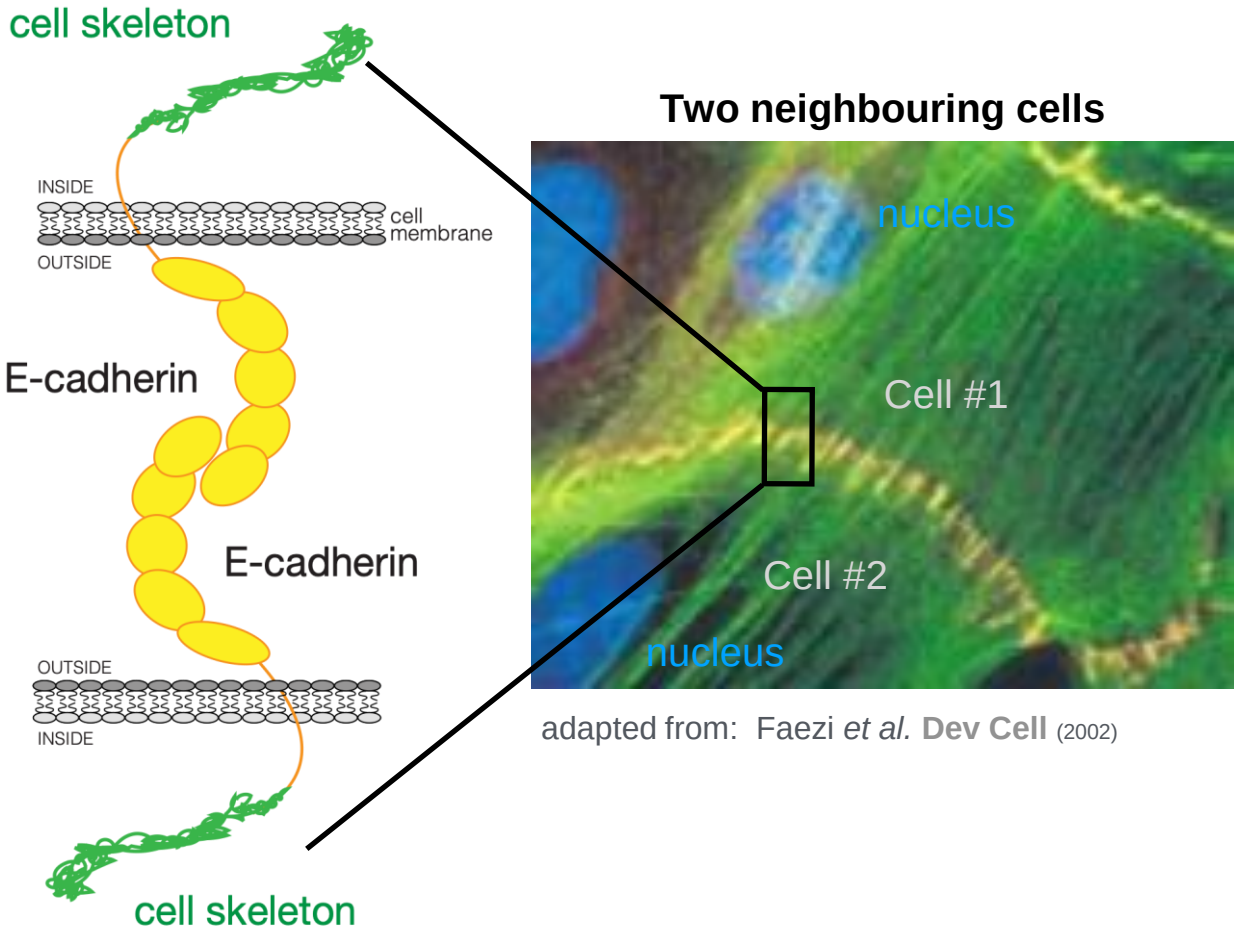
DerksenLab.org

cell adhesion and cancer progression

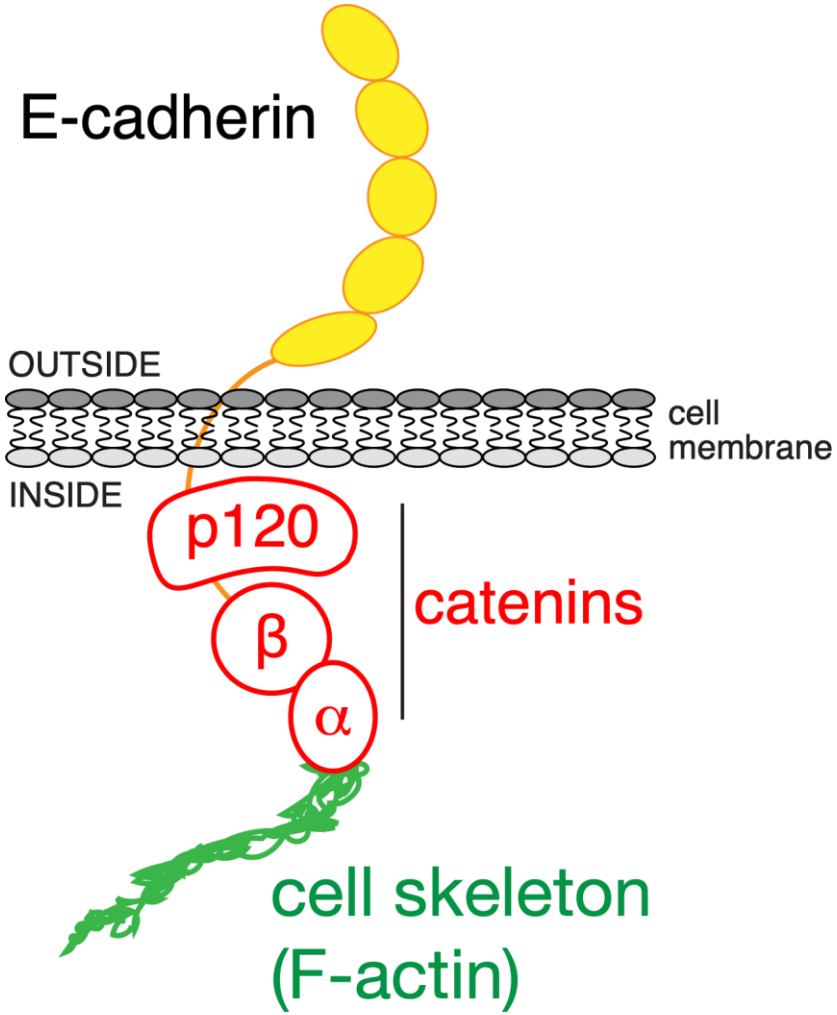
European Lobular Breast Cancer Consortium

September 28 @ The Assembly
Pittsburgh, PA

UMC Utrecht



adapted from: Faezi *et al.* **Dev Cell** (2002)



PATRICK DERKSEN.

ALTERNATIVE DRIVERS OF ILC

histological ILC (154 samples)

RATHER

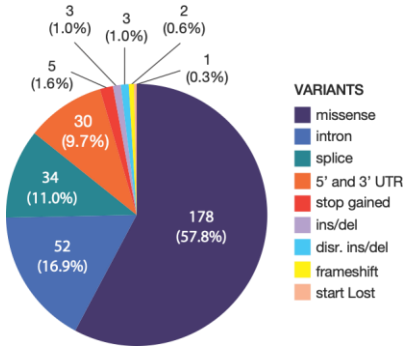
Michaut M.. ..Bernards R **Cell Rep** (2016)

exon capture (~100 genes)
passing grade seqs. (146 samples)

62 *CDH1*^{WT} (43%)

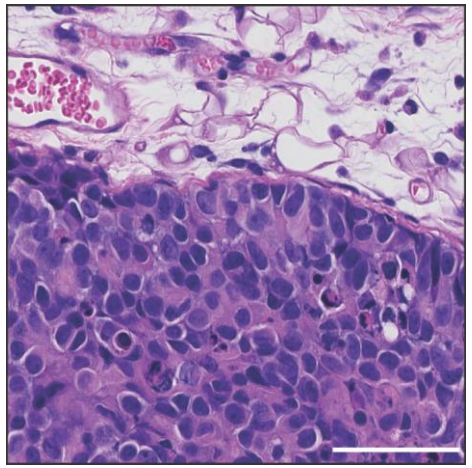
84 *CDH1*^{MUT} (57%)

308 *candidates*

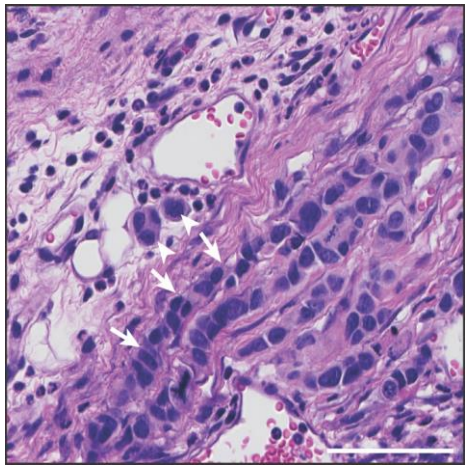


ILC R-L1047-D
(*CDH1*^{WT}; *AFDN* p.Phe629fs)

tumor in mouse model (control)

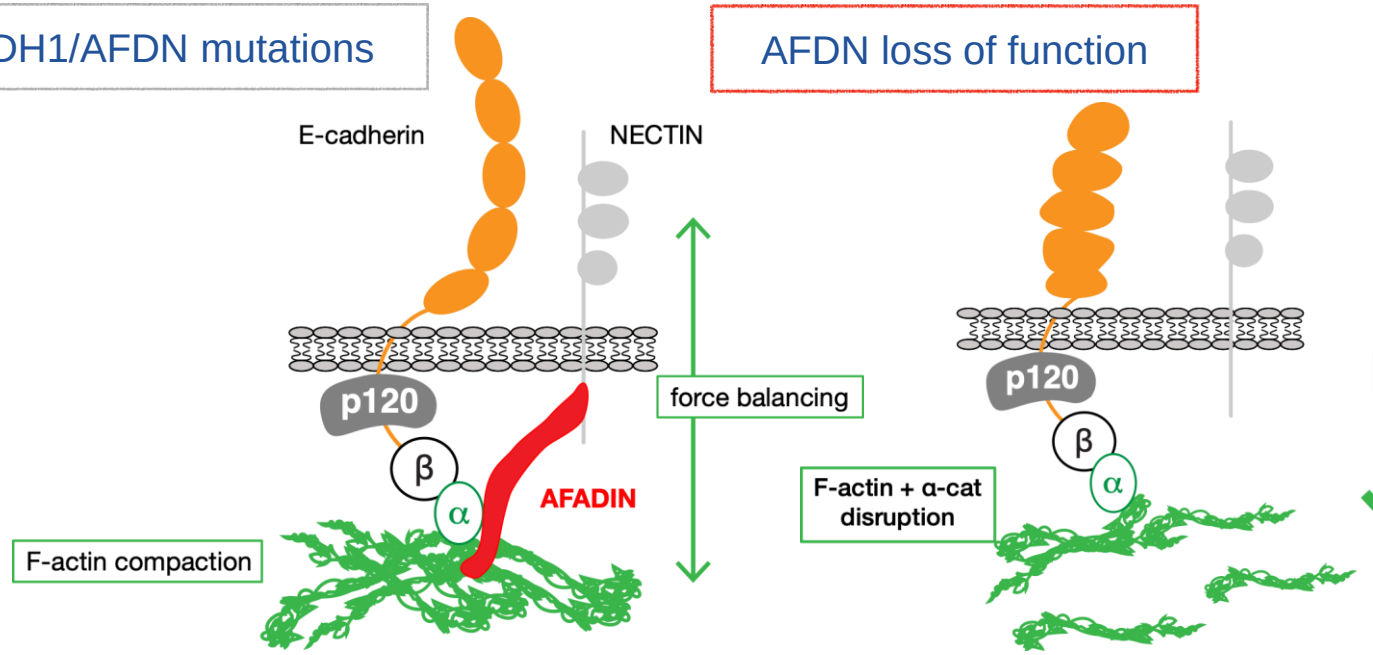


tumor in mouse model (AFDN knockout)



no CDH1/AFDN mutations

AFDN loss of function



CLINICAL RAMIFICATIONS:

Define biomarkers for:

- Breast cancer diagnosis
- Inclusion and treatment

classical ILC

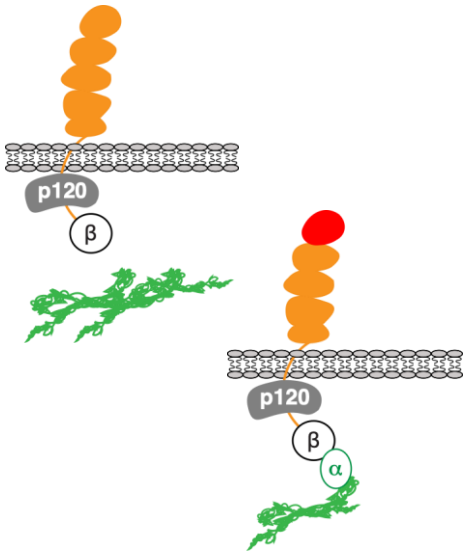
TYPE
- E-cadherin mutation *CDH1 (nonsense, fs, epigenetic?)*

BIOLOGY
- F-actin disruption
- GFR activation
- cell cycle repression

non-classical ILC

TYPE
- Adhesome mutation *CNTTA1*, *AFDN*, *CDH1*^{S180Y}

BIOLOGY
- F-actin disruption / aberrant function
- ~~GFR activation (?)~~
- ~~cell cycle repression~~

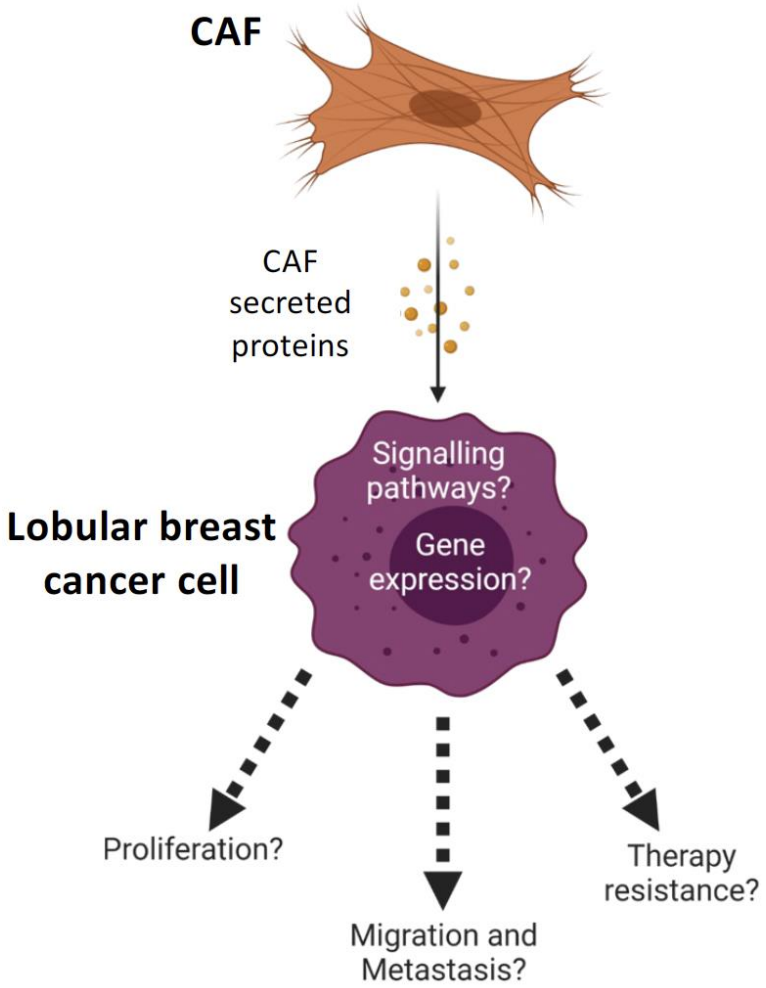


VAL BRUNTON. ILC ASSOCIATED FIBROBLASTS

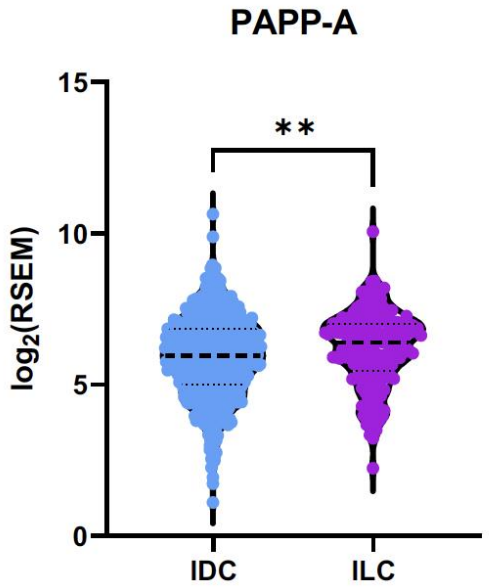
Cancer associated fibroblasts (CAFs) are 'healthy' cells that can support breast cancer progression but until recently haven't been investigated in Invasive Lobular Cancer

Valerie Brunton

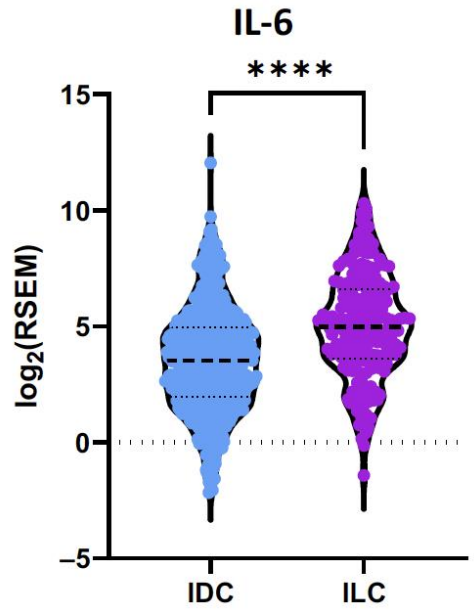
THE UNIVERSITY of EDINBURGH



We have identified two ILC CAF secreted proteins – **PAPP-A** and **IL-6** – that are more highly expressed in Invasive Lobular (ILC) than Invasive Ductal (IDC) Cancer



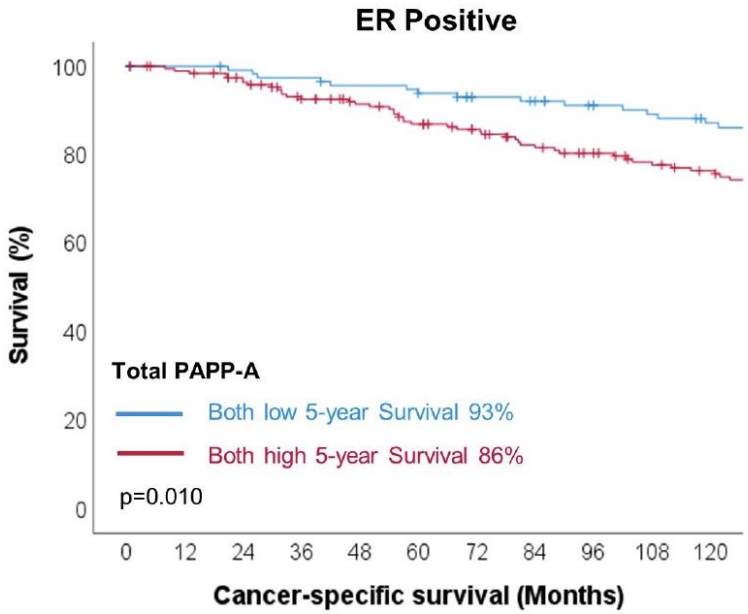
PAPP-A cuts IGF-1 binding proteins so more IGF-1 is available and can activate the tumour promoting IGF-1/PI3K pathway



IL-6 switches on genes in Lobular Breast Cancer cells that can promote increased migration and metastasis

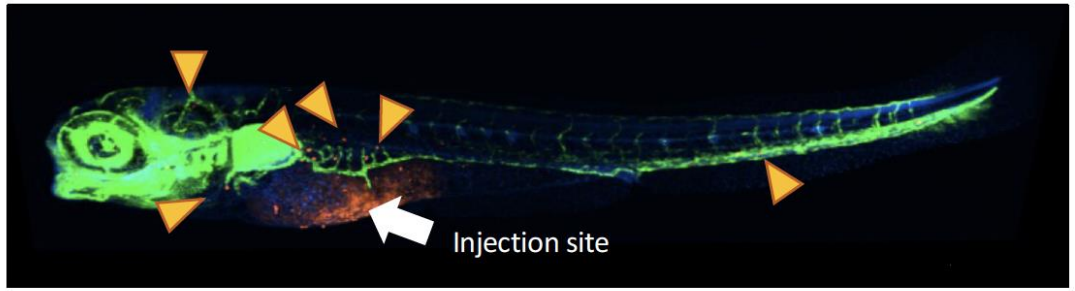
VAL BRUNTON. ILC ASSOCIATED FIBROBLASTS

High levels of **PAPP-A** are associated with poorer survival for ER+ Breast Cancer patients



IL-6 treated Lobular breast cancer cells more readily migrate away from the injection site in this Zebrafish model of metastasis

Untreated Lobular Breast Cancer Cells



IL-6 Treated Lobular Breast Cancer Cells

Human Lobular Breast Cancer Cells Zebrafish blood vessels Human and fish nuclei

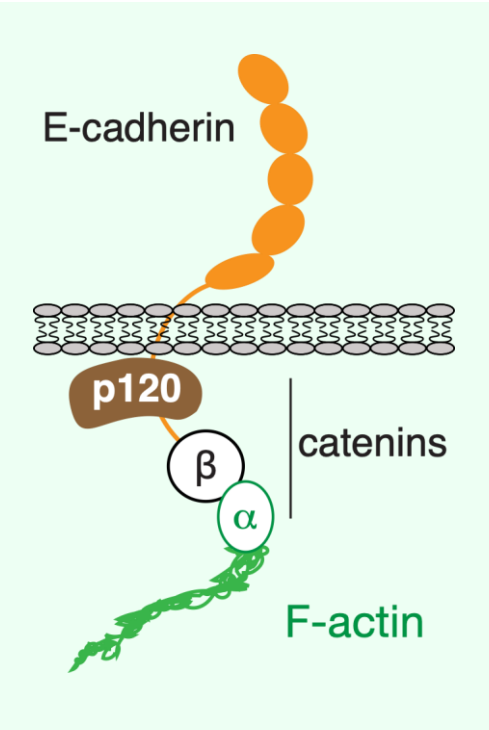
Breast cancer cells that have migrated away from the injection site

CANCER RESEARCH UK | SCOTLAND CENTRE

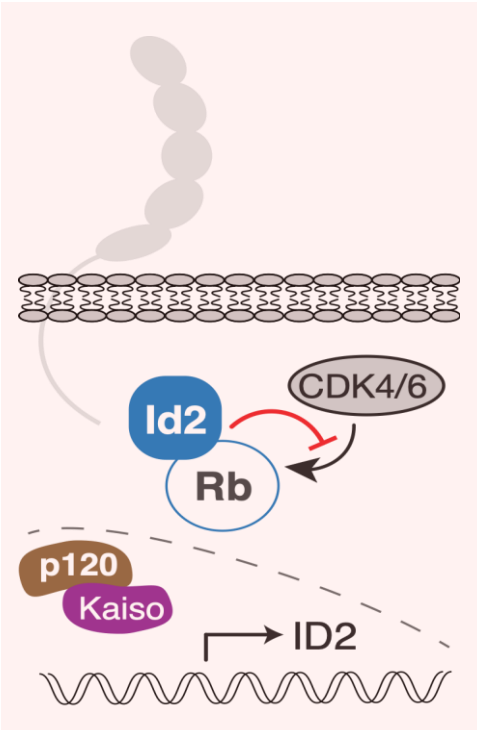
THIJS KOORMAN. TARGETING SURVIVAL CUES IN ILC

UMC Utrecht

E-cadherin loss



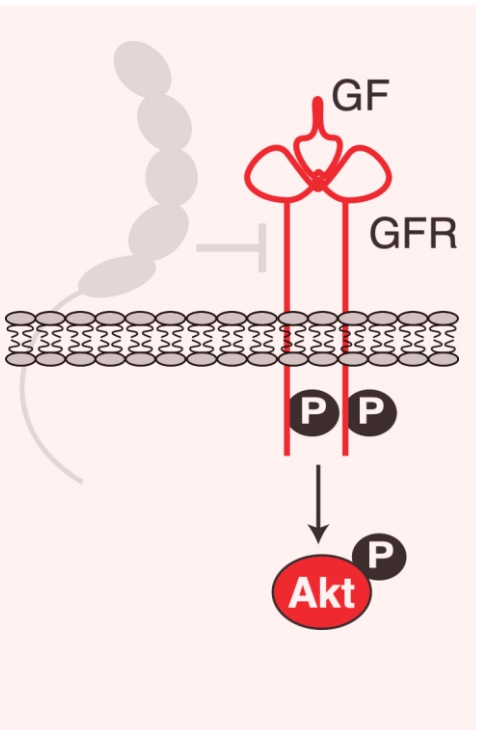
activation of KART



slow growth

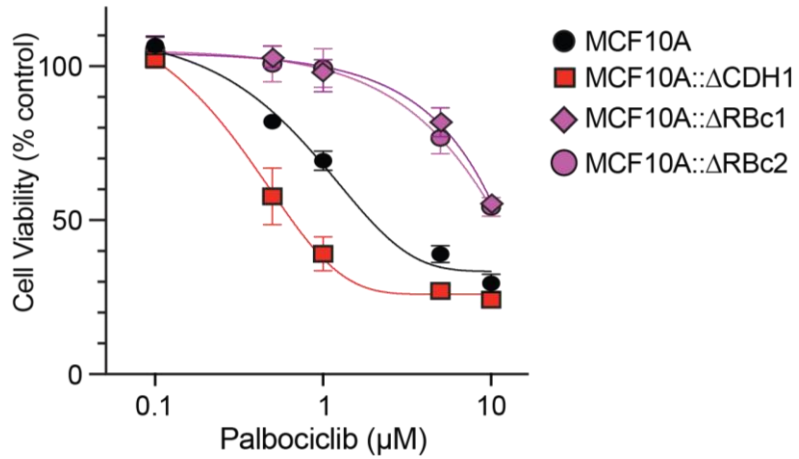
Rätze & Koorman *et al.* **Oncogene** (2022)
Sijnesael *et al.* **J Pathol** (2023)

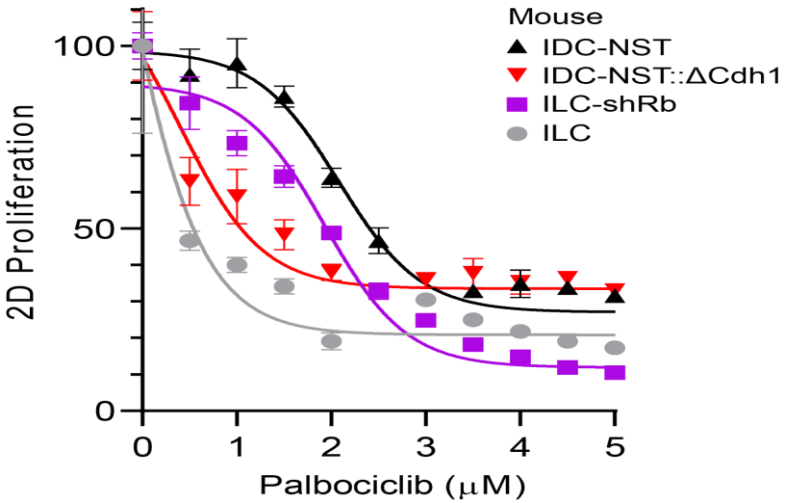
GFR/AKT Activation



survival

Hornsveld *et al.* **Cell Death Differ** (2016)
Teo *et al.* **Sci Rep** (2018)

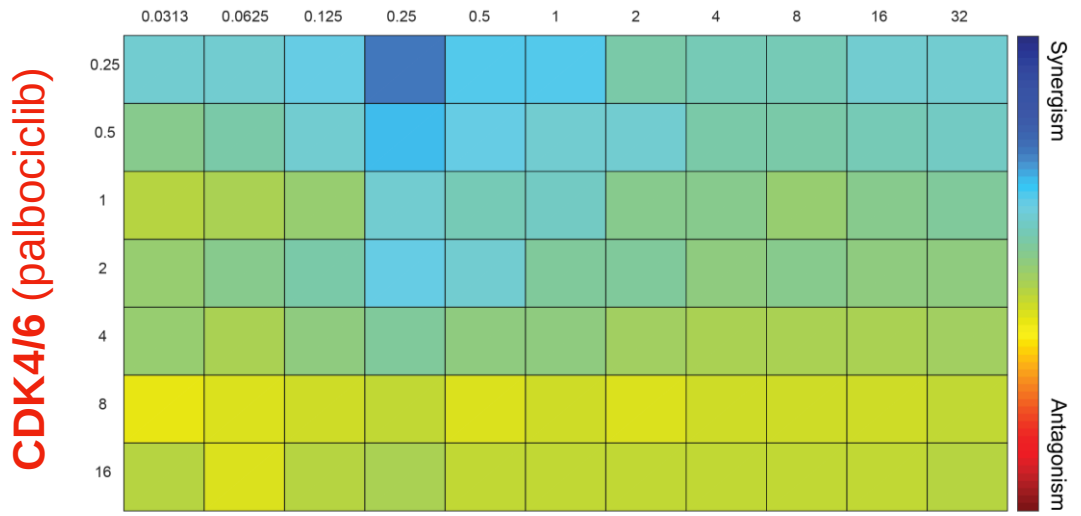


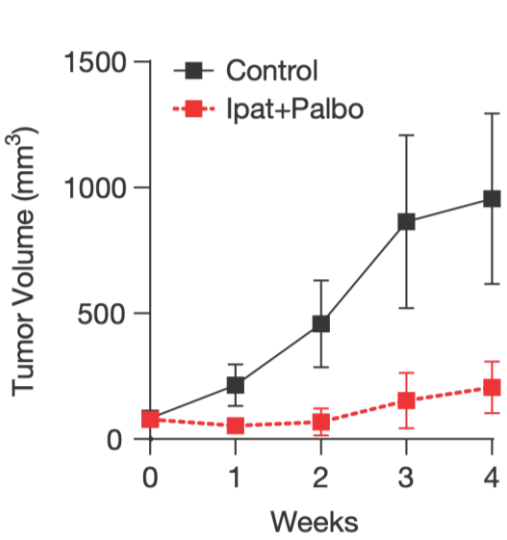


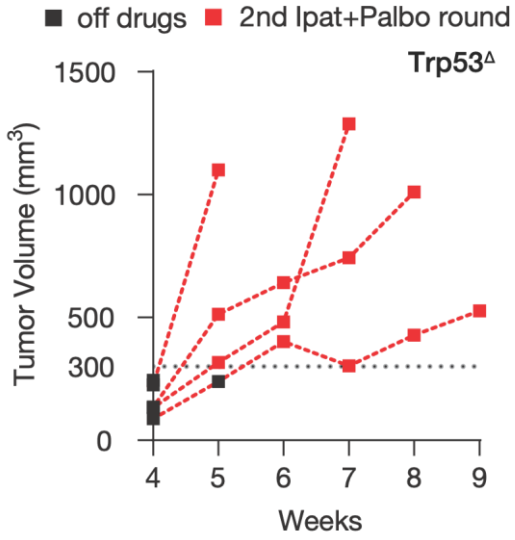
THIJS KOORMAN. TARGETING SURVIVAL CUES IN ILC

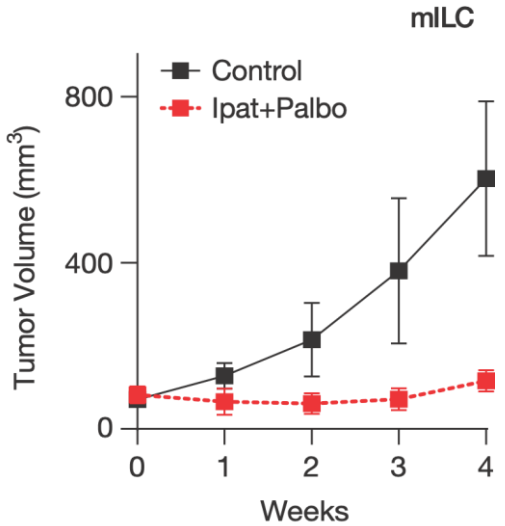
Invasive Ductal BC cells

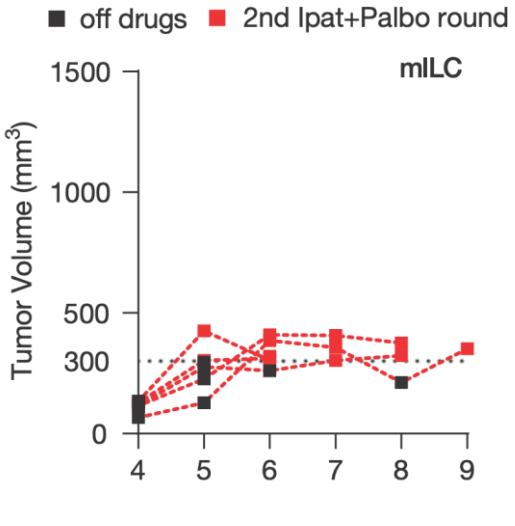
Invasive lobular BC cells



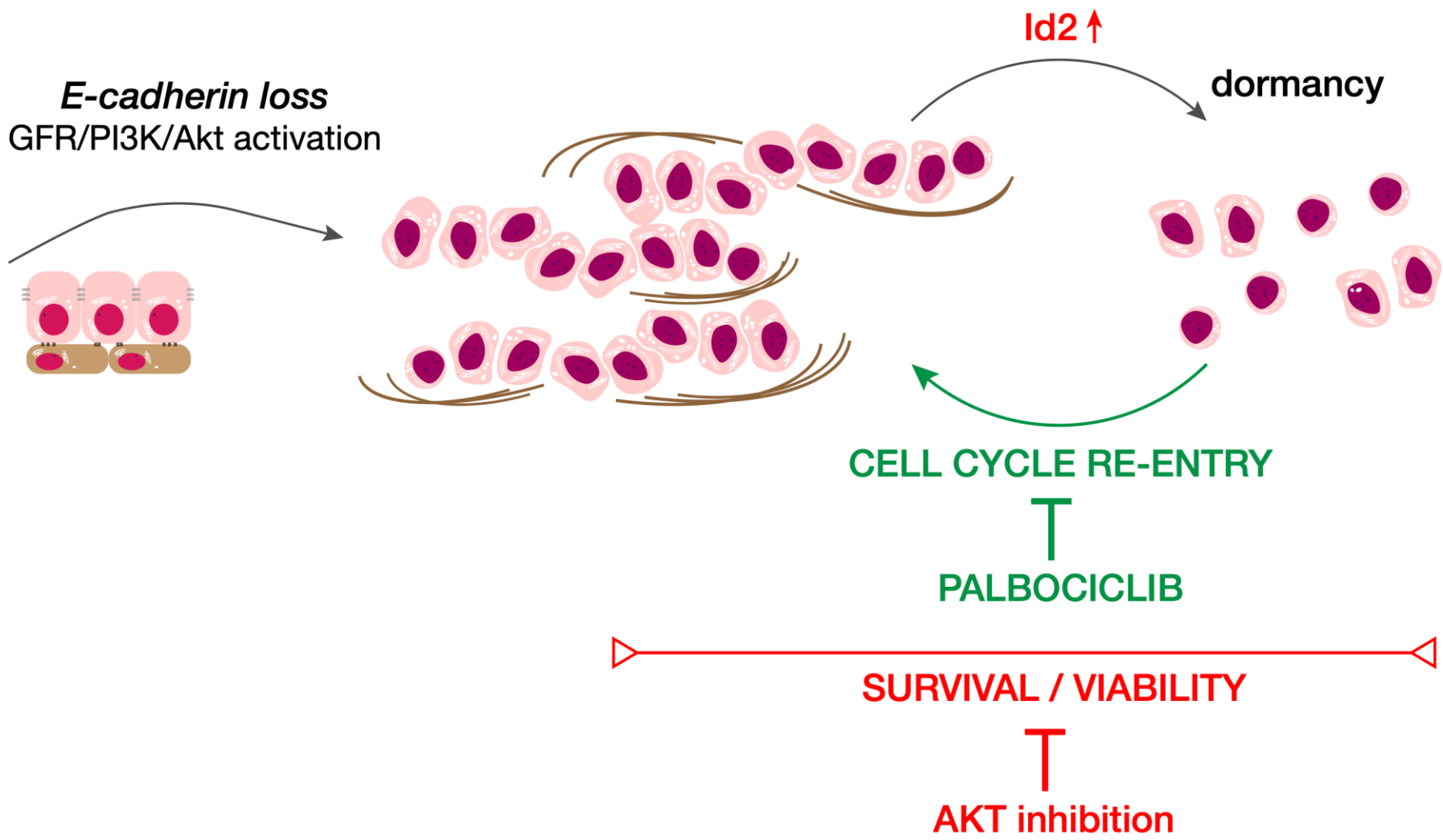








THIJS KOORMAN. TARGETING SURVIVAL CUES IN ILC



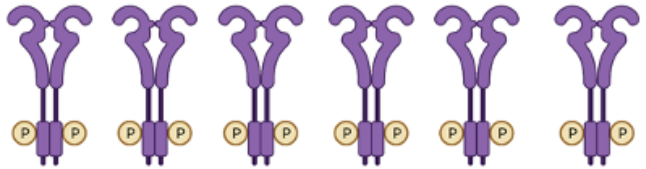
ARIELLA HANKER.

HER2/ERBB2 MUTANT ILC AND TREATMENT OPTIONS

European Lobular Breast Cancer Consortium

UT Southwestern Medical Center

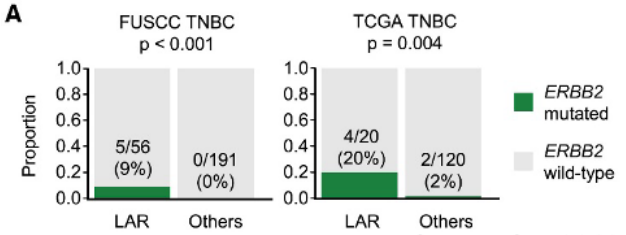
HER2 amplification



"HER2+" only

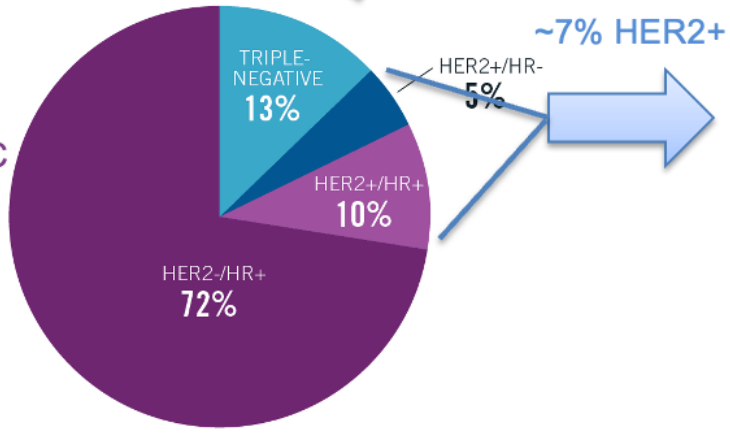
HER2 mutations

All clinical subtypes



Jiang et al., *Cancer Cell* 2019

<2% TNBC
~9-20% LAR subtype
~20% triple-negative ILC

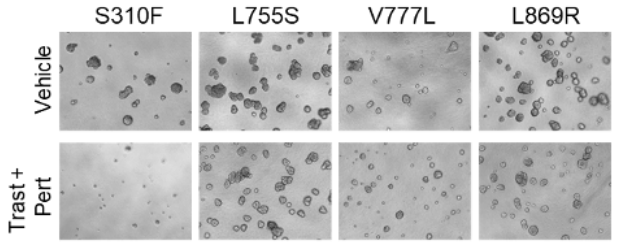


~7% HER2+

~5% HER2-/ER+ MBC
~10% lobular ER+ MBC

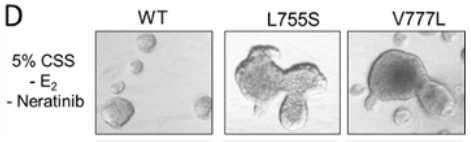
HR+ = hormone receptor+ (ER+/PR+)

Resistance to anti-HER2 therapies



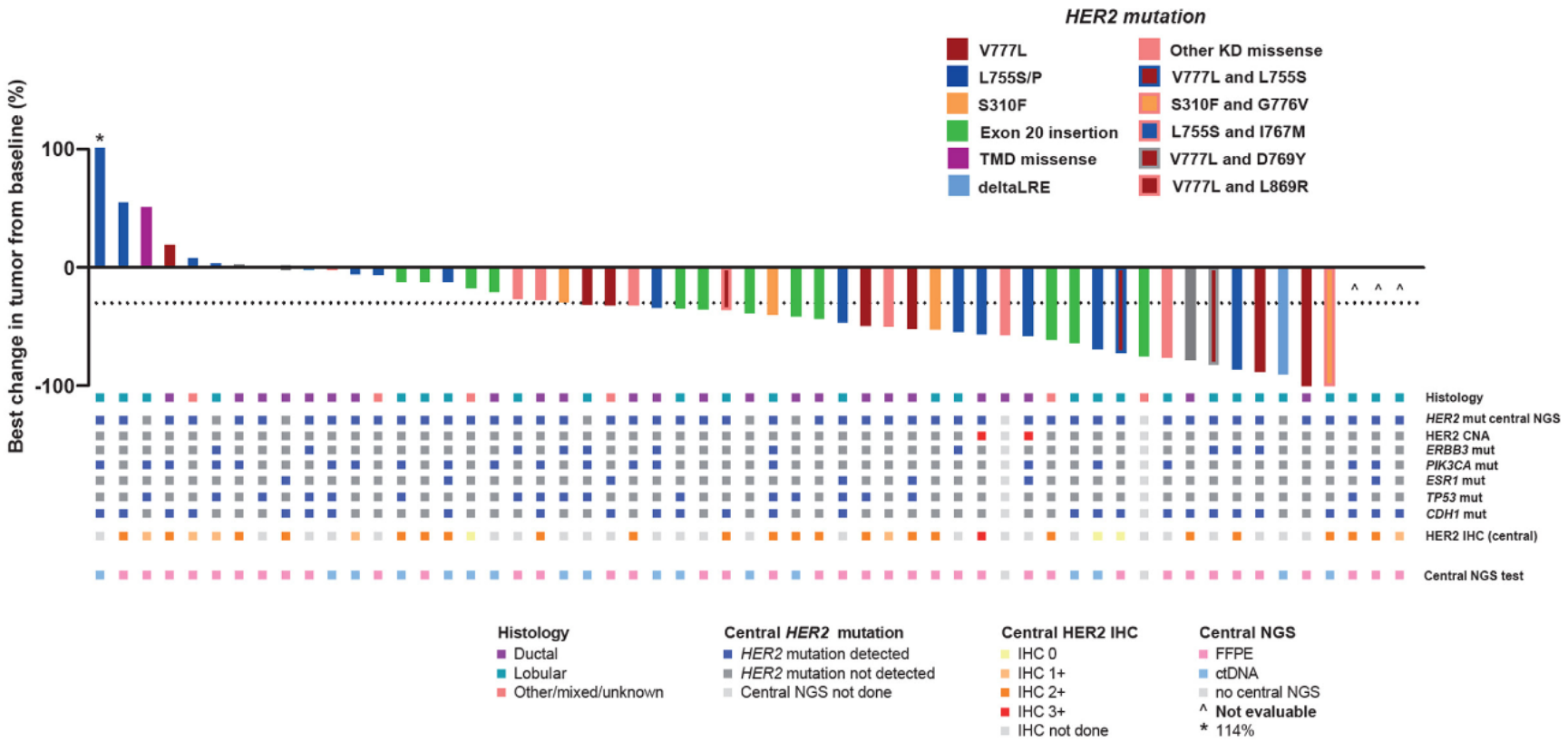
Hanker et al., *Cancer Cell* 2021
Cocco et al., *Sci Signal.* 2018
Smith et al., *Nature Commun.* 2021

Endocrine resistance



Croessmann et al., *Clin Cancer Res.* 2019
Razavi et al., *Cancer Cell* 2018
Nayar et al., *Nat Genet.* 2019
Kalra et al., *Cancer Res.* 2022

A

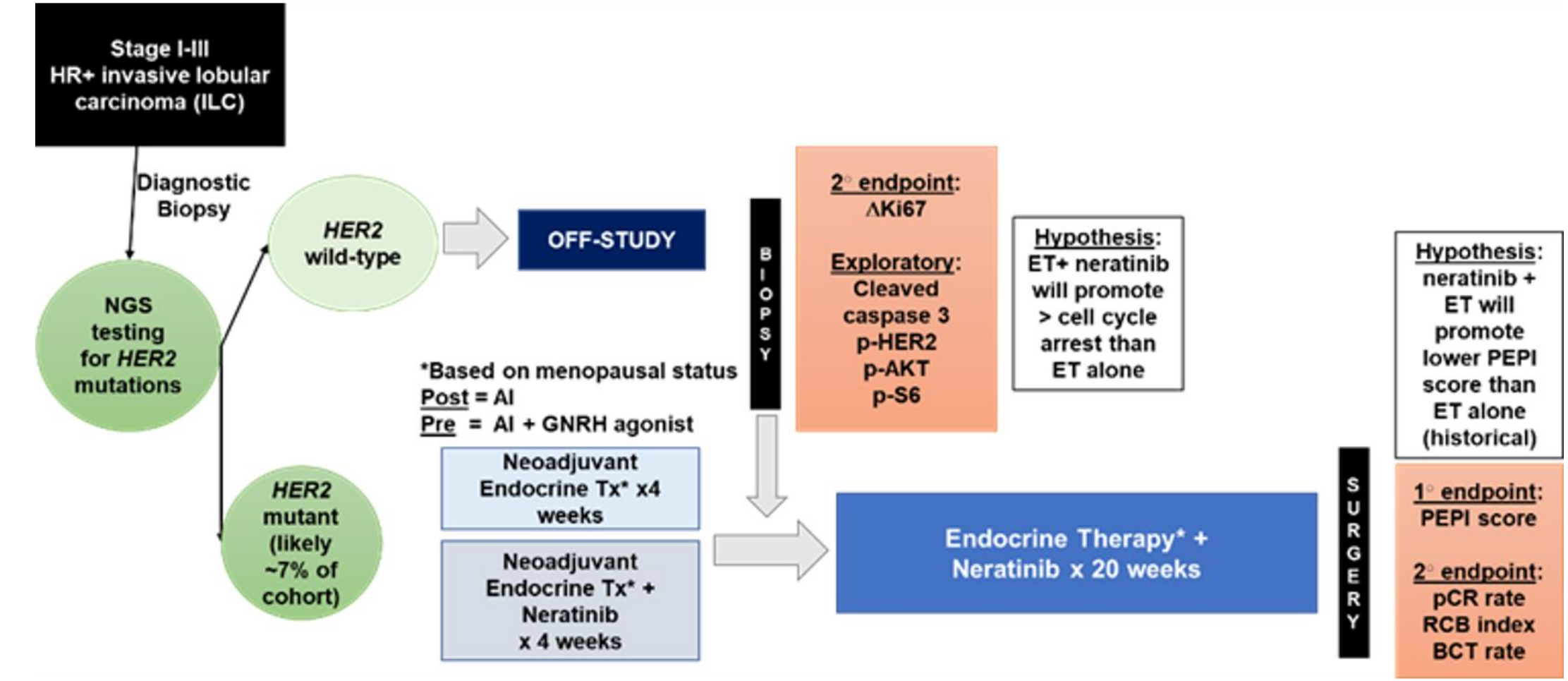


- Patients previously treated with CDK4/6i + endocrine therapy
- ILC ORR: 41%
- CBR: 52%
- Median PFS: 8.3 months
- Median DOR: 14.4 months
- Acquired HER2 mutations (including gatekeeper mutation) identified at progression, suggesting that resistant tumors remain dependent on mutant HER2

Jhaveri et al., *Ann Oncol.* 2023

SUMMIT trial: ER+ breast cancer expansion cohort

NCT05919108: Neoadjuvant Neratinib in Stage I-III HER2-Mutated Lobular Breast Cancers

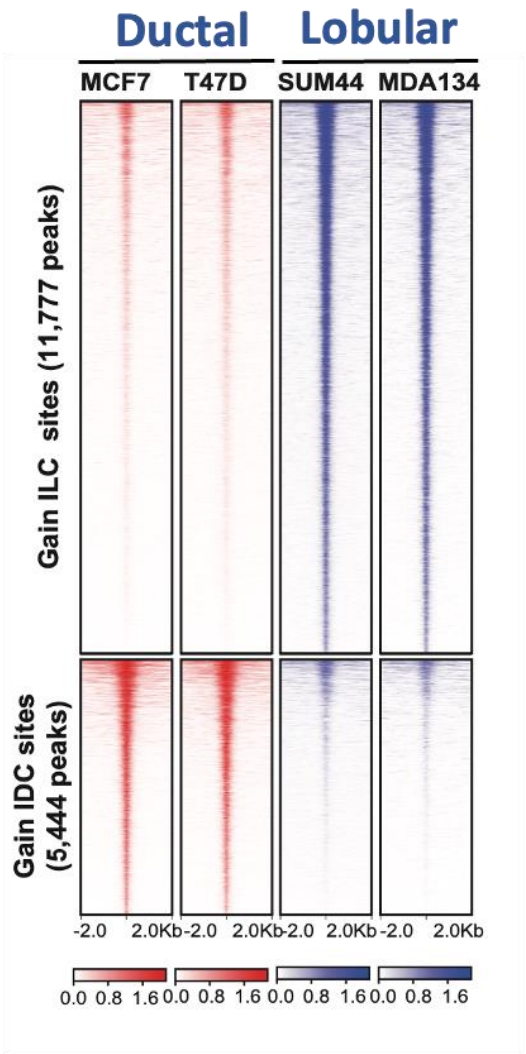


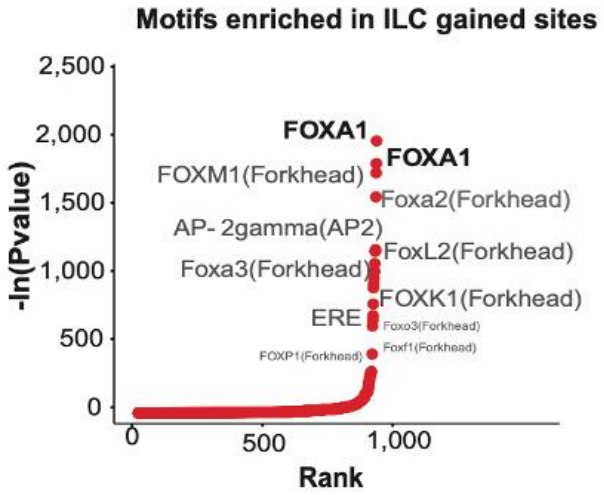
NCI R01 CA273246

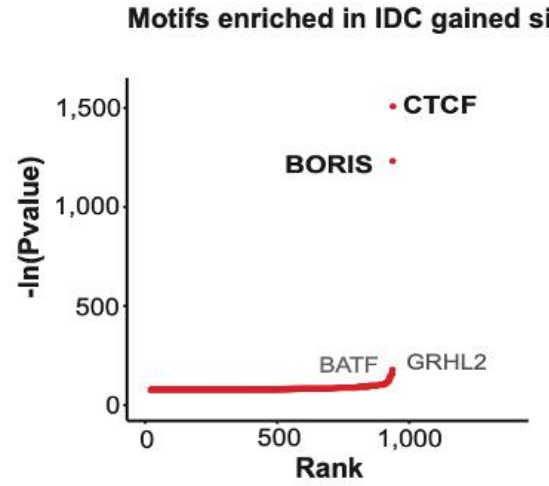
RINATH JESELSOHN.

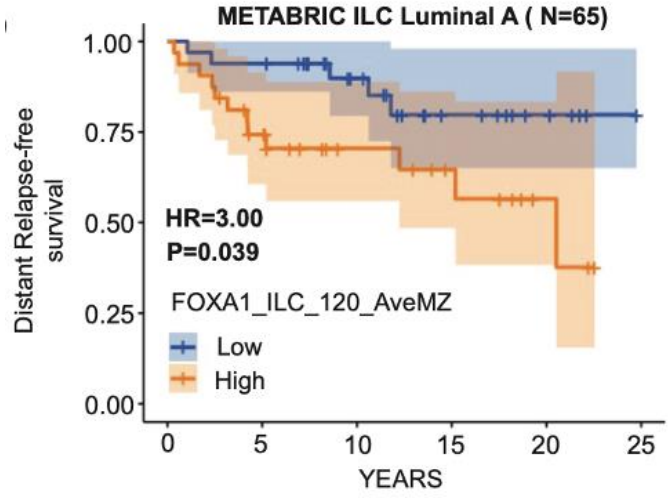
EPIGENETIC REGULATION OF ILC THERAPY RESISTANCE

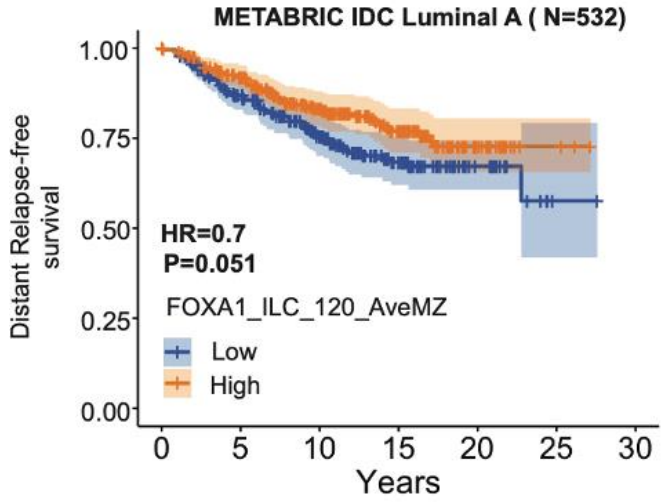
Dana-Farber Cancer Institute







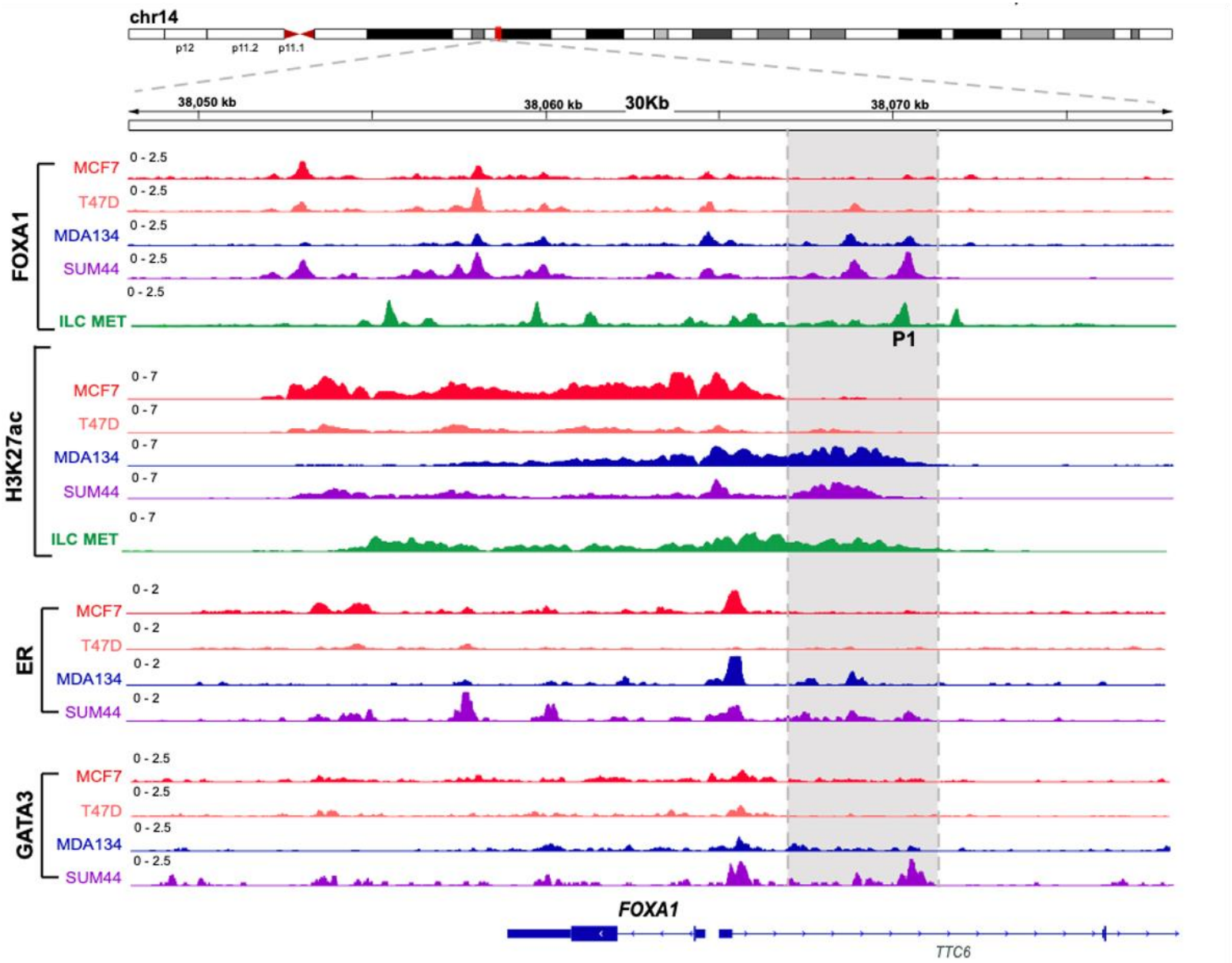




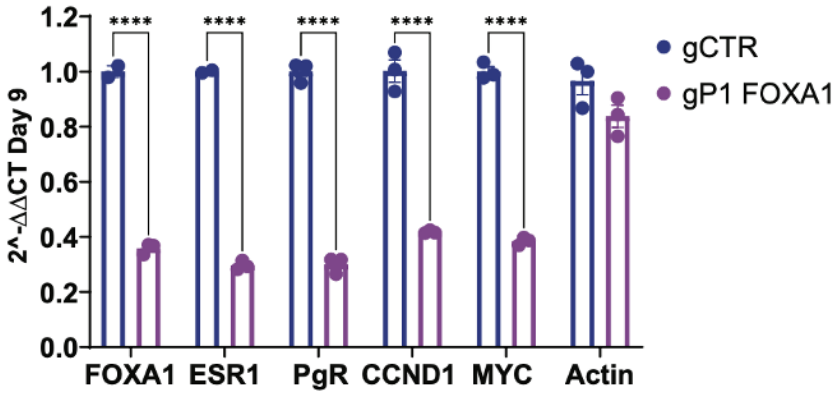
Nardone A, Can Res 2022

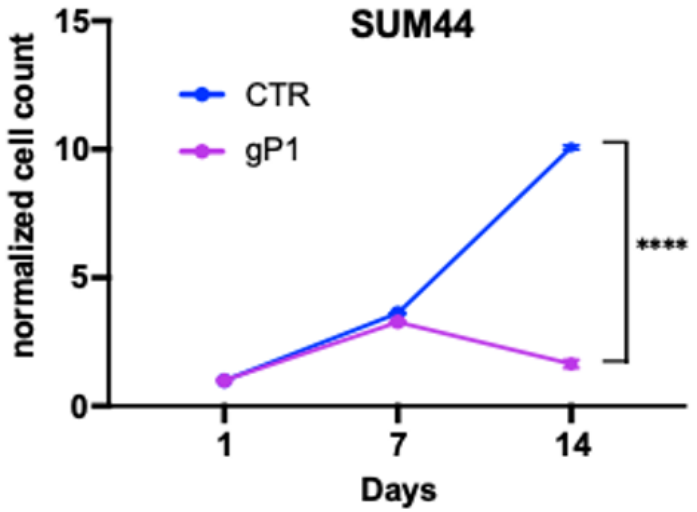
RINATH JESELSOHN.

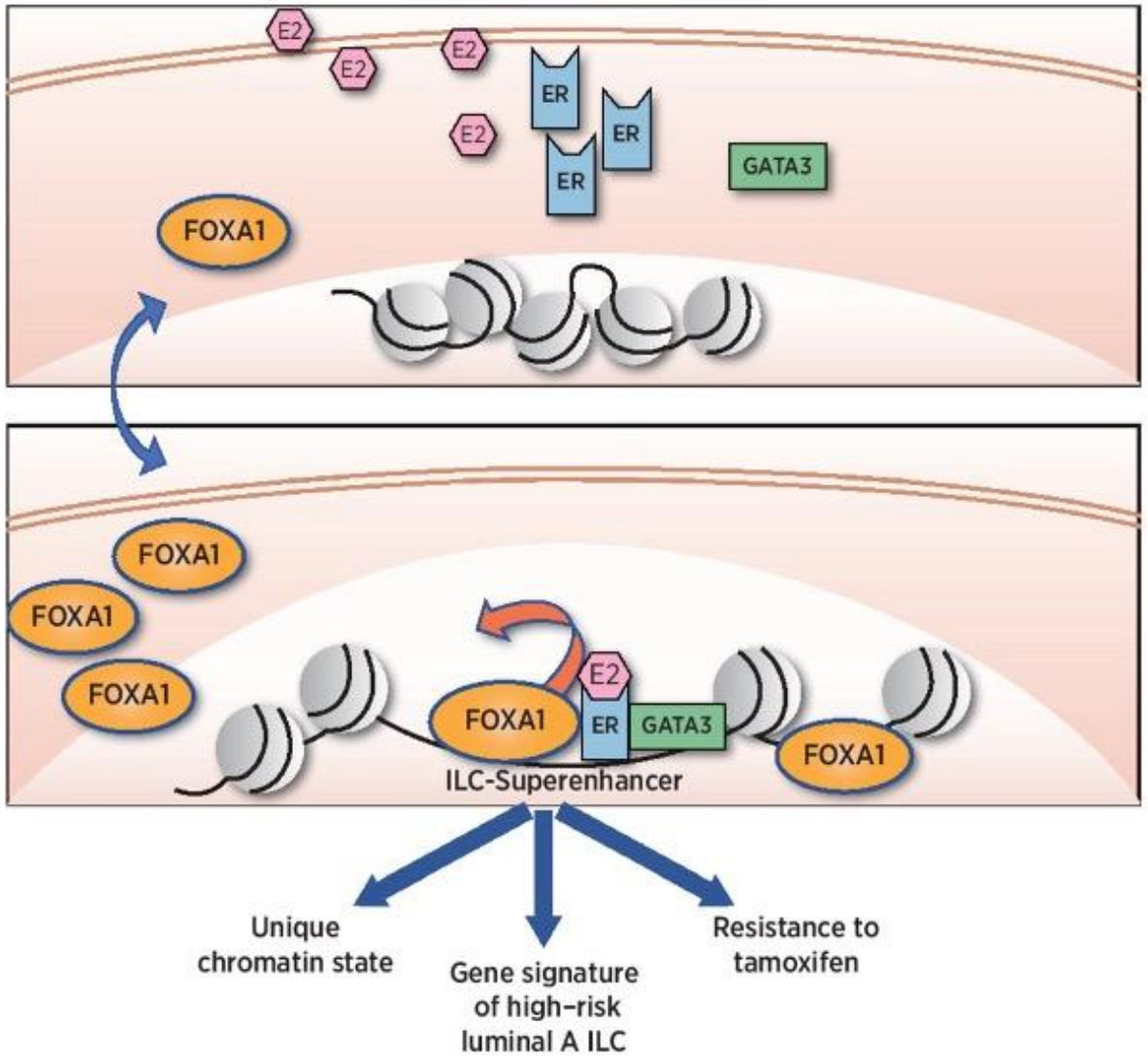
EPIGENETIC REGULATION OF ILC THERAPY RESISTANCE



FOXA1 peak knockout



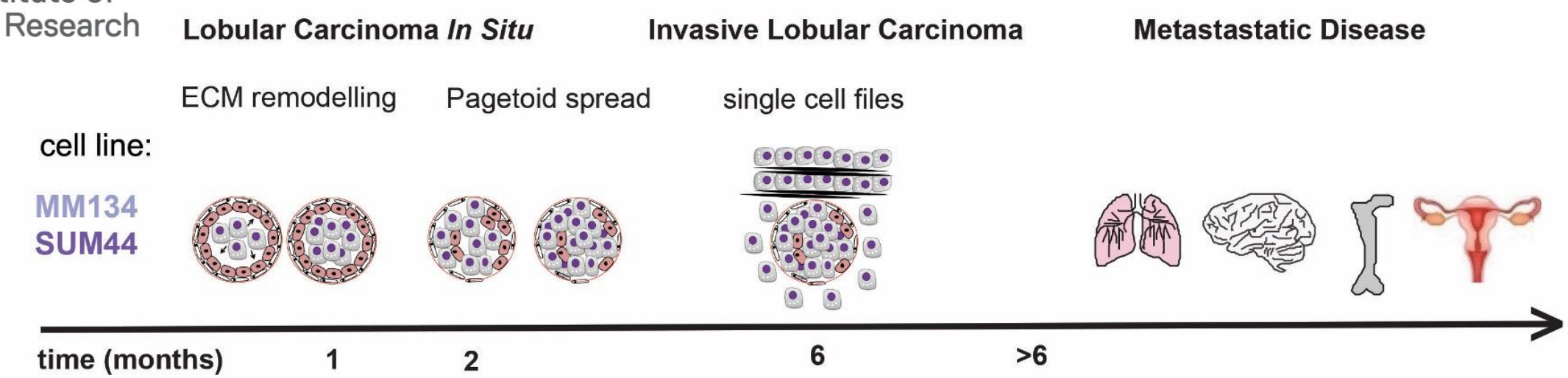




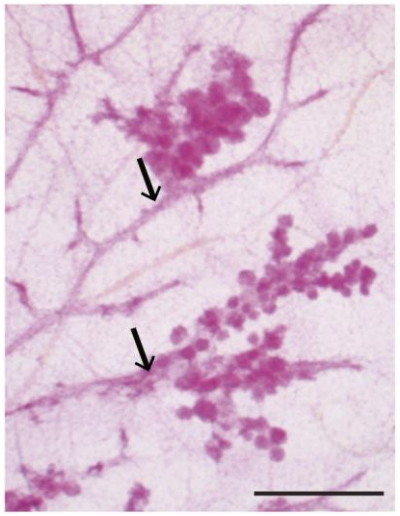
Epigenomic analysis of invasive lobular breast cancer reveals an altered chromatin state and a FOXA1-ER axis, which drives therapy resistance and tumor progression.

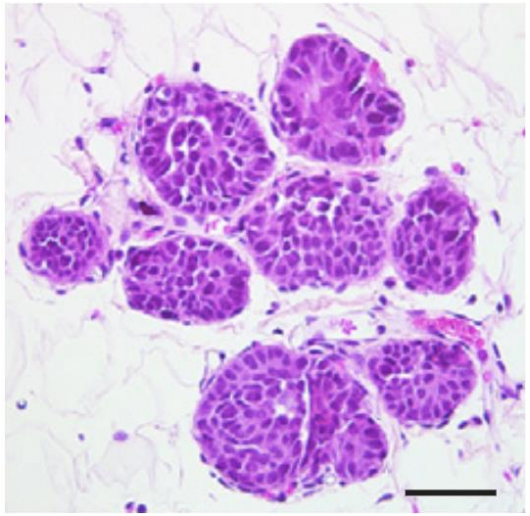
CATHRIN BRISKEN. KEYNOTE LECTURE

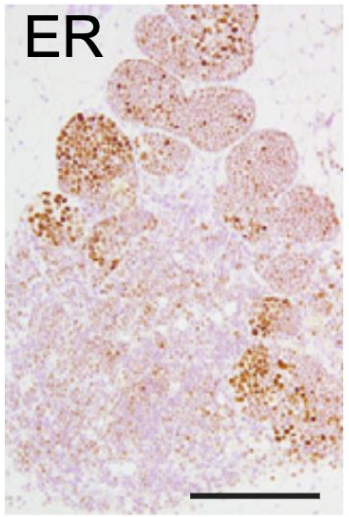
MIND MODELS OF ILC

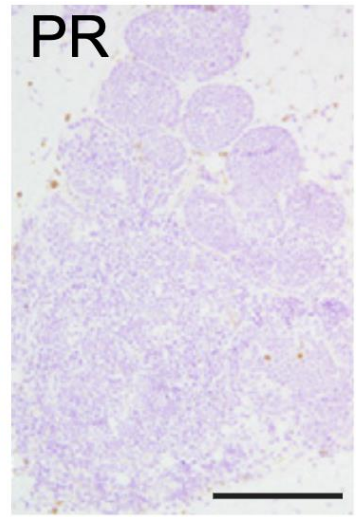


MDA-MB-134IV (ILC cell line)







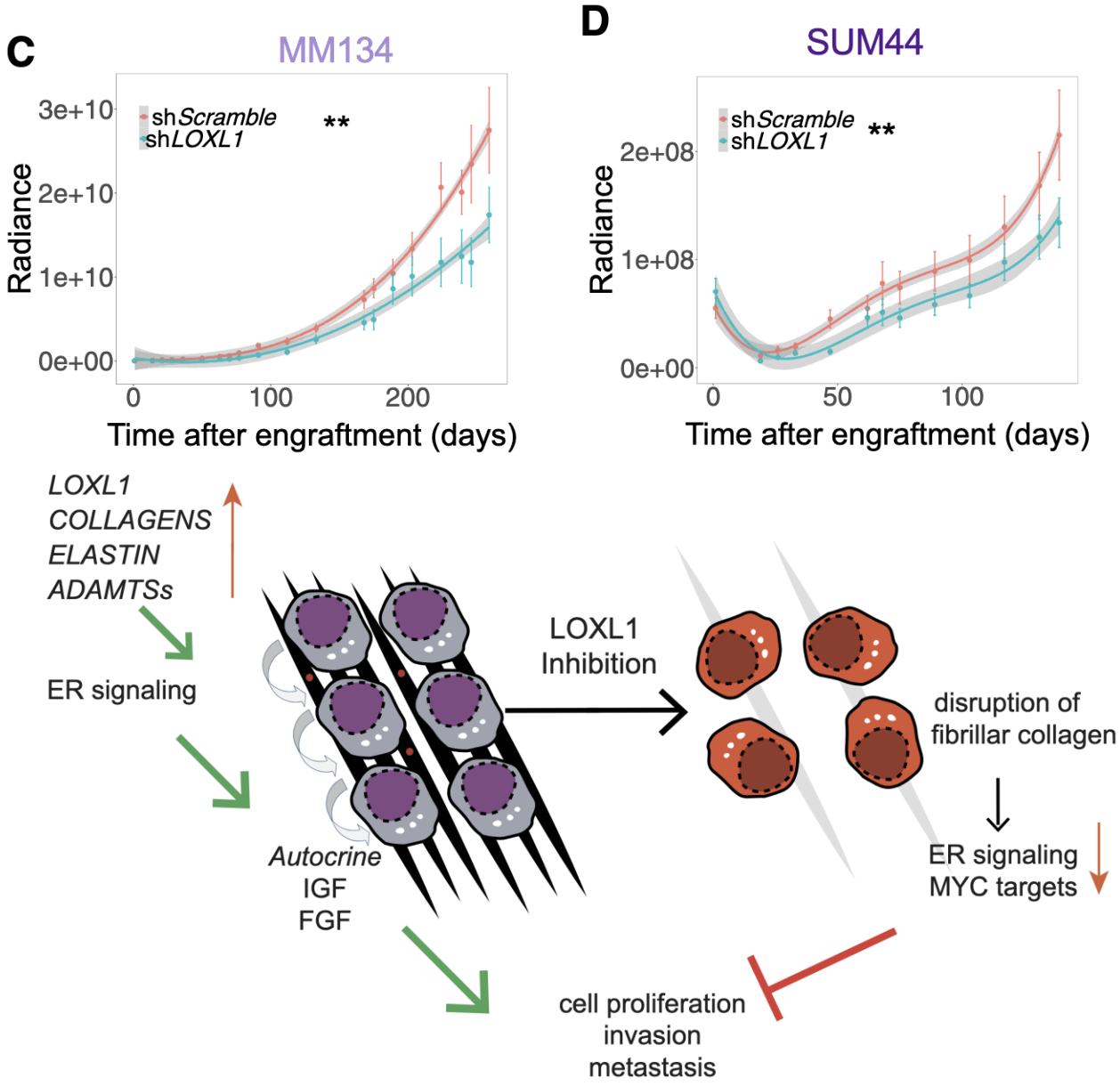


mammary intraductal (MIND) injections

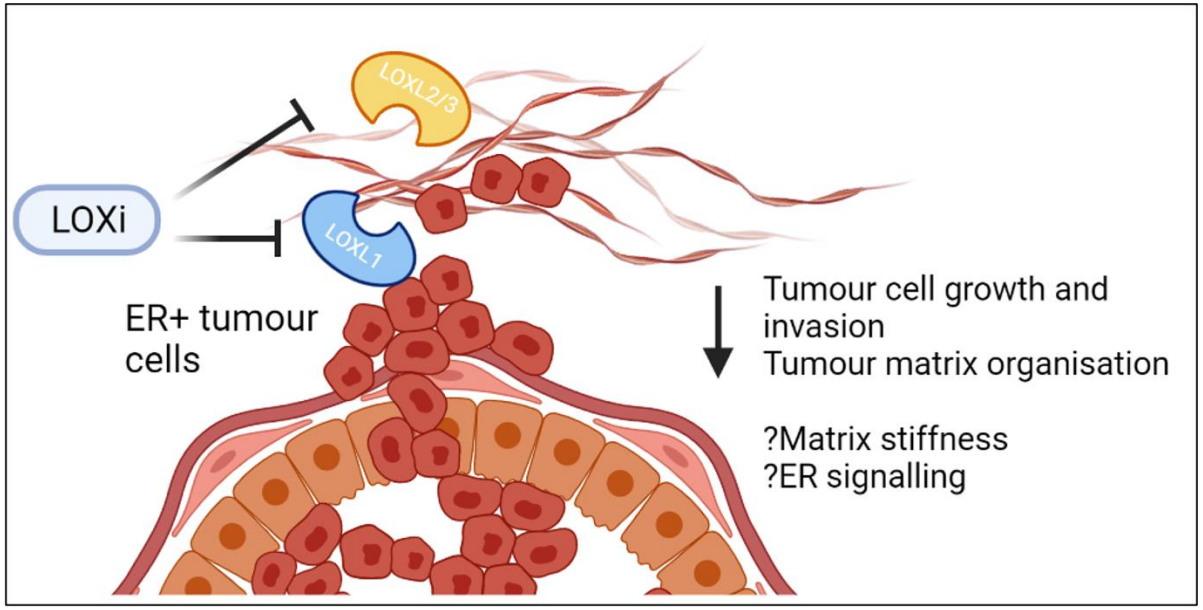
Sflomos *et al.* (2021) *EMBO Mol. Med.*

CATHRIN BRISKEN. KEYNOTE LECTURE

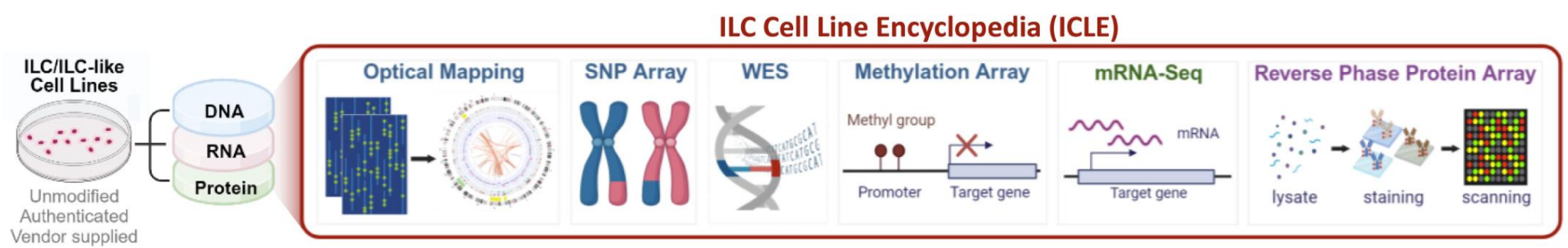
MIND MODELS OF ILC

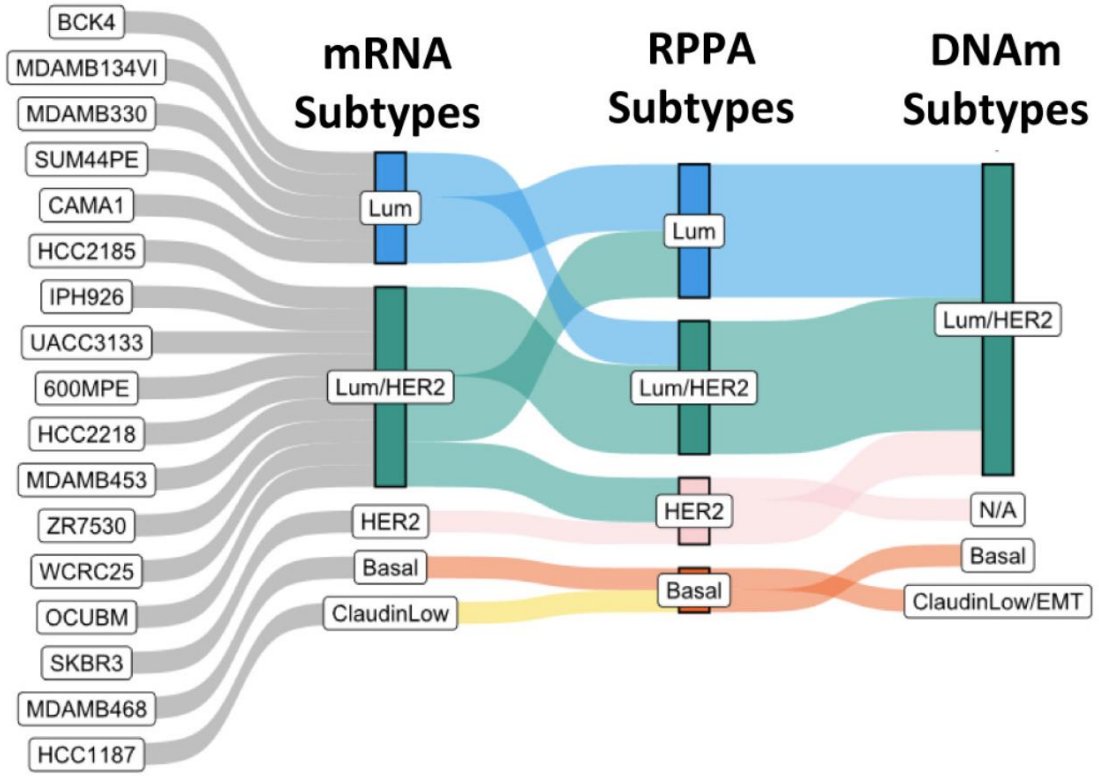


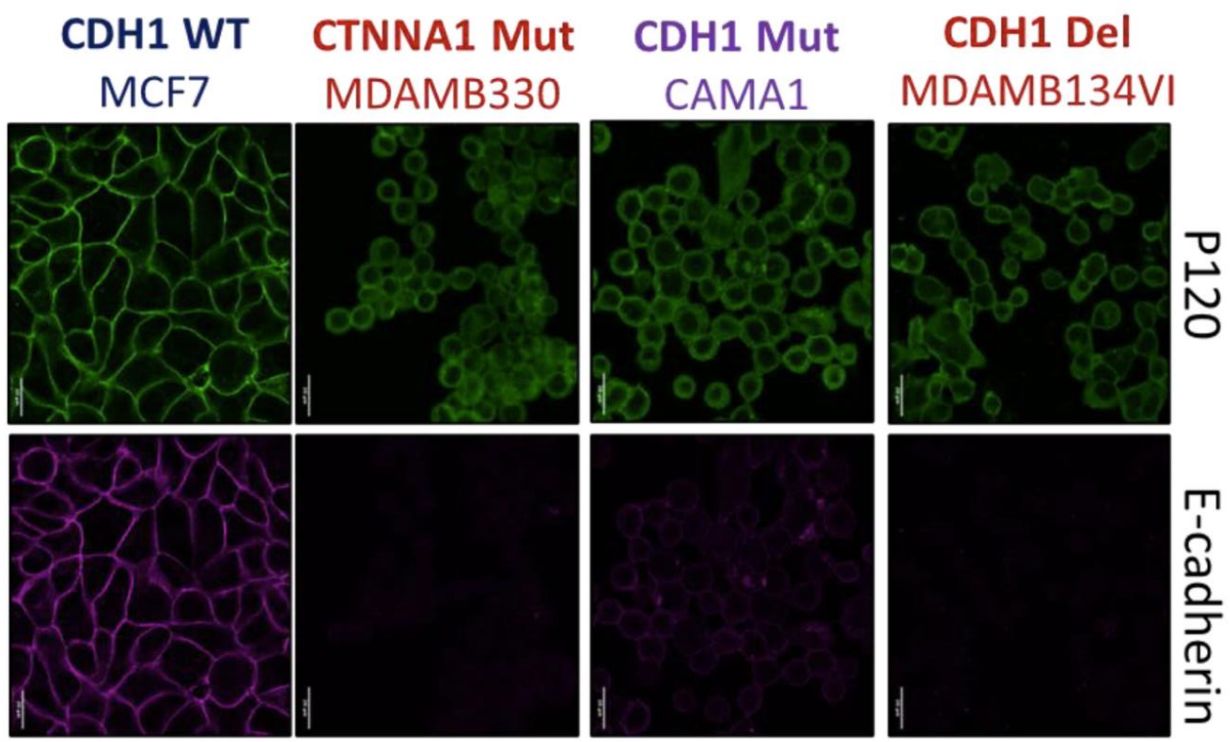
The LOX inhibitor PXS-5505 inhibits tumor progression in preclinical xenograft models



UPMC
LIFE CHANGING MEDICINE

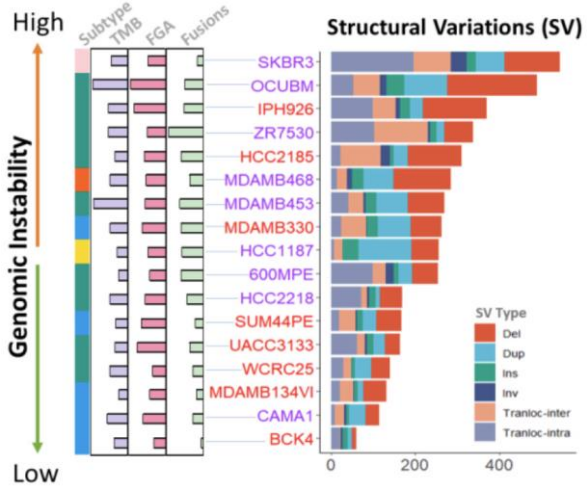




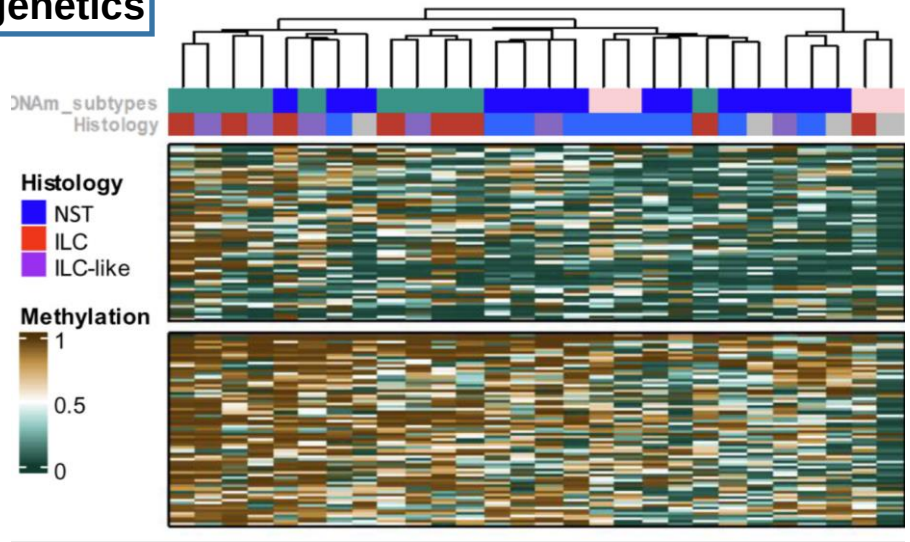


Available on: https://www.biorxiv.org/content/10.1101/2023.09.26.559548v1

Genomics



Epigenetics



Pathway Dependencies

Actin Cytoskeleton

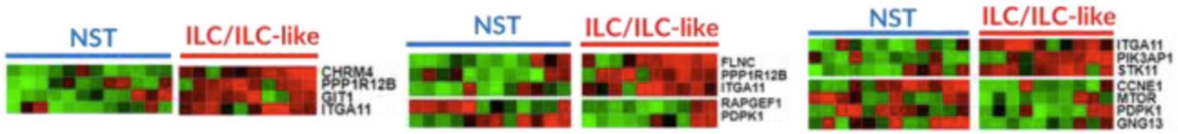
Gene	LogFC	Dependency
PPP1R12B	0.5	High
GIT1	0.2	High
CHRM4	0.2	High
ITGA11	0.3	High

Focal Adhesion

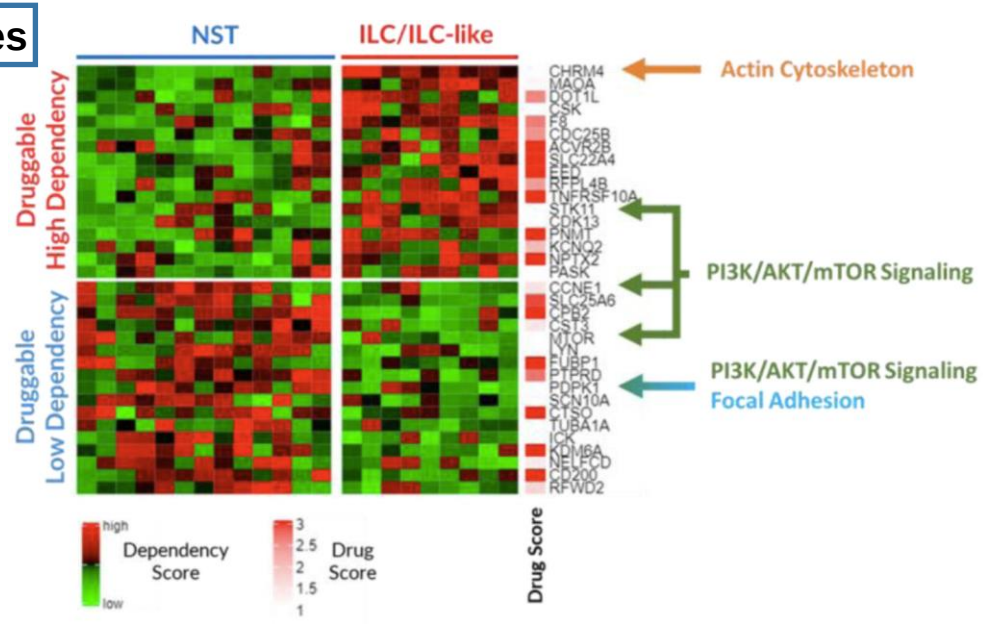
Gene	LogFC	Dependency
ITGA11	0.3	High
FLNC	0.2	High
PPP1R12B	0.5	High
PDPK1	-0.2	Low
RAPGEF1	-0.2	Low

PI3K/AKT/mTOR Signaling

Gene	LogFC	Dependency
ITGA11	0.3	High
PIK3AP1	0.2	High
STK11	0.1	High
MTOR	-0.4	Low
PDPK1	-0.2	Low
GNG13	-0.2	Low
CCNE1	-0.2	Low



Pathway Dependencies



Available on: https://www.biorxiv.org/content/10.1101/2023.09.26.559548v1

		ILC Driver Alterations		Other Altered Genes					Molecular Similarity to ILC Patient Tumors		
Cell Line	Molecular Subtype	CDH1	CTNNA1	TP53	PIK3CA	ERBB2	PTEN	FOXA1	Copy Number	RNA Expression	Suitable Model for ER+/Luminal ILC Disease
BCK4	Lum	MUT;LOH			MUT	MUT			0.5	0.6	Yes
CAMA1	Lum	MUT		MUT;LOH			MUT;LOH		0.3	-0.1	Yes, but low RNA similarity
MDAMB134VI	Lum	EXON6;LOH		MUT;LOH					0.5	0.3	Yes
MDAMB330	Lum		MUT	MUT;LOH		AMP			0.2	0.2	Yes
SUM44PE	Lum	MUT;LOH		MUT;LOH				AMP	0.4	0.2	Yes
600MPE	Lum/HER2	MUT;LOH		MUT;LOH					0.6	0.3	Yes
HCC2185	Lum/HER2	DEL		MUT	MUT;AMP				0.2	NS	Yes, but low RNA similarity
HCC2218	Lum/HER2	DEL		MUT;LOH		AMP			0.5	0.3	Yes
IPH926	Lum/HER2	MUT;LOH		MUT;LOH					0.2	0.3	Yes
MDAMB453	Lum/HER2	MUT;LOH		DEL	MUT;GAIN		MUT	AMP	0.3	0.1	Yes
OCUBM	Lum/HER2	EXON2;LOH		MUT;LOH	MUT;GAIN	AMP			0.3	-0.2	Yes, but low RNA similarity
UACC3133	Lum/HER2	MUT;LOH		MUT;LOH		MUT;GAIN			0.5	0.3	Yes
WCRC25	Lum/HER2	MUT;LOH		MUT;LOH					0.5	0.3	Yes
ZR7530	Lum/HER2	MUT;LOH				AMP			0.5	0.1	Yes
SKBR3	HER2	DEL		MUT;LOH		AMP			0.1	NS	No, HER2 subtype
HCC1187	ClaudinLow		MUT	MUT					0.3	-0.3	No, claudinLow subtype
MDAMB468	Basal		EXON4,5;MUT	MUT;LOH		MUT;LOH	MUT;GAIN		NS	-0.4	No, basal subtype

Alteration
- AMP
- DEL
- MUT
- MUT;AMP
- MUT;DEL
- MUT;GAIN
- MUT;LOH

Available on: https://www.biorxiv.org/content/10.1101/2023.09.26.559548v1

Also see: Hollestelle *et al.* (2010) Breast Cancer Res Treat

Our Panelists

Patrick Derksen, PhD

Peter Simpson, PhD

Bhuvaneswari Ramaswamy, MD

Matt Covington, MD

Priscilla McAuliffe, MD, PhD

Jason Mouabbi, MD

European Lobular Breast Cancer Consortium

LBCA Lobular Breast Cancer Alliance

ILC 2023 Pittsburgh, PA

BENCH-BEDSIDE- CAN WE TRANSLATE OUR DISCOVERIES TO IMPROVE LIVES OF PATIENTS WITH INVASIVE LOBULAR CANCERS?

Bhuvaneswari Ramaswamy MD
Professor

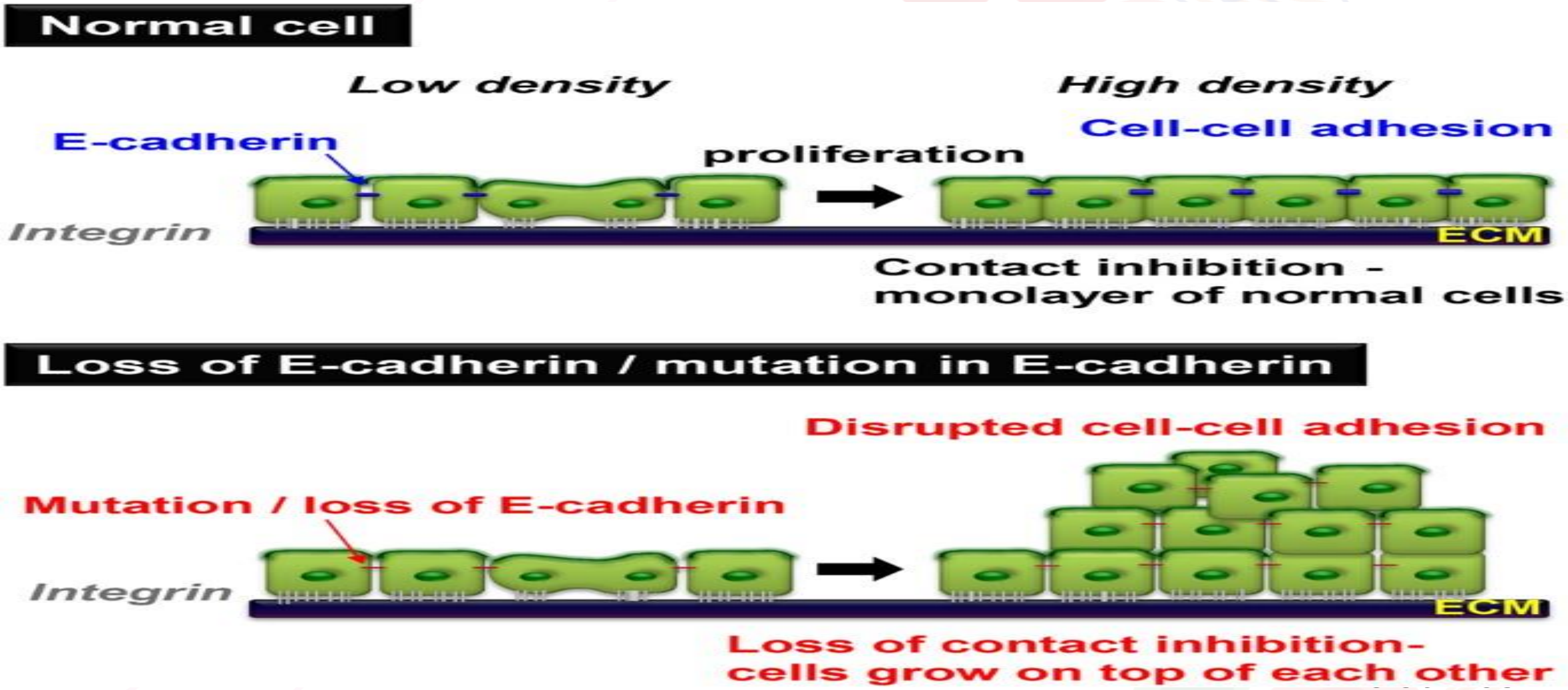
The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

DISCLOSURES

- Seagen- Honoraria- 2022

Distinct Molecular Feature: Loss of E-Cadherin



Oncogene (2018) 37:4769–4780

CLINICAL CHALLENGES ONCOLOGIST FACE IN MANAGING ILC.

Delayed/late diagnosis

Local Therapy

-Distinct molecular features

Choice of Adjuvant Therapy

Role of Oncotype

Late recurrence

Role of Disseminated tumor cells/dormancy

Unusual metastatic sites.

Why??

Common Theme for the Challenges

Giovanni Corso, MD, PhD
Hereditary lobular breast cancer syndrome associated with germline CDH1 variants

Ethan Sokol, PhD
Identification of Targetable Vulnerabilities in ILC Using Comprehensive Genomics Profiling

Massimo Cristofanilli, MD
Liquid biopsy in ILC: What can we learn about clinical and molecular evolution?

Peter Simpson, PhD
ILC-focused biomarkers of progression and prognosis

Karen Van Baelen, MD
Metastatic Spread in Patients with Mixed ILC/NST: Results from Post-Mortem Tissue Donation Programs

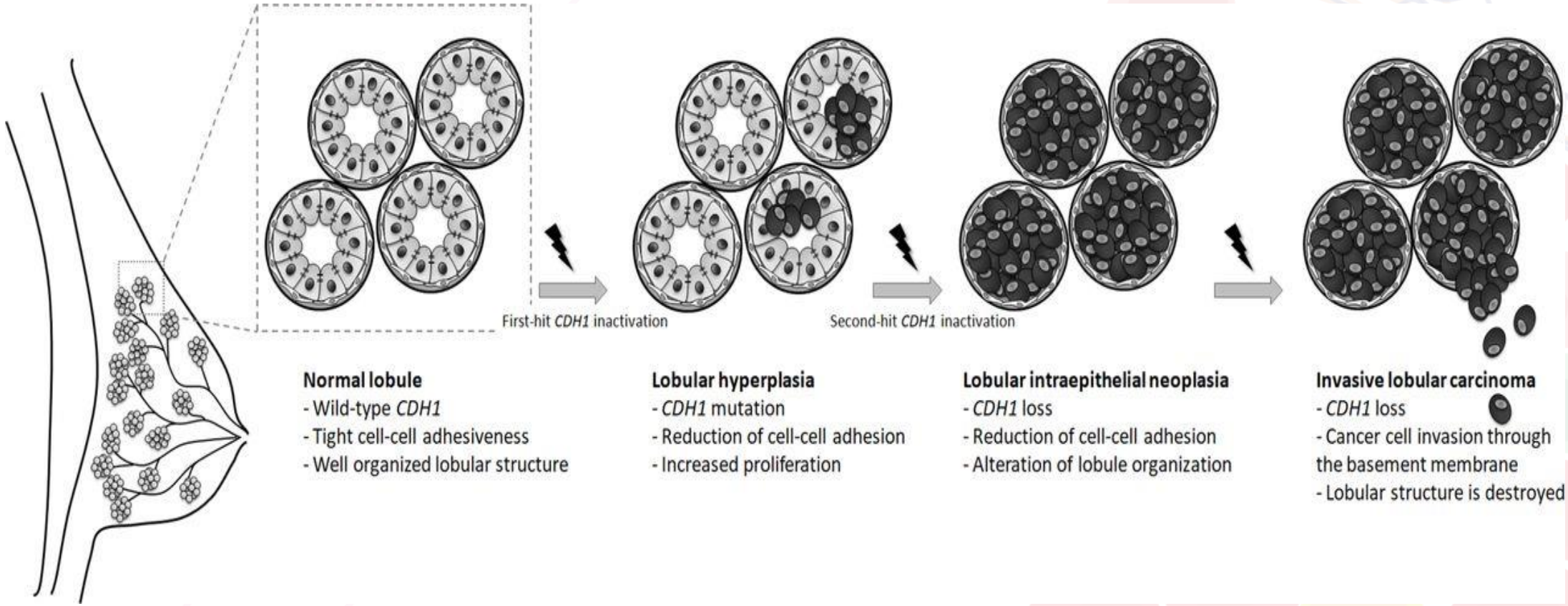
- Few clinical studies for patients with ILC alone. **Use of retrospective data and tissue.**
- Treatment Resistance and Metastases- Finding markers of dormancy and resistance and using it as a therapeutic target.
- Tissue donation.

The James
The Ohio State University
Comprehensive Cancer Center

Hereditary lobular breast cancer (HLBC) syndrome associated with germline CDH1 variants, Corso et al

- Considering the 'so-called' HLBC, without family history of gastric tumour, E-cadherin genetic test should be proposed in the following cases: (A) bilateral LBC with or without family history of LBC, with age at onset <50 years, and (B) unilateral LBC with family history of LBC, with age at onset <45 years. Whenever possible, *BRCA1/2* germline mutations should be excluded in both groups, since they are mutually exclusive with *CDH1* germline mutations.
- Given the high prevalence of ILC in *CDH1* germline mutation carriers, and the histopathological and imaging features of these tumours, ***breast screening in CDH1-mutated patients should be performed annually with DM (possibly with DBT), ultrasound and contrast-enhanced MRI.*** A 6-month interval between the US and the MRI is preferable but not mandatory.

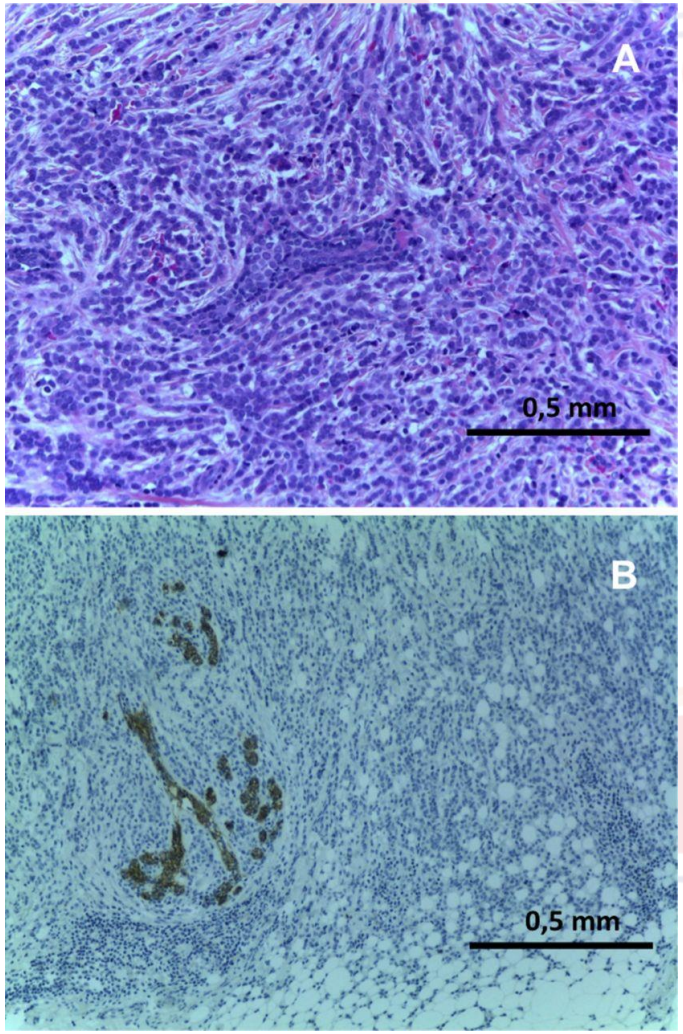
Representative model of lobular breast cancer (LBC) progression in CDH1 mutation carries.



Giovanni Corso et al. J Med Genet 2018;55:431-441

JMG

Invasive lobular carcinoma.



Giovanni Corso et al. J Med Genet 2018;55:431-441

Identification of Targetable Vulnerabilities in ILC Using Comprehensive Genomics Profiling- Ethan Sokol

Loss of function of NF1 is a mechanism of acquired resistance to endocrine therapy in lobular breast cancer ***Sokol, E, Annals of oncology 2011***

Key Message

This study identifies an enrichment of *NF1* loss of function alterations and high tumor mutational burden in metastatic, therapy-refractory ILC. Our findings reveal potential targeted interventions in this population, with possible sensitivities to RAS/RAF inhibition or Immune checkpoint inhibitors

FGFR4 overexpression and hotspot mutations in metastatic ER+ breast cancer are enriched in the lobular subtype. ***Levine K et al, NPJ breast cancer***

Targeting FGFR with Dovitinib (TKI258): Preclinical and Clinical Data in Breast Cancer

Identification of Targetable Vulnerabilities in ILC Using Comprehensive Genomics Profiling- Ethan Sokol

APOBEC Mutational Signatures in Hormone Receptor–Positive Human Epidermal Growth Factor Receptor 2–Negative Breast Cancers Are Associated With Poor Outcomes onCDK4/6 Inhibitors and Endocrine Therapy

Sammos. S et al JCO Precis Oncology

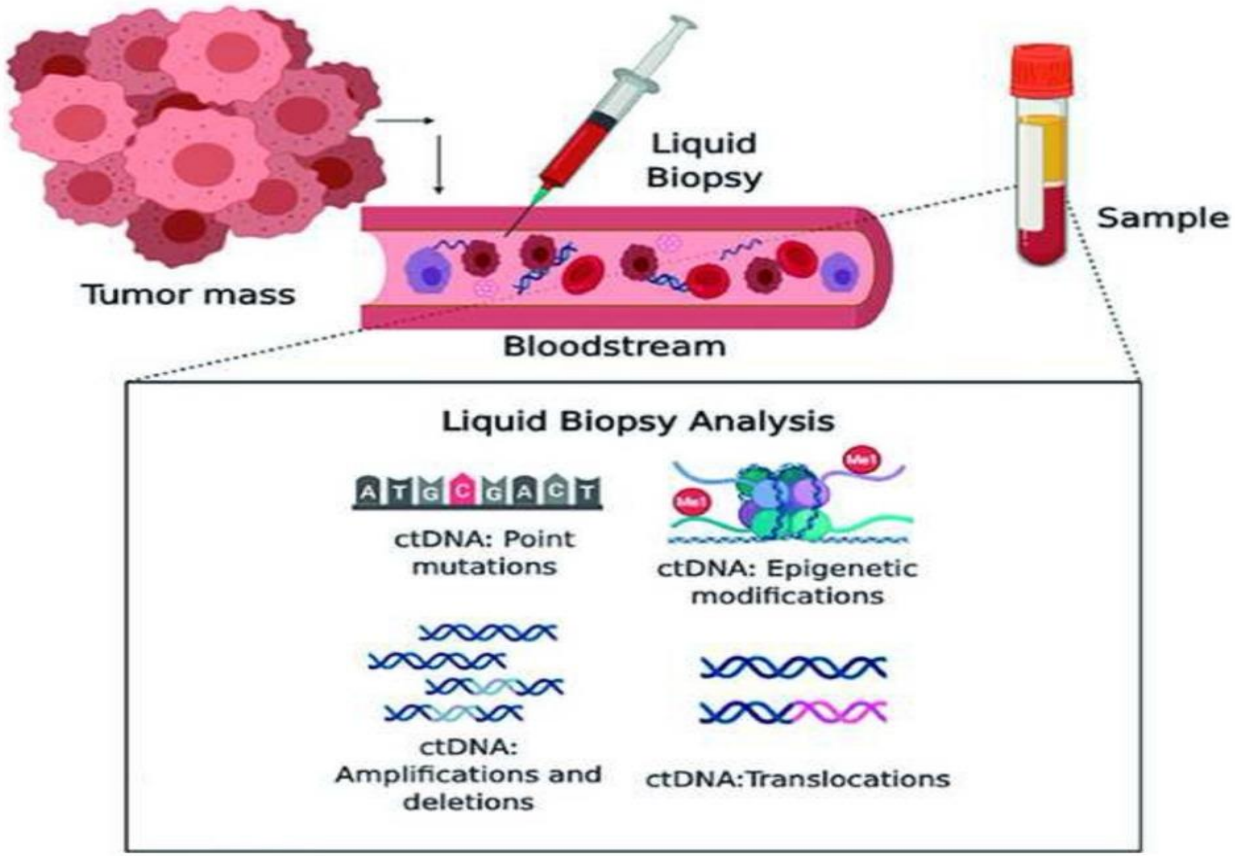
Key Message:

APOBEC mutational signatures were common and identified in 16.7% of lobular and 10% of metastatic HR+/HER2– tumors. APOBEC+ HR+ HER2– patients had a significantly shorter time-to-treatment discontinuation and numerically shorter overall survival on first-line ET and CDK4/6i relative to APOBEC– patients. The clinical benefit of immune checkpoint inhibition was observed in a series of APOBEC+ patients. **APOBEC or apolipoprotein B mRNA-editing enzyme catalytic polypeptides are a family of cytidine deaminases, which protect against viral infection by degrading viral genomes via cytosine deamination.**

PARTICIPATION IN CLINICAL TRIALS, EVEN FOR A TISSUE COLLECTION STUDY, IT WILL IMPROVE SCIENTIFIC PROGRESS!

ROLE OF LIQUID BIOPSY AND GENOMIC SEQUENCING IN ILC

- L. Pessoa et al ,Nov 2020



CLINICAL IMPLICATIONS OF CTDNA LIQUID BIOPSY IN CANCER INCLUDING ILC

- ctDNA – Diagnosis of cancer- ??
- ctDNA-- To help to monitor disease and response to treatment.
- Genomics on ctDNA- This is the greatest advantage to identify targetable mutations, such as PI3K , ESR-1, FGFR, Tumor mutational burden.

ILC Based prognostic markers.

- Dr. Simpson et al had undertaken an integrative analysis of gene expression and DNA copy number to identify novel drivers and prognostic biomarkers, using in-house (n = 25), METABRIC (n = 125) and TCGA (n = 146) samples.
- Using in silico integrative analyses, a 194-gene set was derived that is highly prognostic in ILC —we named this metagene ‘LobSig’.
- Assessing a 10-year follow-up period, LobSig outperformed the Nottingham Prognostic Index, PAM50 risk-of-recurrence (Prosigna), OncotypeDx, and Genomic Grade Index (MapQuantDx) in a stepwise, multivariate Cox proportional hazards model, particularly in grade 2 ILC cases which are difficult to prognosticate clinically.
- Importantly, LobSig status predicted outcome with 94.6% accuracy amongst cases classified as ‘moderate-risk’ according to Nottingham Prognostic Index in the METABRIC cohort. Network analysis identified few candidate pathways, though genesets related to proliferation were identified, and a LobSig-high phenotype was associated with the TCGA proliferative subtype ILC with a poor outcome as predicted by LobSig were enriched with mutations in ERBB2, ERBB3, TP53, AKT1 and ROS1. LobSig has the potential to be a clinically relevant prognostic signature and warrants further development.
- npj Breast Cancer (2019) 5:18 ; https://doi.org/10.1038/s41523-019-0113-yd

ILC-FOCUSED BIOMARKERS OF PROGRESSION AND PROGNOSIS

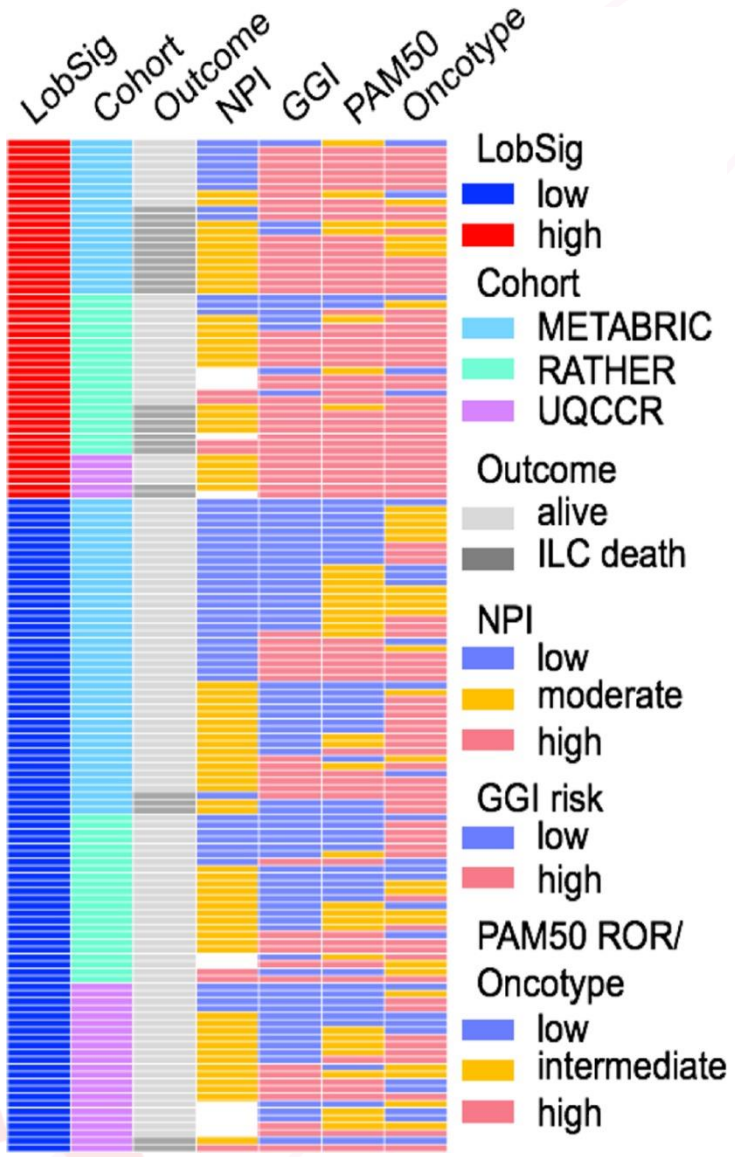
There was a notable prevalence of ERBB2 (20%), ERBB3 (14.28%), AKT1 (8.57%) and ROS1 (8.57%) mutations in the LobSig high group, raising exciting possibilities for applying targeted therapies in LobSig high tumors, with evidence emerging of the value of anti-HER2 therapies, AKT inhibitors and the recently described ROS1 inhibitors via synthetic lethal interaction with CDH1 mutant ILC.

Multivariate analysis demonstrated the significant value of LobSig above individual clinico-pathology features, but more importantly, the value of this signature resides in its ability to stratify the NPI moderate tumors—effectively moving from the 'intermediate', unclear group, into one of two groups with clear prognostic outcomes.

The data presented supports LobSig low-risk patients need not receive adjuvant chemotherapy. Our signature is not predictive for chemotherapy administration per se, but likely identifies a group of ILC patients in whom chemotherapies may be beneficial.

A paucity of highly annotated ILC cohorts with sufficient follow-up, as well as molecular profiling data in a clinical trial setting, precludes us from determining if and whether there are specific therapies that may have efficacy.

LobSig is a multigene predictor of outcome in invasive lobular carcinoma Amy E. McCart Reed , Samir Lal1, Jamie R. Kutasovic ,,, …..and ***Peter T. Simpson*** *npj Breast Cancer (2019) 5:18*



In conclusion, the molecular signature, LobSig, which captures the peculiar genomic landscape of ILC tumors, and together with clinico-pathology information, provides a robust mechanism for prognostication in ILC. This signature warrants further analysis and development, and validation on expanded retrospective cohorts of ILC with detailed treatment information.

POSTMORTEM TISSUE DONATION PROGRAM : KAREN VAN BAELEN

Background. Research in metastatic breast cancer is hampered by limited sample availability. Post-mortem tissue donation programs can help to overcome this problem but are logistically challenging and have thus far mainly focused on histopathological and genomic research. We here present the UPTIDER program (NCT04531696), aimed at the multilevel characterization of advanced breast cancer and generation of tumour models.

Patients and Methods. Patients with stage IV breast cancer receiving their last line(s) of treatment are eligible for participation. Blood, urine and saliva samples are collected upon inclusion. Upon death, a post-mortem MRI (when possible) followed by a rapid autopsy is performed. Liquid biopsies from all body fluids and tissue samples from all macroscopically identified metastatic sites are collected. Samples are processed as mirrored biopsies in different conditions, such as fresh frozen for omics analyses, formalin fixed paraffin-embedded for histopathology, and slowly frozen in freezing medium or fresh for generation of xenograft and organoid models.

POSTMORTEM TISSUE DONATION PROGRAM : KAREN VAN BAELEN

- Results. A post-mortem MRI was performed in 6 patients. Peripheral blood, central blood and bone marrow were collected from all patients; urine, ascites, cerebrospinal, pericardial and pleural fluid all in more than 2/3 of patients. On average, 232 (range 90-406) tissue samples of which 164 (45-303) pathological from 42 (15 – 79) metastases were collected for each patient. Most often sampled metastatic sites were lymph nodes, liver, bones, pleura and peritoneum. Samples from the primary tumour could be retrieved from all patients, either during the autopsy (n=6) or from historical archives.
- In total, 133 tumour samples were sent to collaborating partners for patient-derived xenograft creation. Already some have been successfully established and stored, including models derived from a patient with invasive lobular carcinoma (ILC) and one with metaplastic squamous cell carcinoma. When correlating microscopic and macroscopic findings, patients could largely be divided into three main categories. Eleven patients presented with overt and extensive disease burden, often characterized by diffuse visceral, pleural, peritoneal, bone and lymph node involvement. **Two patients, both with ILC, presented with underestimated yet extensive disease burden. While gross examination and cross sectioning of organs did not reveal clear involvement, microscopical invasion of stomach and liver, amongst others, was found. Lastly, limited disease burden was seen in two patients, both with leptomeningeal involvement. In those patients, massive tumoral infiltration in the subarachnoid space and along the blood-brain barrier was seen microscopically, with no grey matter invasion**

POSTMORTEM TISSUE DONATION PROGRAM : KAREN VAN BAELEN

They have launched a new and comprehensive post-mortem tissue donation program for patients with metastatic breast cancer, enrolling ~ 1 patient per month. Post-mortem tumour samples already resulted in successful establishment of some patient-derived xenografts.
From a clinical point of view, vast underestimation of the disease extent on imaging during life as well as macroscopically during the autopsy was observed in some patients with metastatic ILC.
For patients with leptomeningeal metastasis, they showed that the highly aggressive nature of their disease might be explained by extensive meningeal infiltration disrupting the blood-brain barrier. Further work on multi-omics will reveal tumor heterogeneity.

WHAT CAN WE ALL DO?

ADVOCACY- This becomes very important for any rarer tumor

SCIENTISTS- More Basic research to understand markers of dormancy and identify therapeutic targets and development of patient derived cell lines and murine models.

PATIENTS- Participate in clinical trials including tissue collection studies

Clinical Investigators- Identity ILC as Unique disease and open ILC specific clinical trials

GOVERNMENT/NCI- Recognize ILC as rare cancer

INDUSTRY- Focus on discovering novel therapies in ILC

FUNDING AGENCIES- Allocate funds for ILC research.

CHALLANGES- DISPARITY IN OUTCOMES

EQUITY
ACCESS
EDUCATION
RESOURCES

The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

Thank you

The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

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Jason Mouabbi, MD

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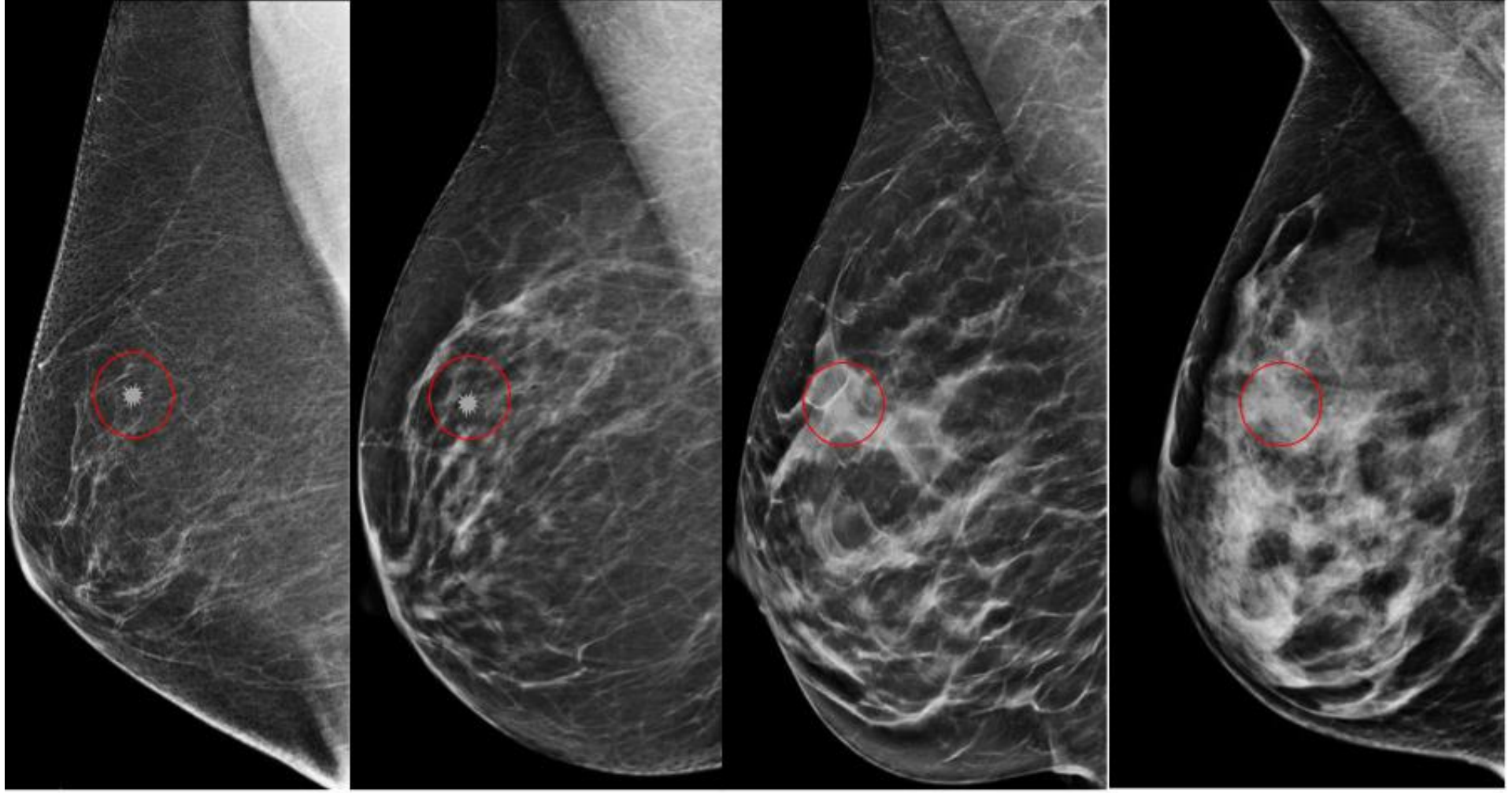
ILC Imaging Science Summary

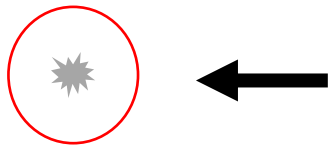
- Imaging of ILC was a hot topic at the 2023 ILC Symposium
- Formal imaging session:
  - Speakers:
    - Matt Covington, MD: Challenges and Potential Solutions for Imaging of ILC
      - Huntsman Cancer Institute, University of Utah
    - Hannah Linden, MD: Imaging and ILC, Advances and Opportunities
      - Fred Hutch Cancer Center, University of Washington
    - Gary Ulaner, MD: ER-targeted PET: Clinical Applications and Interpretation
      - HOAG Family Cancer Institute, University of Southern California
    - Vincent Vandecavaye, MD, PhD: Whole body diffusion-weighted MRI in Lobular Breast Cancer
      - KU Leuven, Belgium

Challenges in imaging of ILC

- It starts with detection of ILC on screening mammography and clinical breast exam
- It continues throughout the course of diagnosis, treatment, and monitoring for many individuals with ILC



Fatty Breast Density | Scattered Breast Density | Heterogeneously Dense | Extremely Dense



Hypothetical cancer in red circle, also placed in the mammograms above. This is easily seen in the breasts with fatty and scattered density but is obscured on the heterogeneously and extremely dense breasts.

ILC challenges for pre-surgical staging

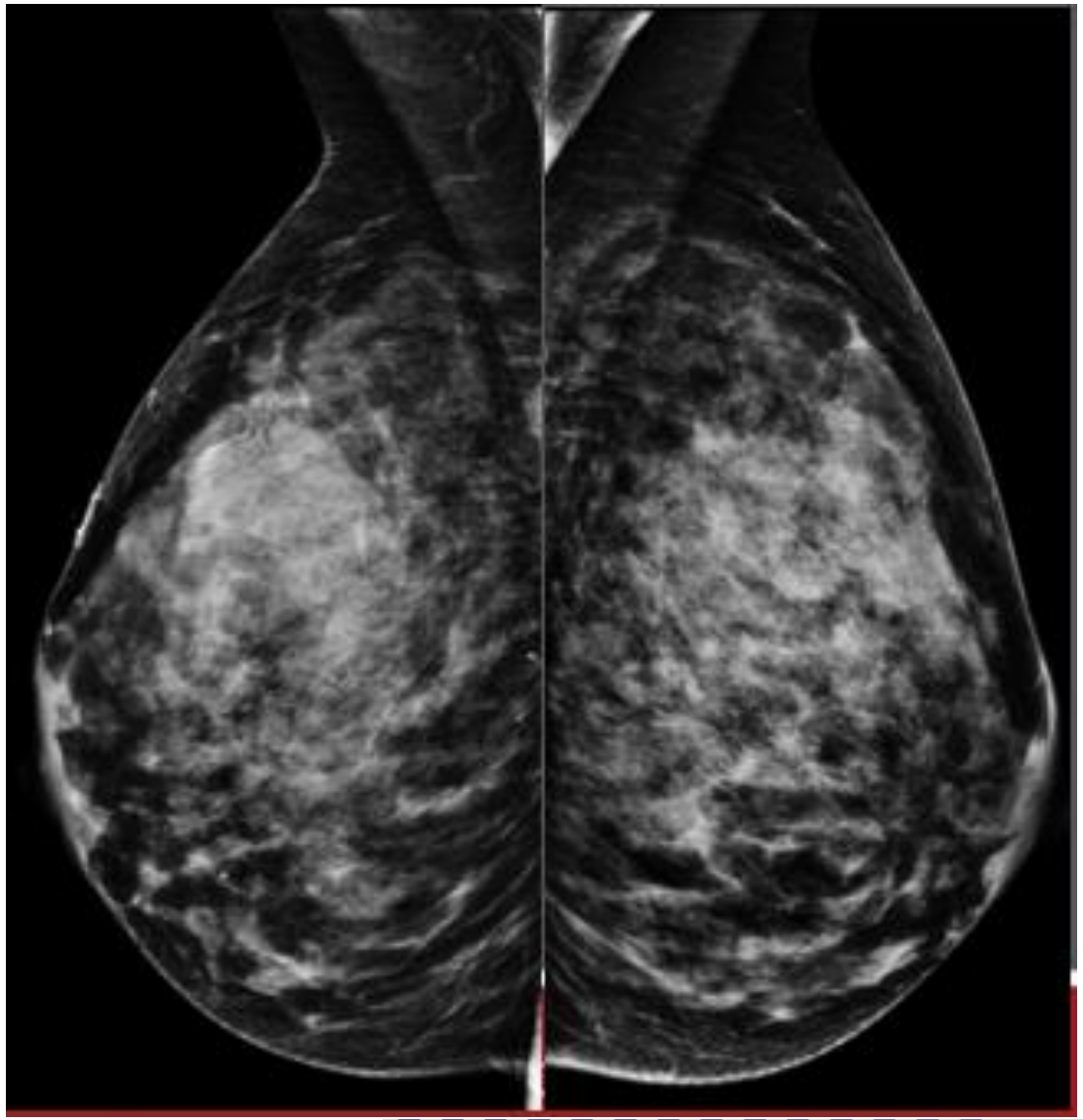
- Problems:
  - Common understaging due to failure to detect disease on mammography, ultrasound, MRI, FDG PET/CT
  - Lymph nodes may be involved with ILC but not enlarged
  - FDG PET/CT may have reduced sensitivity for ILC compared to IDC
  - High rate of surgical re-excisions due to positive margins
- Solutions:
  - Leverage other imaging technologies to include 18F-Fluoroestradiol PET/CT
  - Increased education to radiologists on challenges of ILC detection
    - Lower thresholds for calling disease potentially positive

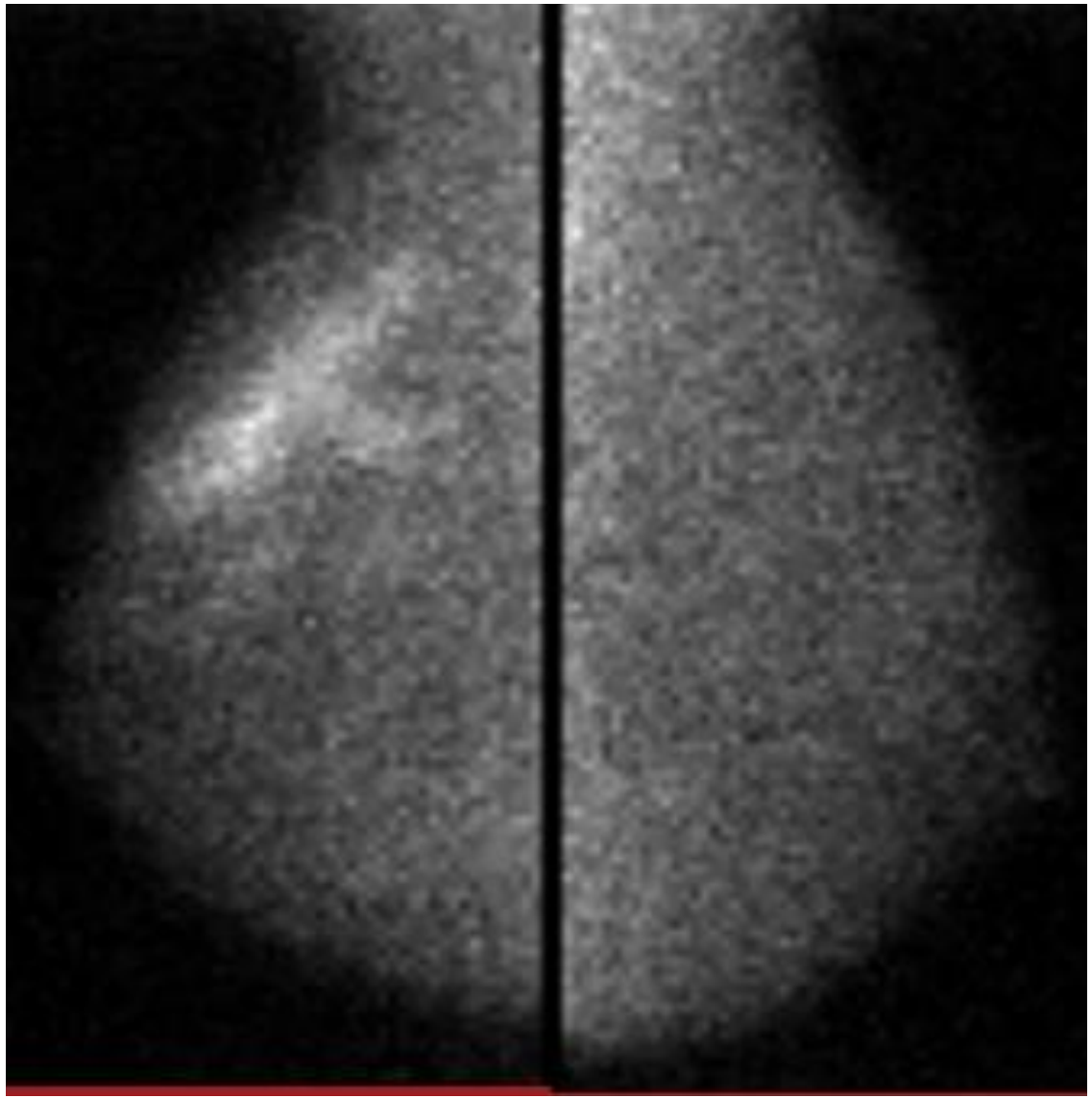
ILC challenges for surveillance

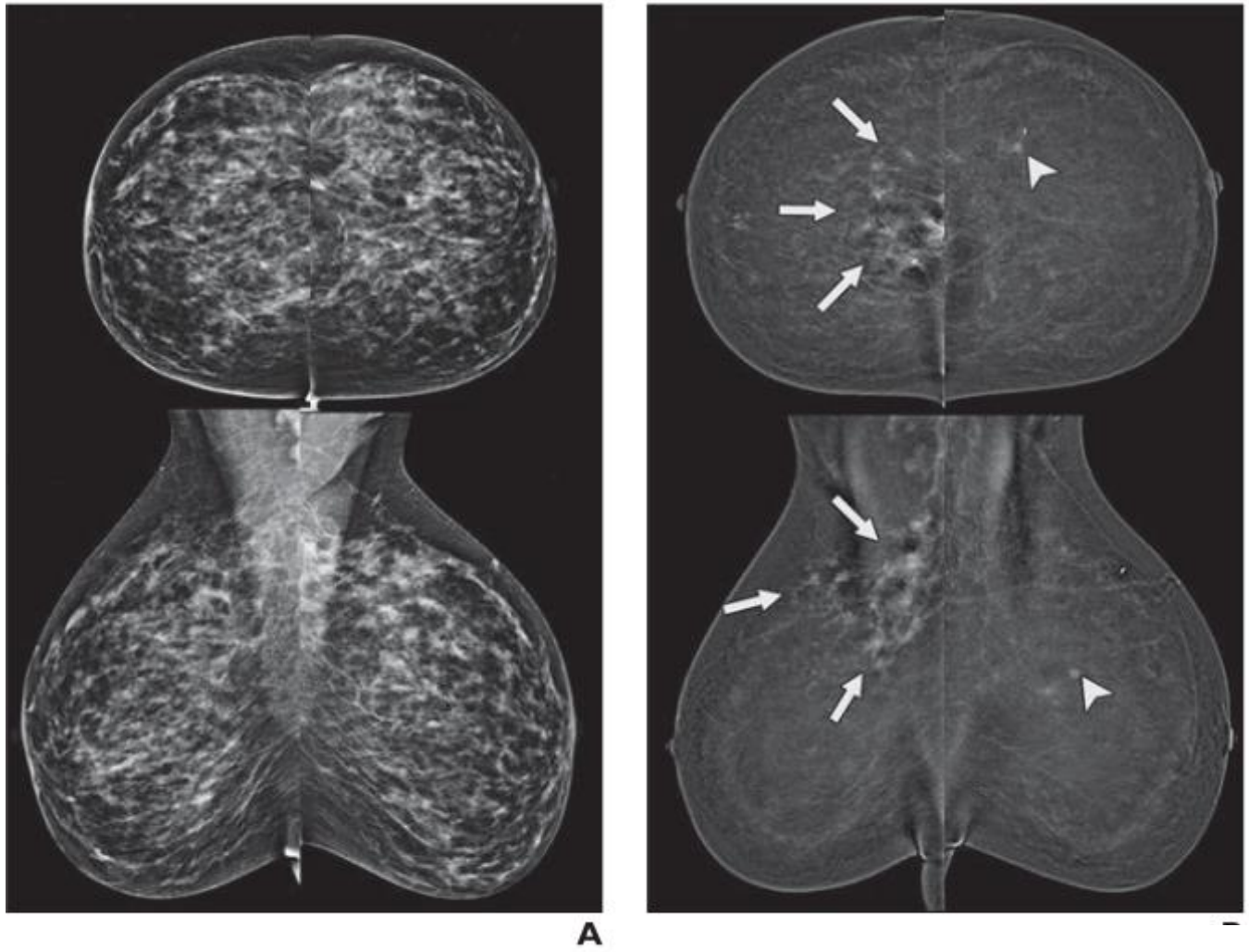
- Problems
  - Same as before and
  - ILC metastasizes to areas difficult to detect on imaging
    - GI tract, CSF, peritoneum, blastic bone lesions
  - Disseminated cancer cells may transition to active disease at 5-20 years after diagnosis
    - Long latency likely leads to less aggrtessive monitoring
- Solutions
  - Improved importance of imaging for local staging compared to IDC
  - Circulating tumor DNA and other blood tests

How to improve ILC detection on imaging

- Leverage every technological advance available!
- Breast imaging:
  - breast MRI (abbreviated and full-protocol)
  - contrast-enhanced mammography
  - molecular breast imaging
  - whole breast ultrasound
  - breast CT
- Systemic imaging:
  - Fluoroestradiol PET/CT (and other emerging PET radiopharmaceuticals)
  - DWI whole-body MRI





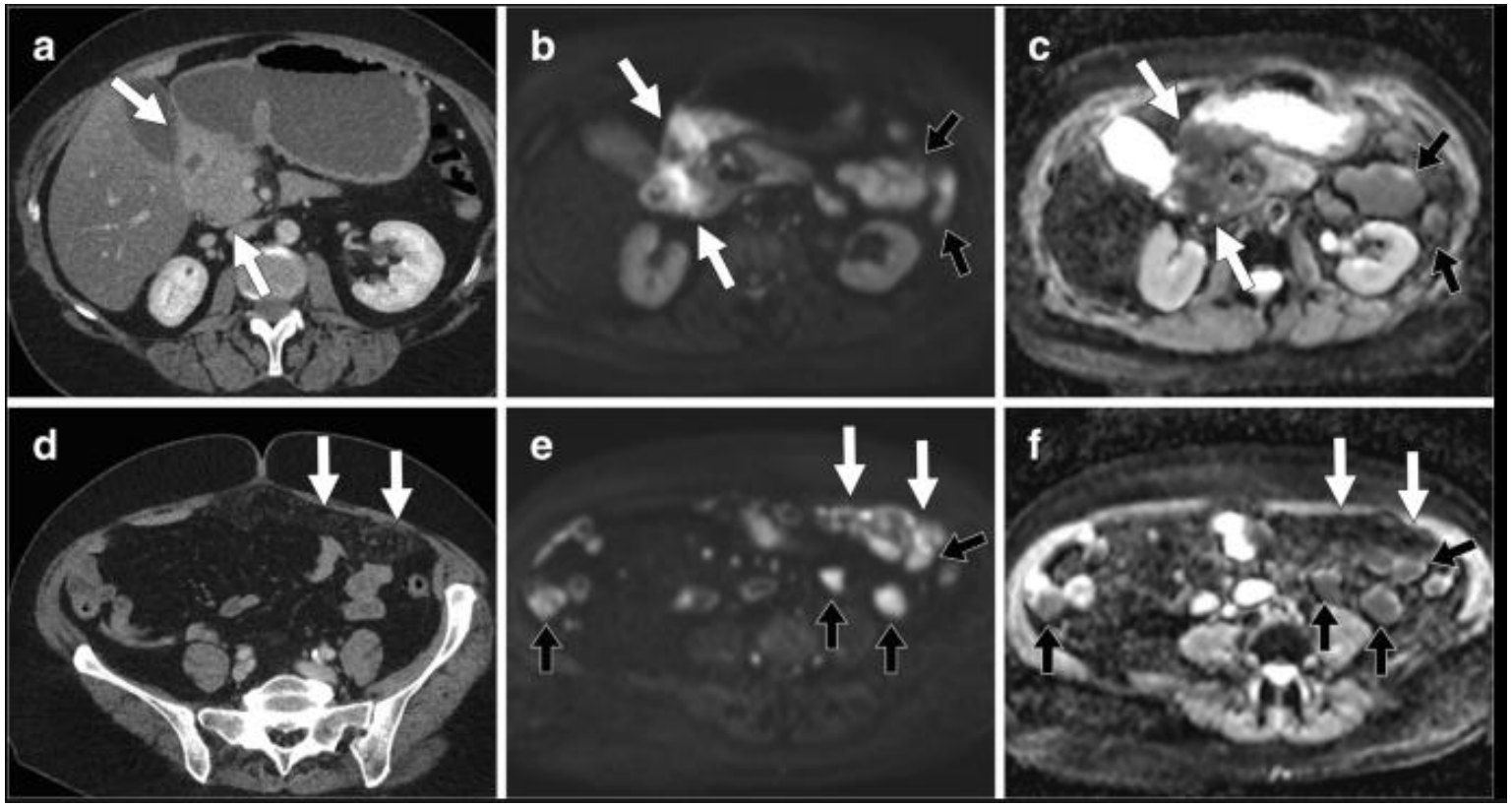


A

AJR Am J Roentgenol. 2018 Feb;210(2):292-300. doi: 10.2214/AJR.17.18749. Epub 2017 Oct 24.

The Future of Contrast-Enhanced Mammography.

Covington MF[1,2], Pizzitola VJ[1], Lorans R[1], Pockaj BA[3], Northfelt DW[4], Appleton CM[2], Patel BK[1].



Home › European Radiology › Article

A review on the added value of whole-body MRI in metastatic lobular breast cancer

Magnetic Resonance | Published: 06 April 2022 | 32, 6514–6525 (2022)

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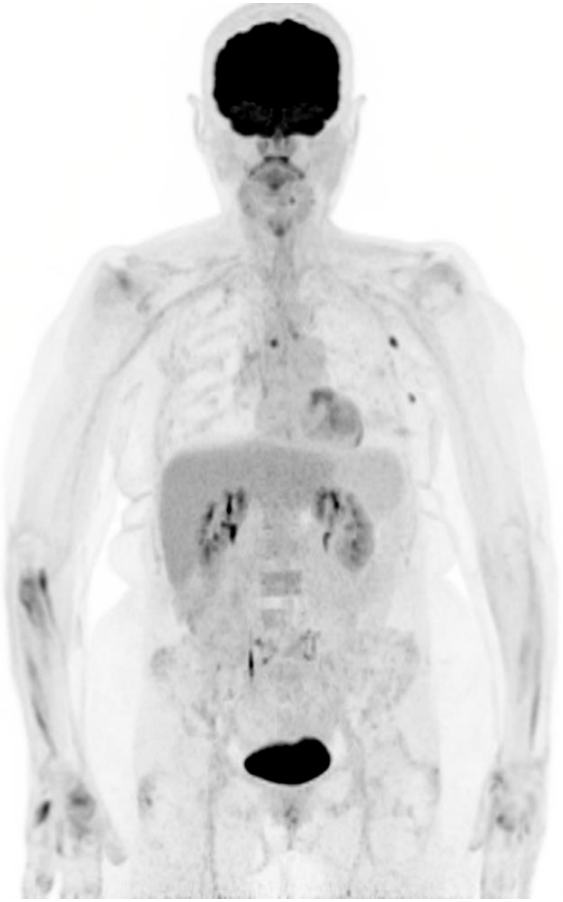
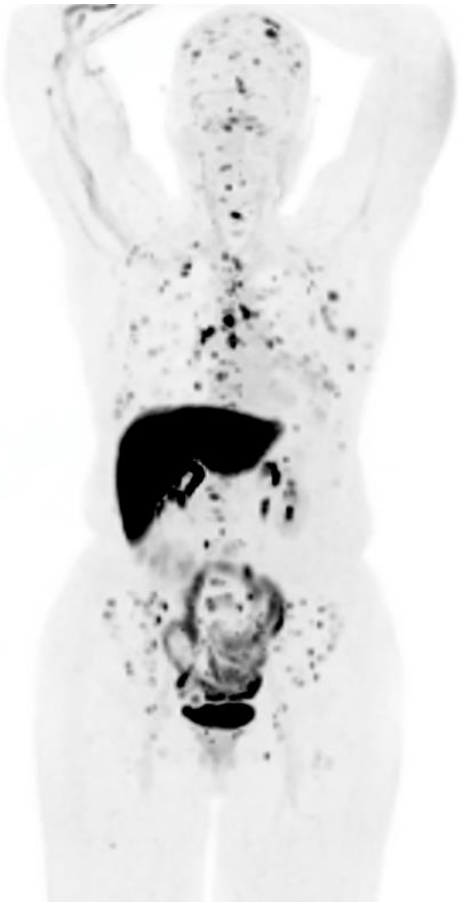
FDG



FES

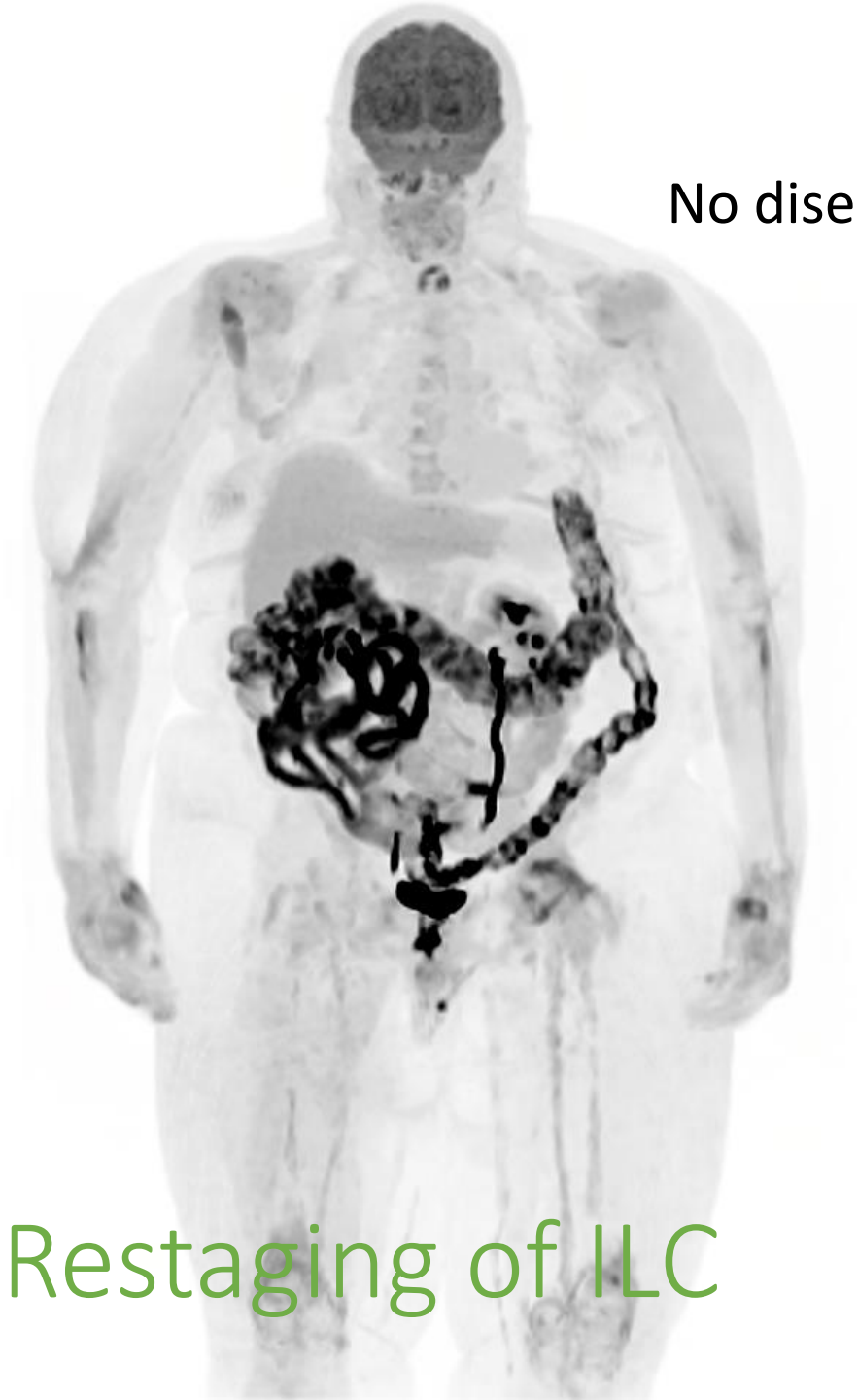


75-year-old with prior ILC, prior bilateral mastectomies, recurrence biopsy-proven in left chest wall

FDG revealed 2 left chest wall masses and some indeterminate mediastinal lymph nodes

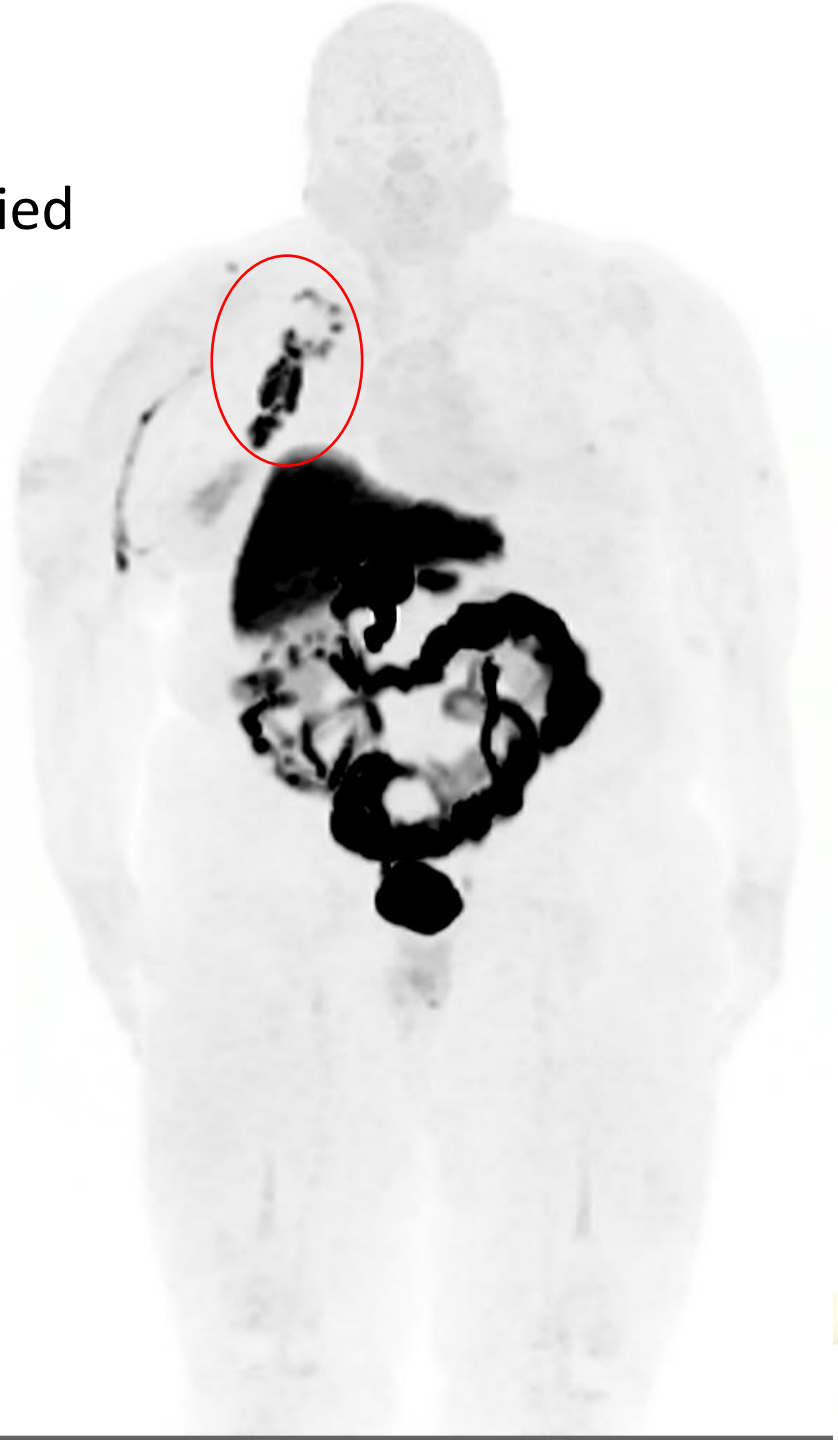
FES revealed additional disease:

- >100 bone metastases
- Metastatic lymph nodes (left axilla, mediastinum, left internal mammary)



FDG

No disease identified



FES

Extensive nodal metastatic disease

Osseous metastatic disease

Restaging of ILC

Summary

- We need to shake things up!
- We must use ILC-specific imaging strategies
- More aggressive use of technologies with higher rates of ILC detection used earlier in presentation of disease
  - If dense breasts: supplement screening to allow earlier detection (3D mammography doesn't count, breast MRI highest detection rate, other options: CEM, MBI, US)
  - Upon initial detection: breast MRI, CEM, or MBI for local staging
  - Fluoroestradiol PET/CT for staging locally advanced ER+ disease at initial presentation and subsequently for monitoring/recurrence
    - Especially if FDG negative at initial presentation

Our Panelists

Patrick Derksen, PhD

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Priscilla McAuliffe, MD, PhD

Jason Mouabbi, MD

European Lobular Breast Cancer Consortium

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Clinical Science

Priscilla McAuliffe MD, PhD, FACS

University of Pittsburgh

UPMC | HILLMAN CANCER CENTER

UPMC | MAGEE-WOMENS HOSPITAL

MAGEE-WOMENS RESEARCH INSTITUTE & FOUNDATION

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Clinical take-aways from the ILC Symposium

Session 6: Challenges in Treatment of ILC

4:35pm	**Session 6: Challenges in Treatment of ILC** **Chair: Vikram Gorantla, MD** (UPMC, Pittsburgh)
4:40pm-5:00pm	**Suzanne Fuqua, PhD** (Baylor College of Medicine, Houston) *When the Breast Cancer Researcher Becomes the Patient with ILC*
5:00pm-5:20pm	**Jason Mouabbi, MD** (University of Texas, MD Anderson Cancer Center, Houston) *Differential Genomic and Transcriptomic Analysis of Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma*
5:20pm-5:40pm	**Julia Foldi, MD, PhD** (University of Pittsburgh, UPMC, Pittsburgh, PA) *Distinct features of ILC vs IDC in four NSABP randomized trials of adjuvant chemotherapy*
5:40pm-6:00pm	**Kathryn Schmitz, PhD, MPH** (University of Pittsburgh, UPMC Hillman Cancer Center, PA) *Exercise is Medicine in the Setting of Oncology*

Session 7: Local Treatment of ILC

8:55am	**Session 7: Local Treatment of ILC** **Chair: Bhuvaneswari Ramaswamy, MD** (The Ohio State, Columbus, OH)
9:00am-9:20am	**Rita Mukhtar, MD** (UCSF, San Francisco, CA) *Surgical management of ILC: challenges and opportunities*
9:20am-9:40am	**Priscilla McAuliffe, MD, PhD** (UPMC Magee-Womens Hospital and UPMC Hillman Cancer Center, Pittsburgh, PA) *Surgical management of the axilla in lobular cancer.*

2 hours → 15 minutes??

When the Breast Cancer Researcher Becomes the Patient with ILC

INTERNATIONAL INVASIVE LOBULAR BREAST CANCER SYMPOSIUM 2023

Suzanne AW Fuqua, PhD, MS

Research Patient Advocate

European Lobular Breast Cancer Consortium

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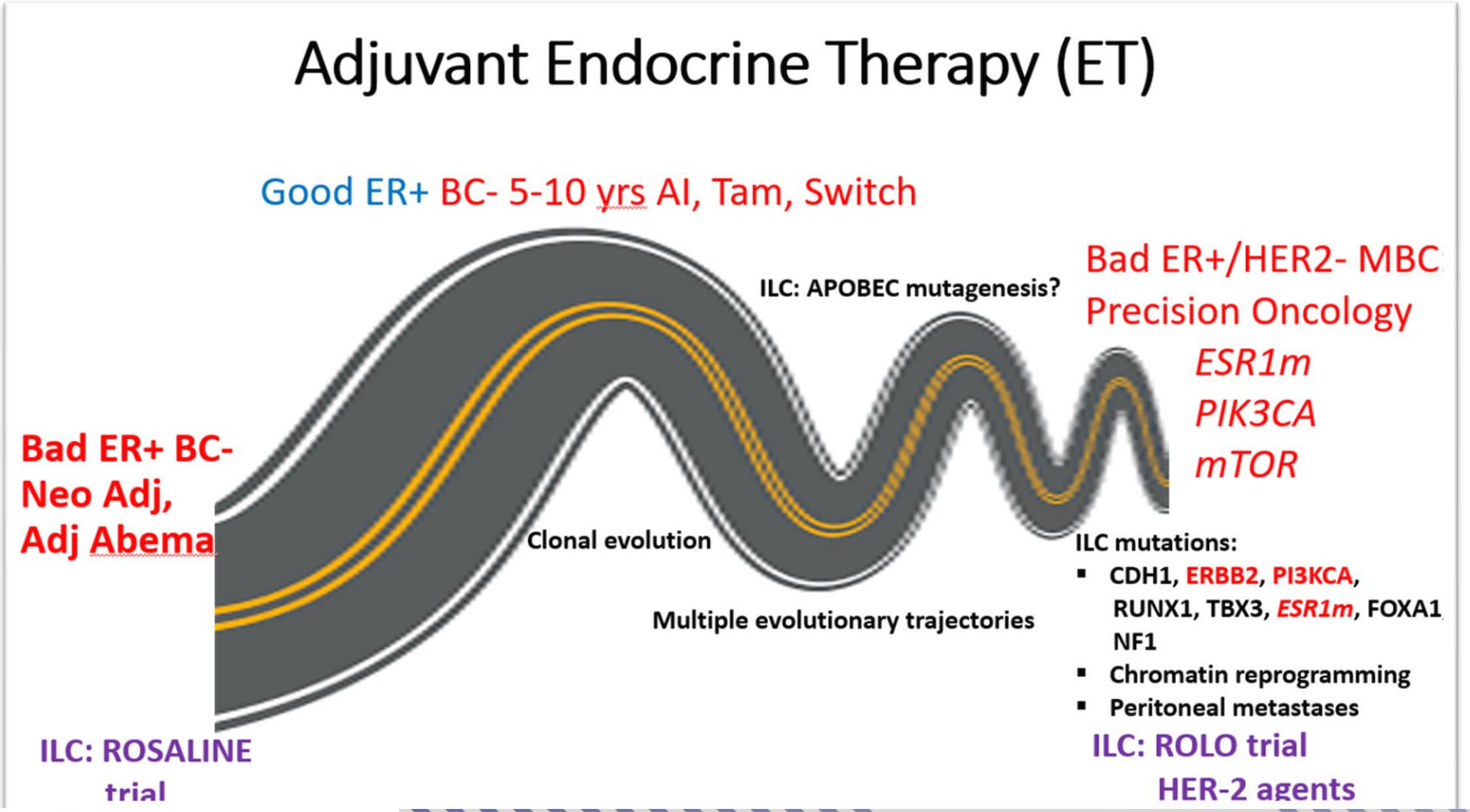
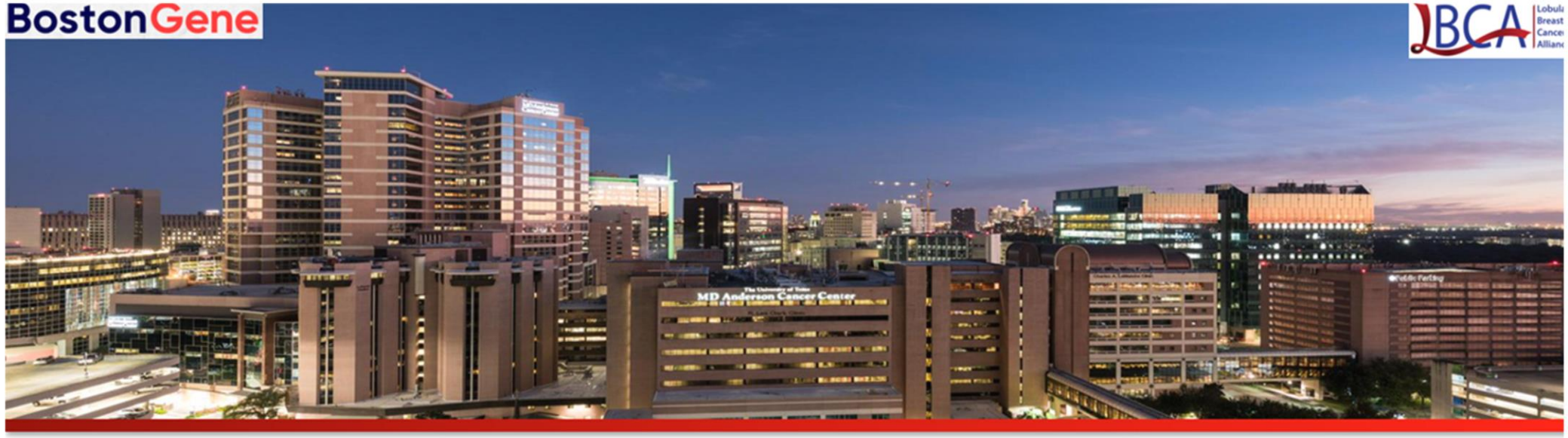
“It’s a long road.”



- Goal: Bring precision medicine to ALL moments of ILC care.



Differential Genomic and Transcriptomic Analysis of Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma

Jason A. Mouabbi MD

Assistant Professor

Department of Breast Medical Oncology at MD Anderson Cancer Center

SAB Chair of the Lobular Breast Cancer Alliance

European Lobular Breast Cancer Consortium

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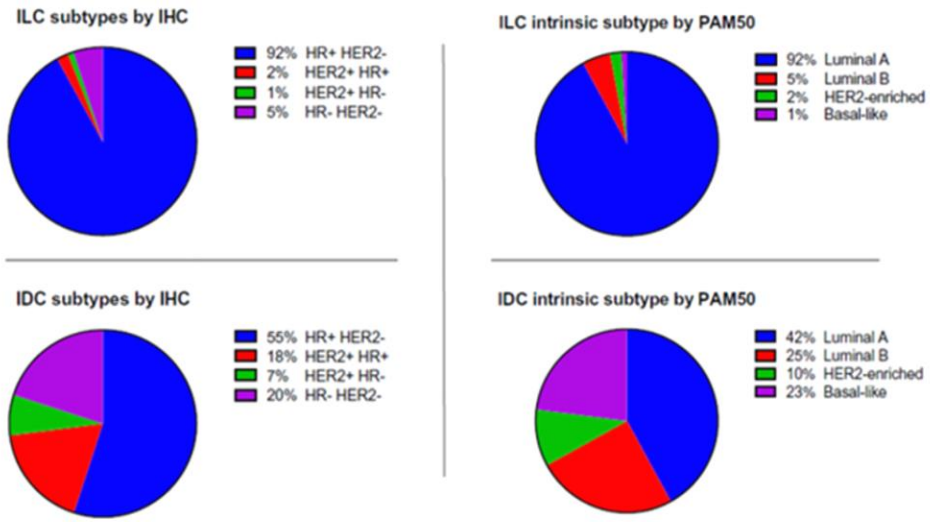
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Introduction: Features of ILC vs IDC – Clinicopathology

	IDC	ILC
Stage at diagnosis[1]		
Stage I	55%	46%
Stage II	35%	33%
Stage III	8%	**17%**
Stage IV	2%	**5%**
Grade[2]		
Grade 1-2	60%	90%
Grade 3	40%	**10%**
Proliferation Activity (Ki67)[3]		
Low (<20%)	35%	**60%**

[1]Oesterreich S et al., JNCI, 2022
[2]Pestalozzi BC et al., J Clin Oncol, 2006
[3]Biglia G et al, Eur J Surg Oncol., 2013



- **90%** of ILC express **AR** (compared to ~50 of IDC)
- All **TN ILC** (5%) are **lumAR** and have high AR expression

Mouabbi JA et al., BCRT, 2022

UCSF Department of Surgery

Surgical management of ILC: challenges and opportunities

Rita Mukhtar, MD
Associate Professor of Clinical Surgery
University of California, San Francisco

INTERNATIONAL INVASIVE LOBULAR BREAST CANCER (ILC) SYMPOSIUM 2023 PITTSBURGH, PA – SEPTEMBER 28-30, 2023

UCSF Department of Surgery

European Lobular Breast Cancer Consortium

LBCA® Lobular Breast Cancer Alliance

ILC 2023 Pittsburgh, PA

Background

- Patients with ILC have **worse <u>surgical</u> outcomes** compared to patients with invasive ductal carcinoma (IDC)
  - Measured by positive margin rates, mastectomy rates, and axillary dissection rates
- Many potential causes:
  - Higher stage at presentation
  - Higher discordance between clinical stage and pathologic stage
  - Lower sensitivity of standard imaging tools

Johnson K et al. Lobular breast cancer series: imaging. Breast Cancer Res 2015
Sledge G et al. Collective Wisdom: Lobular Carcinoma of the Breast. ASCO Educational Book 2016

Should patients with ILC always choose mastectomy?

- Not necessarily!
  - National Cancer Database Analysis of >160,000 showed **same or better overall survival with breast conserving therapy (lumpectomy + radiation)** compared to mastectomy
  - Swedish study of nearly 50,000 patients showed **improved overall survival with breast conserving therapy (lumpectomy + radiation)** compared to mastectomy

  - Lymph node positivity → increased likelihood of needing post mastectomy radiation
    - Implications for reconstruction and long-term sequelae

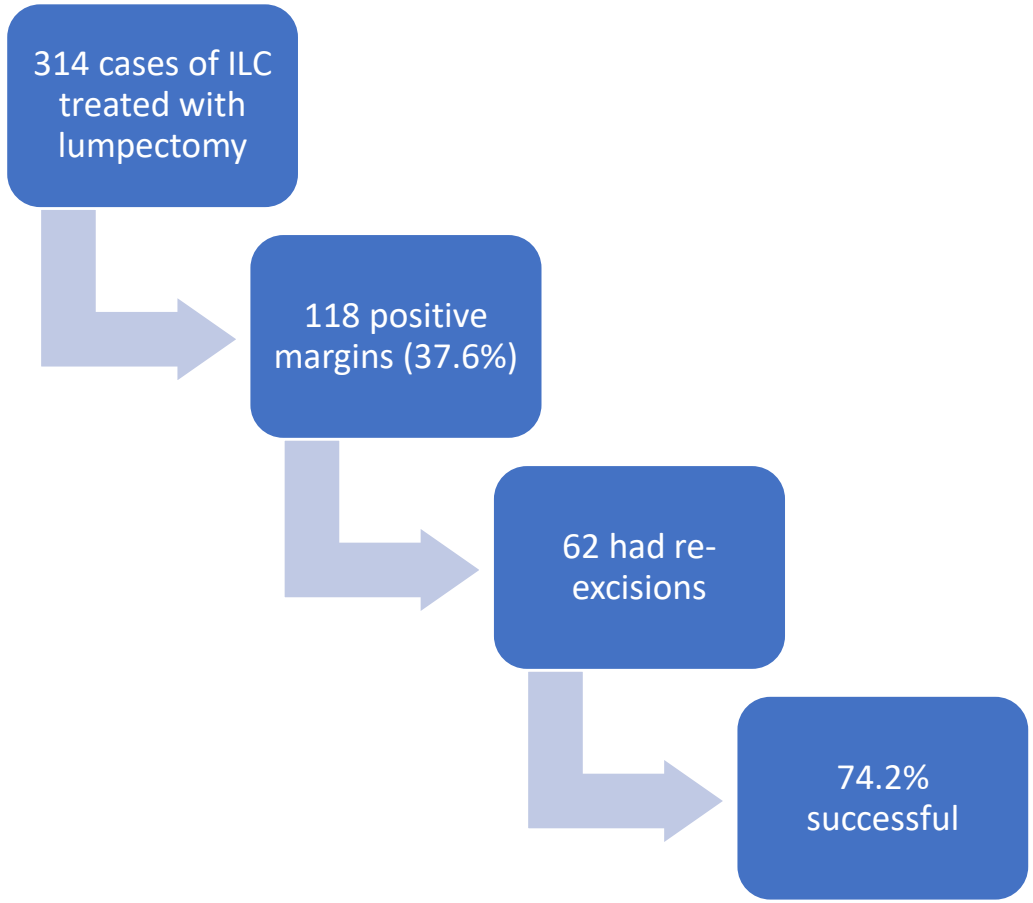
- Chen K et al. Comparative effectiveness study of breast-conserving surgery and mastectomy in the general population: A NCDB analysis. Oncotarget. 2015
- Boniface J et al. Survival After Breast Conservation vs Mastectomy Adjusted for Comorbidity and Socioeconomic StatusA Swedish National 6-Year Follow-up of 48 986 Women. JAMA Surgery 2021

Positive margins have negative consequences

- Significantly higher rates of surgical site infection, seroma, hematoma, and fat necrosis
- Significantly lower breast satisfaction and sexual well being
- Healthcare costs increased 4-fold for patients requiring re-excision
- Increased risk of recurrence if negative margins NOT achieved

- Chakedis J et al. Economic impact of reducing reexcision rates after breast conserving surgery in a large, integrated health care system. Ann Surg Onc 2022
- Matar-Ujvary R et al. The Impact of Breast-Conserving Surgery Re-excision on Patient-Reported Outcomes Using the BREAST-Q. Ann Surg Onc 2023
- Metcalfe L et al. Beyond the margins—Economic costs and complications associated with repeated breast conserving surgeries. JAMA Surgery 2017

If a positive margin occurs, what is the chance of success for re-excision in ILC?



Good success rates!

Piper M et al. Success rates of re-excision after positive margins for invasive lobular carcinoma of the breast. NPJ Breast Cancer 2019

Summary

- Breast conservation therapy (lumpectomy + radiation) is safe for ILC, even for ILC >4 cm; positive margins are common
  - Goal is to achieve negative margins
  - Consideration for oncoplastic techniques for re-contouring/cosmesis
    - Level 1: local tissue rearrangement only
    - Level 2: parenchymal flaps and skin resection (reduction mastopexy)
- Importantly, for T3 (>5 cm) ILC, even mastectomy can have high positive margin rates. Has implications related to reconstruction, radiation.

- TAKE AWAY: Underscores the need for better imaging for ILC and better systemic therapy for ILC to shrink tumors pre-operatively

Surgical management of the axilla in lobular cancer

Priscilla McAuliffe, MD, PhD, FACS

University of Pittsburgh | UPMC Hillman Cancer Center | UPMC Magee-Womens Hospital | Magee-Womens Research Institute & Foundation

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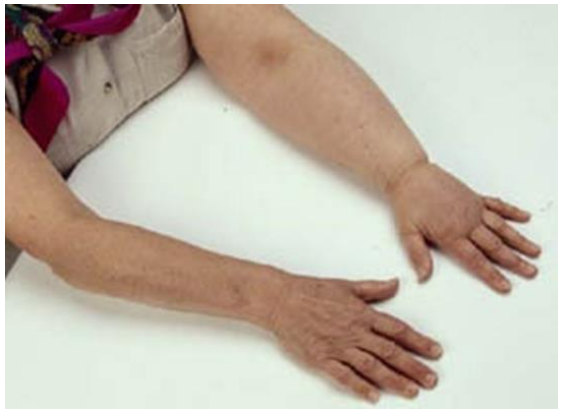
Axillary management in ILC: Background

- Why is axillary nodal surgery important?
  - Accurate breast cancer staging
  - Major prognostic predictor for breast cancer outcomes
  - Helps determine the extent of oncologic surgery, reconstructive surgery, radiation therapy and systemic therapy



- Why can axillary nodal surgery be a problem?

Morbidity

- Paresthesia (~20-70% of patients)
- Lymphedema (~3-25% of patients)

No significant impact on relapse-free or overall survival

- NSABP B04 study

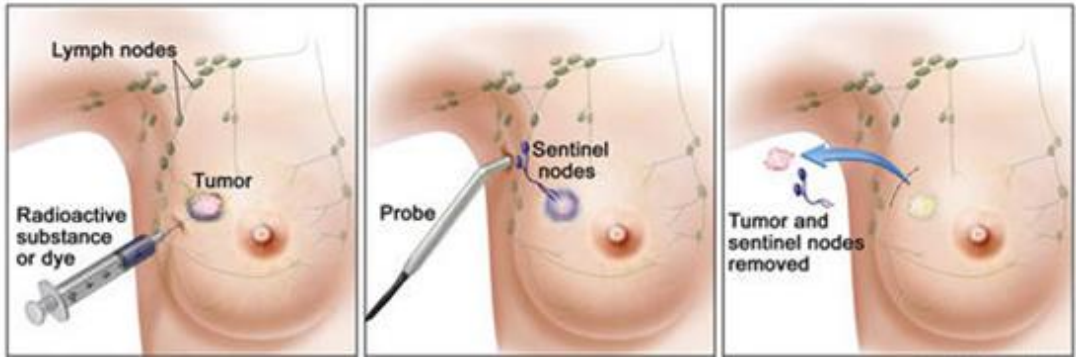
- Do current data support similar management of the axilla in ILC, as with IDC?
  - Lobular histology independently predicts risk of micrometastatic axillary disease

Fisher B, et al. N Engl J Med. 1985;312:674–81.

Axillary management in ILC – take away

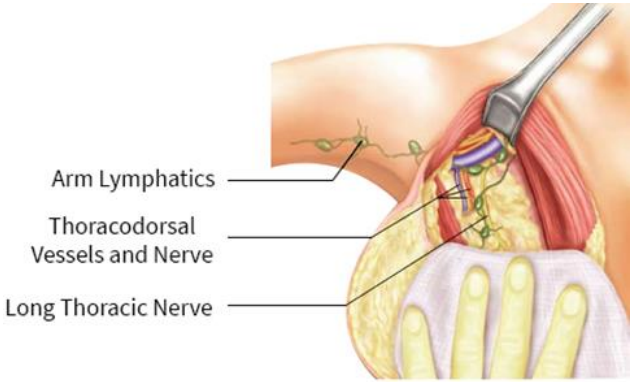
- For patients who present with a <u>normal axilla</u> on physical exam and imaging:
  - Sentinel lymph node biopsy (SLNB) adequately stages the axilla

SLNB



  - Surgical results:
    - If no lymph node involvement: no further axillary surgery needed
    - If low volume lymph node involvement: ~2 or fewer lymph nodes involved, no completion axillary lymph node dissection (ALND)
    - If high volume lymph node involvement: ALND

ALND



Axillary management in ILC: Take away

- For patients who present with lymph node involvement on exam/imaging:
  - Generally, ALND is recommended
    - For *appropriately selected patients*, sometimes after a good response to neoadjuvant systemic therapy, ALND can be avoided

Right-sizing axillary surgical management

for lobular cancer is critical and evolving

Systemic therapy

Distinct features of ILC vs NST/IDC in four NSABP randomized trials of adjuvant chemotherapy

Julia Foldi, MD PhD, Stewart Anderson, PhD, Neil Carleton, Priya Rastogi, MD, Adrian Lee, PhD, Charles Geyer, MD, Steffi Oesterreich, PhD

University of Pittsburgh Medical Center
Hillman Cancer Center
NSABP – National Surgical Adjuvant Breast and Bowel Project

2023 ILC Symposium

UPMC | HILLMAN CANCER CENTER MAGEE-WOMENS RESEARCH INSTITUTE University of Pittsburgh NCI Comprehensive Cancer Center

Summary of four large NSABP RCTs

Trial	ILC/NST (IDC) sample size	% ER+	Chemotherapy being tested	Endocrine therapy	Outcome measures	Median follow-up (yrs)	Major clinical conclusion of trial	Ref
B-22	143/1975	66%	AC vs AC with intensification of C	TAM x 5 yrs if age ≥ 50 yrs	DFS, OS	15.0	No benefit from C dose intensification.	(1)
B-25	197/2252	60%	AC vs AC with intensification of C	TAM x 5 yrs if age ≥ 50 yrs	DFS, OS	12.1	No benefit from C dose intensification.	(2)
B-28	275/2720	66%	AC vs AC→T (T=Paclitaxel)	TAM x 5 yrs if age ≥ 50 yrs or <50 if ER+	DFS, OS	11.2	The addition of T to AC led to significant improvement in DFS but not OS, with acceptable toxicity.	(3)
B-30	616/4304	75%	AC→T vs AT vs ACT (T=docetaxel)	TAM x 5 yrs if ER+; anastrozole allowed after 10/2002 in postmenopausal patients	DFS, OS	10.2	Sequential AC→T improved DFS compared with AT and concurrent ACT; and improved OS compared with AT.	(4)

Abbreviations: ER: estrogen receptor; A: adriamycin; C: cyclophosphamide; T: paclitaxel/docetaxel; TAM: tamoxifen; DFS: disease-free survival; OS: overall survival

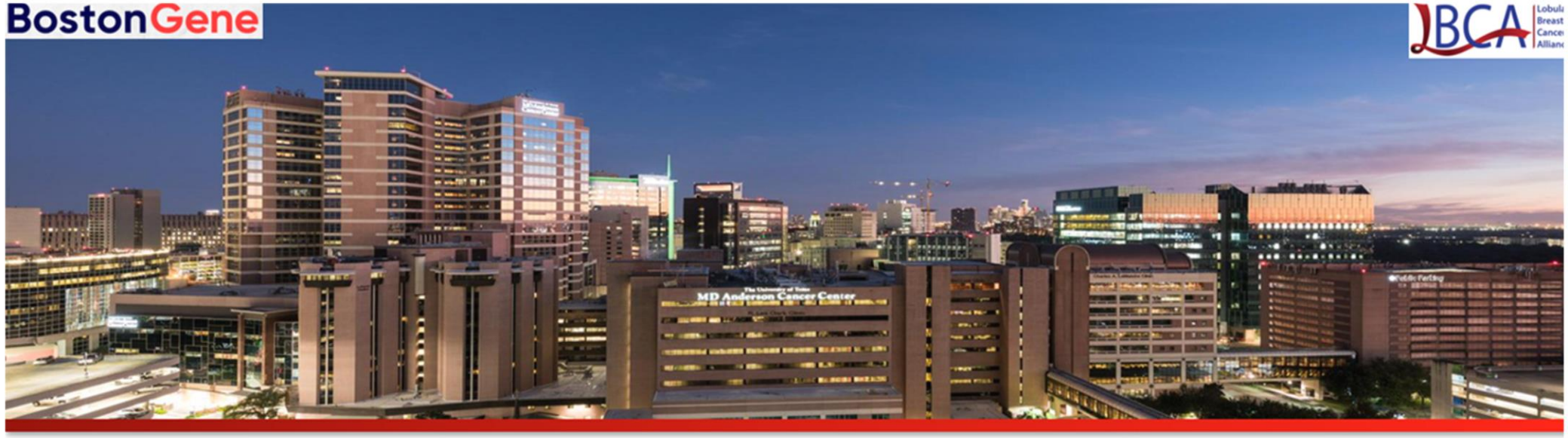
1. Fisher B, Anderson S, Wickerham DL, DeCillis A, Dimitrov N, Mamounas E, et al. Increased intensification and total dose of cyclophosphamide in a doxorubicin-cyclophosphamide regimen for the treatment of primary breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-22. J Clin Oncol. 1997 May;15(5):1858–69.
2. Fisher B, Anderson S, DeCillis A, Dimitrov N, Atkins JN, Fehrenbacher L, et al. Further Evaluation of Intensified and Increased Total Dose of Cyclophosphamide for the Treatment of Primary Breast Cancer: Findings From National Surgical Adjuvant Breast and Bowel Project B-25. J Clin Oncol. 1999 Nov;17(11):3374–88.
3. Mamounas EP, Bryant J, Lembersky B, Fehrenbacher L, Sedlacek SM, Fisher B, et al. Paclitaxel After Doxorubicin Plus Cyclophosphamide As Adjuvant Chemotherapy for Node-Positive Breast Cancer: Results From NSABP B-28. J Clin Oncol. 2005 Jun;23(16):3686–96.
4. Swain SM, Jeong JH, Geyer CE, Costantino JP, Pajon ER, Fehrenbacher L, et al. Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. N Engl J Med. 2010 Jun 3;362(22):2053–65.

Summary and conclusions

In four large RCTs conducted by the NSABP including a total of **12,494** patients (**1,233 with ILC**) accrued between 1989 and 2004, we found:

- Significant differences in baseline characteristics between patients with ILC and NST/IDC:
  - Older age, higher prevalence of ER+ disease, higher number of involved LN's and larger tumors
- After propensity matching for age, ER status, tumor size and LN status, we found:
  - Overall, no differences in clinical outcomes of DFS, OS and recurrences
  - When looking at early (0-5 yrs) and late events (5+ yrs) separately, patients with ILC do better early, while they do worse compared to patients with NST/IDC later in follow-up
  - More late recurrences in patients with ILC
  - Similar pattern of outcomes in patients with ER+ and ER- disease

In this analysis of data from the largest cohort of ILC patients from prospectively randomized clinical trials of adjuvant chemotherapy, long-term clinical outcomes were different between patients with ILC versus NST/IDC despite receiving the same modern adjuvant treatment



Differential Genomic and Transcriptomic Analysis of Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma

Jason A. Mouabbi MD

Assistant Professor

Department of Breast Medical Oncology at MD Anderson Cancer Center

SAB Chair of the Lobular Breast Cancer Alliance

European Lobular Breast Cancer Consortium

LBCA® Lobular Breast Cancer Alliance

ILC 2023 Pittsburgh, PA

Goal

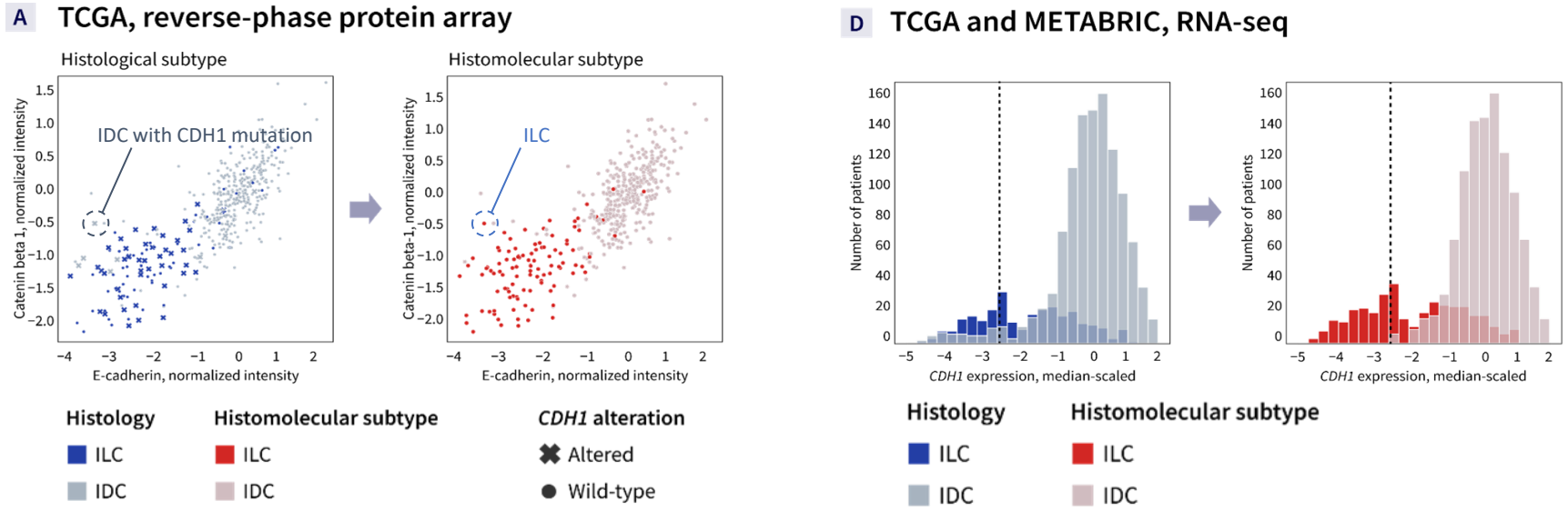
Identify novel biomarkers, genetic alterations, transcriptomic features, and tumor microenvironment (TME) variations to facilitate the development of personalized treatments for patients with ILC

Methods

- We collected ILC and luminal IDC samples from two datasets (TCGA, METABRIC) and performed differential expression and gene set enrichment analyses, revealing novel genomic, transcriptomic, and TME differences.
  - We analyzed 1,735 samples: 1,442 luminal IDCs and 293 ILC

Transition from histological to histo-molecular classification

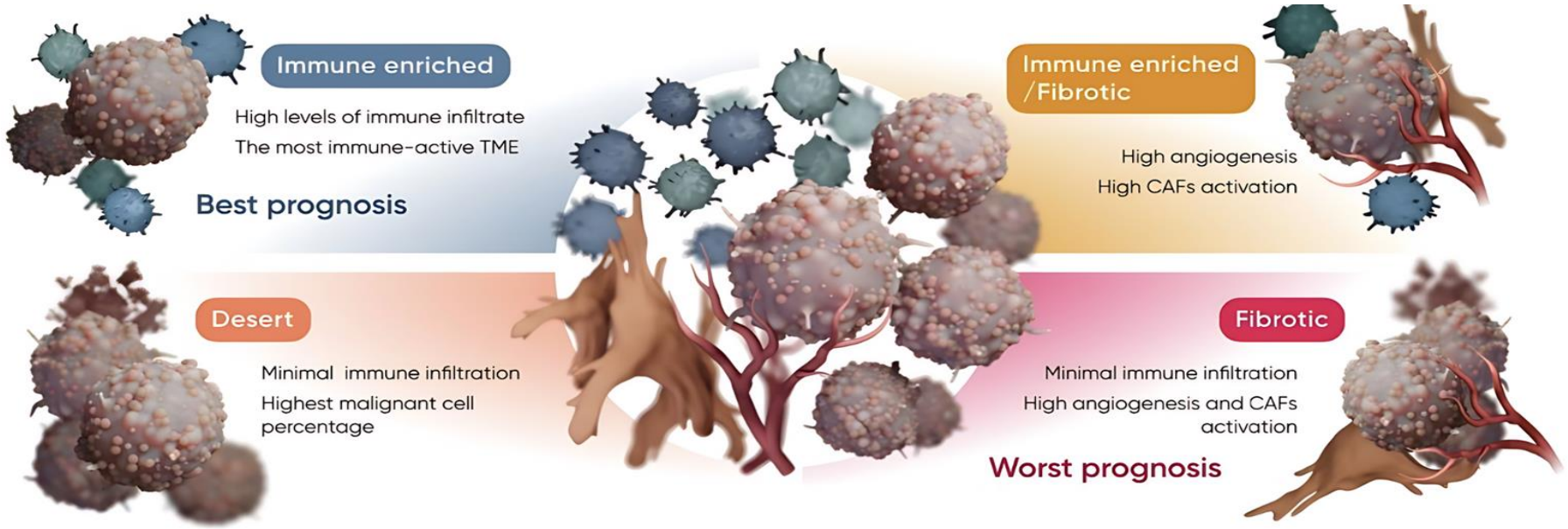
- In the TCGA and METABRIC samples were labeled “IDC” or “ILC solely on morphological analysis (histology)
- *CDH1* alterations and low *CDH1* and *CTNNB1* (catenin beta-1) expression are well established associations with ILC histology
- We established a **histo-molecular classification** that incorporates histological findings in combination with *CDH1* alterations (mutation, deep deletion, or low expression) and *CTNNB1* low expression



Tumor Microenvironment Types (TME)

A component of BostonGene Tumor Portrait™ test

- BostonGene identified 4 distinct Tumor Microenvironment Subtypes by analyzing **29 functional gene expression signatures**
- There are **4 portrait types** associated with disease prognosis
- This model is prognostic in **multiple cancer types**

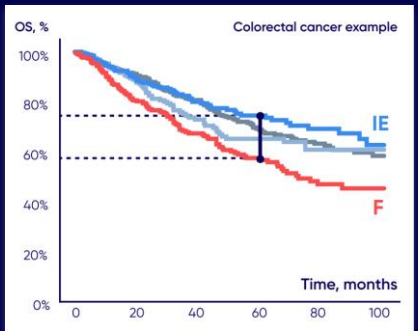


Cancer Cell

Editors' picks in 2021 — Cutting-edge areas of cancer research and oncology in 2021

The proprietary model was published in Cancer Cell

Bagaev et al., Cancer Cell, 2021



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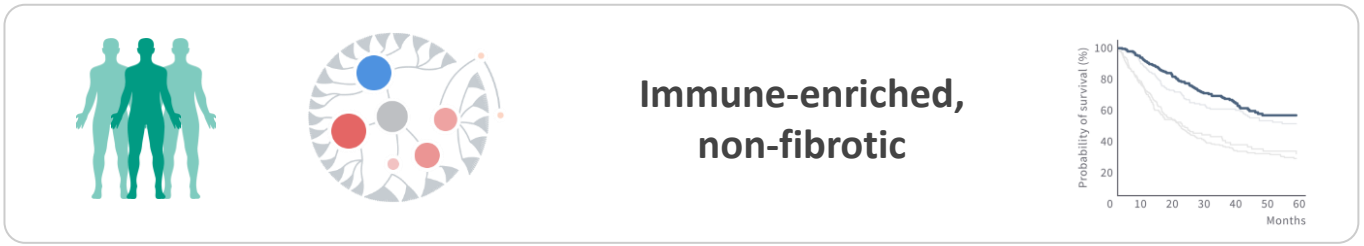
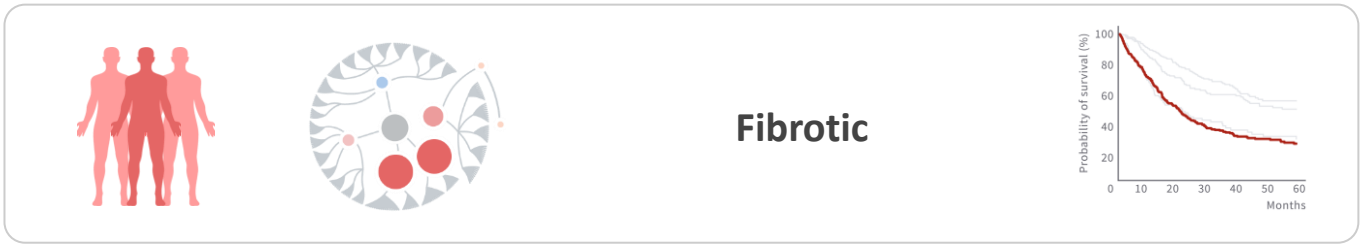
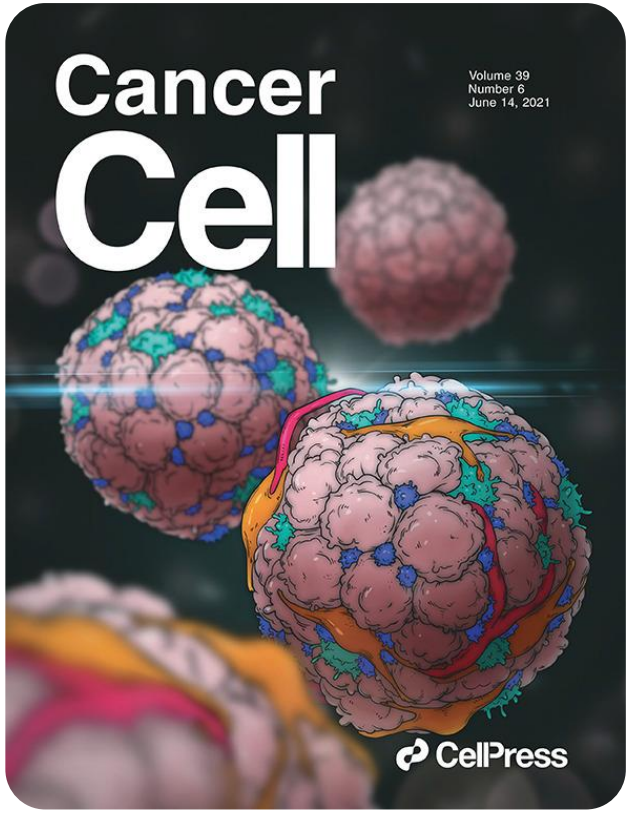
TME Prognostic tool — predicts survival. GOAL: personalize care!

A component of BostonGene Tumor Portrait™ test







Cancer cell. 2021. Bagaev, et.al.
Conserved pan-cancer microenvironment subtypes predict response to immunotherapy

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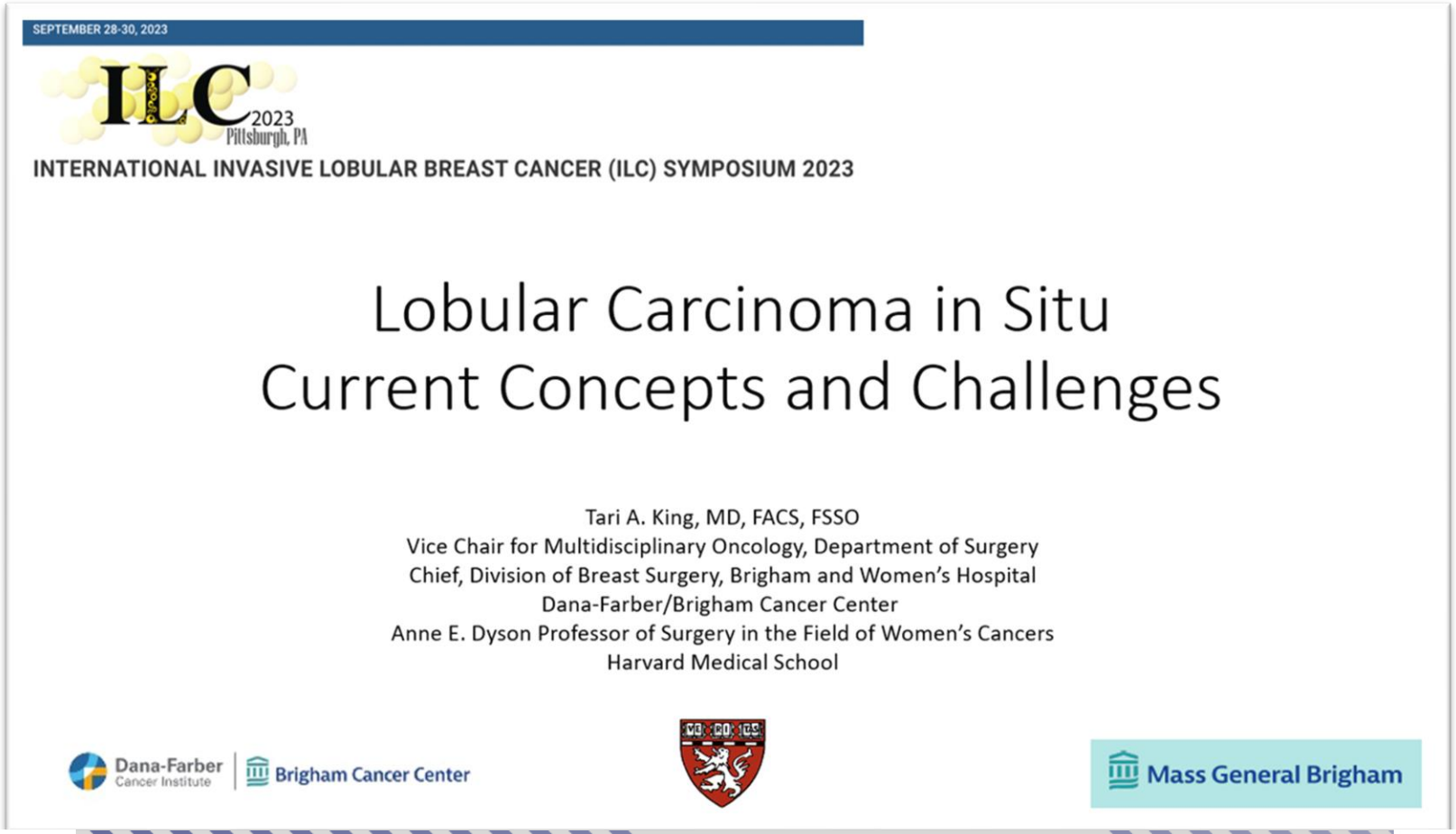
Tickler: what if lobular pathology could be managed before it was ever invasive? (Session 1)



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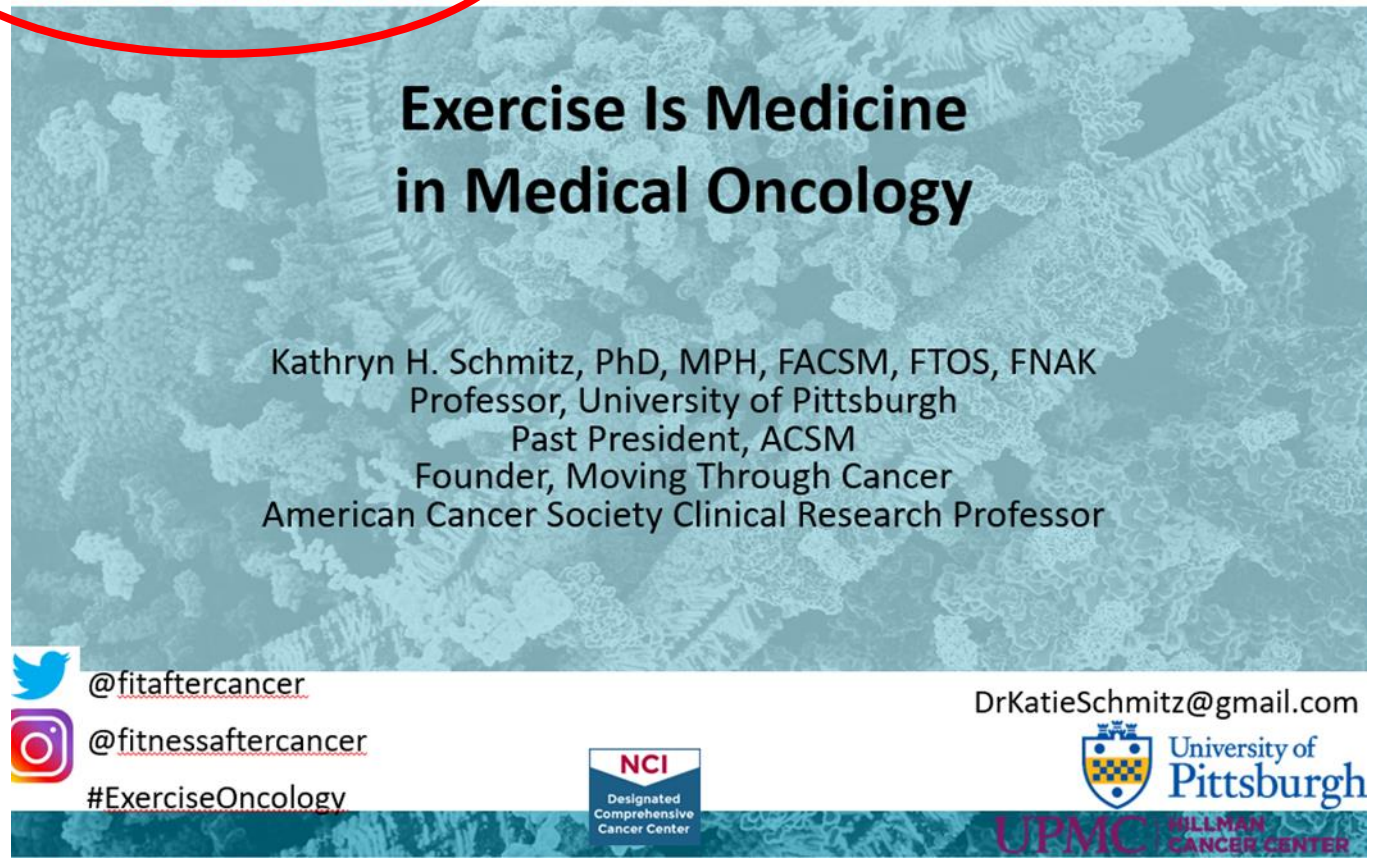
What can you do RIGHT NOW? Exercise!

ExeRxcise is Medicine®

MOVING THROUGH CANCER



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Documented Benefits of Exercise during Cancer Tx

- Fatigue
- Sleep
- Quality of life
- Anxiety
- Depression
- Body composition
- Function
- Breast cancer related lymphedema

Outcomes Documented to be Improved by Exercise with Clinical Relevance during Cancer Treatment

Inflammation

- Contributes to infections, diarrhea, nausea/vomiting, fatigue

Comorbidities

- Cancer patients with worse comorbidities are more likely to be hospitalized

Frailty

- Frail patients more likely to be hospitalized or visit the ER

Dr. Schmitz's Seminal Contribution: The PAL Trial

PAL Physical Activity & Lymphedema

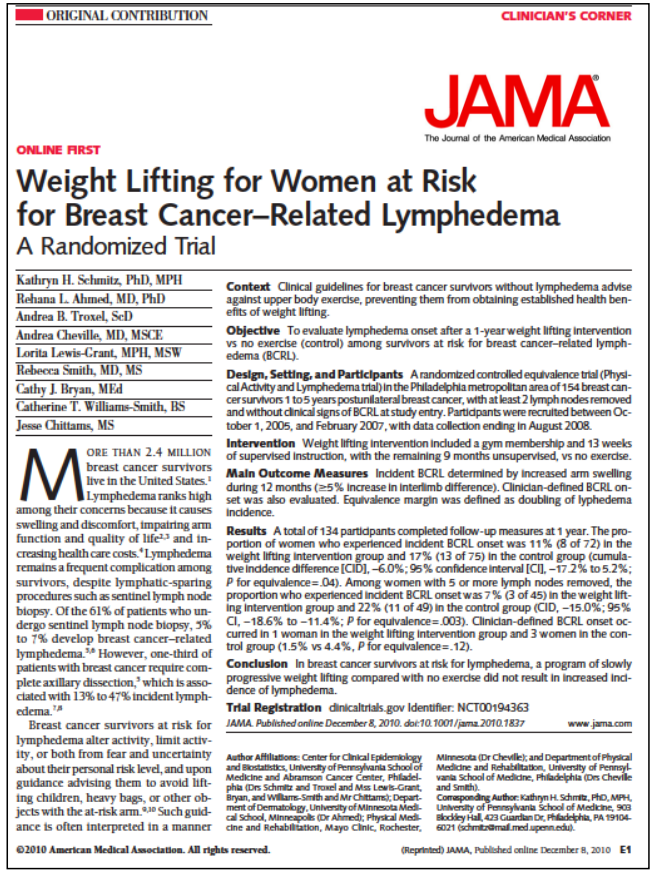
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Weight Lifting in Women with Breast-Cancer–Related Lymphedema

Kathryn H. Schmitz, Ph.D., M.P.H., Rehana L. Ahmed, M.D., Ph.D., Andrea Troxel, Sc.D., Andrea Cheville, M.D., Rebecca Smith, M.D., Lorita Lewis-Grant, M.P.H., M.S.W., Cathy J. Bryan, M.Ed., Catherine T. Williams-Smith, B.S., and Quincy P. Greene

August 18, 2009



ORIGINAL CONTRIBUTION CLINICIAN'S CORNER

JAMA The Journal of the American Medical Association

ONLINE FIRST

Weight Lifting for Women at Risk for Breast Cancer–Related Lymphedema

A Randomized Trial

Kathryn H. Schmitz, PhD, MPH
Rehana L. Ahmed, MD, PhD
Andrea B. Troxel, ScD
Andrea Cheville, MD, MSCE
Lorita Lewis-Grant, MPH, MSW
Rebecca Smith, MD, MS
Cathy J. Bryan, MEd
Catherine T. Williams-Smith, BS
Jesse Chittams, MS

Context Clinical guidelines for breast cancer survivors without lymphedema advise against upper body exercise, preventing them from obtaining established health benefits of weight lifting.

Objective To evaluate lymphedema onset after a 1-year weight lifting intervention vs no exercise (control) among survivors at risk for breast cancer–related lymphedema (BCRL).

Design, Setting, and Participants A randomized controlled equivalence trial (Physical Activity and Lymphedema trial) in the Philadelphia metropolitan area of 154 breast cancer survivors 1 to 5 years postunilateral breast cancer, with at least 2 lymph nodes removed and without clinical signs of BCRL at study entry. Participants were recruited between October 1, 2005, and February 2007, with data collection ending in August 2008.

Intervention Weight lifting intervention included a gym membership and 13 weeks of supervised instruction, with the remaining 9 months unsupervised, vs no exercise.

Main Outcome Measures Incident BCRL determined by increased arm swelling during 12 months (≥5% increase in interlimb difference). Clinician-defined BCRL onset was also evaluated. Equivalence margin was defined as doubling of lyphedema incidence.

Results A total of 134 participants completed follow-up measures at 1 year. The proportion of women who experienced incident BCRL onset was 11% (8 of 72) in the weight lifting intervention group and 17% (13 of 75) in the control group (cumulative incidence difference [CID], −6.0%; 95% confidence interval [CI], −17.2% to 5.2%; *P* for equivalence=.04). Among women with 5 or more lymph nodes removed, the proportion who experienced incident BCRL onset was 7% (3 of 45) in the weight lifting intervention group and 22% (11 of 49) in the control group (CID, −15.0%; 95% CI, −18.6% to −11.4%; *P* for equivalence=.003). Clinician-defined BCRL onset occurred in 1 woman in the weight lifting intervention group and 3 women in the control group (1.5% vs 4.4%, *P* for equivalence=.12).

Conclusion In breast cancer survivors at risk for lymphedema, a program of slowly progressive weight lifting compared with no exercise did not result in increased incidence of lymphedema.

Trial Registration clinicaltrials.gov Identifier: NCT00194363

JAMA. Published online December 8, 2010. doi:10.1001/jama.2010.1837 www.jama.com

Author Affiliations: Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine and Abramson Cancer Center, Philadelphia (Drs Schmitz and Troxel and Mss Lewis-Grant, Bryan, and Williams-Smith and Mr Chittams); Department of Dermatology, University of Minnesota Medical School, Minneapolis (Dr Ahmed); Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, Minnesota (Dr Cheville); and Department of Physical Medicine and Rehabilitation, University of Pennsylvania School of Medicine, Philadelphia (Drs Cheville and Smith).
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R01-CA106851

December 8, 2010

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Summary of Exercise Guidelines

	During Treatment		Post Treatment	
	Aerobic	**Resistance**	**Aerobic**	**Resistance**
American College of Sports Medicine (ACSM)	30 min 3x/week Moderate	2x week	150-300 min/week Moderate	2x week
American Cancer Society (ACS)	Recommended but not specific		150-300 min/week	No comment
American Society of Clinical Oncology (ASCO)	Recommended	Recommended	Not the focus of the guideline	

- Intensity:
  - "Gone are the days of 'don't push yourself, take it easy.'"
  - 'Talk test' to judge intensity: During exercise, if you cannot talk, you're working too hard. If you can sing, you're not working hard enough."

Clinical take-away from the ILC Symposium?

Session 6: Challenges in Treatment of ILC

4:35pm	**Session 6: Challenges in Treatment of ILC** **Chair: Vikram Gorantla, MD** (UPMC, Pittsburgh)
4:40pm-5:00pm	**Suzanne Fuqua, PhD** (Baylor College of Medicine, Houston) *When the Breast Cancer Researcher Becomes the Patient with ILC*
5:00pm-5:20pm	**Jason Mouabbi, MD** (University of Texas, MD Anderson Cancer Center, Houston) *Differential Genomic and Transcriptomic Analysis of Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma*
5:20pm-5:40pm	**Julia Foldi, MD, PhD** (University of Pittsburgh, UPMC, Pittsburgh, PA) *Distinct features of ILC vs IDC in four NSABP randomized trials of adjuvant chemotherapy*
5:40pm-6:00pm	**Kathryn Schmitz, PhD, MPH** (University of Pittsburgh, UPMC Hillman Cancer Center, PA) *Exercise is Medicine in the Setting of Oncology*

Session 7: Local Treatment of ILC

8:55am	**Session 7: Local Treatment of ILC** **Chair: Bhuvaneswari Ramaswamy, MD** (The Ohio State, Columbus, OH)
9:00am-9:20am	**Rita Mukhtar, MD** (UCSF, San Francisco, CA) *Surgical management of ILC: challenges and opportunities*
9:20am-9:40am	**Priscilla McAuliffe, MD, PhD** (UPMC Magee-Womens Hospital and UPMC Hillman Cancer Center, Pittsburgh, PA) *Surgical management of the axilla in lobular cancer.*

Precision treatment for ILC is evolving in all clinical areas!

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Thank you!

Q & A

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Our Panelists

Patrick Derksen, PhD

Peter Simpson, PhD

Bhuvaneswari Ramaswamy, MD

Matt Covington, MD

Priscilla McAuliffe, MD, PhD

Jason Mouabbi, MD

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Thank You!

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