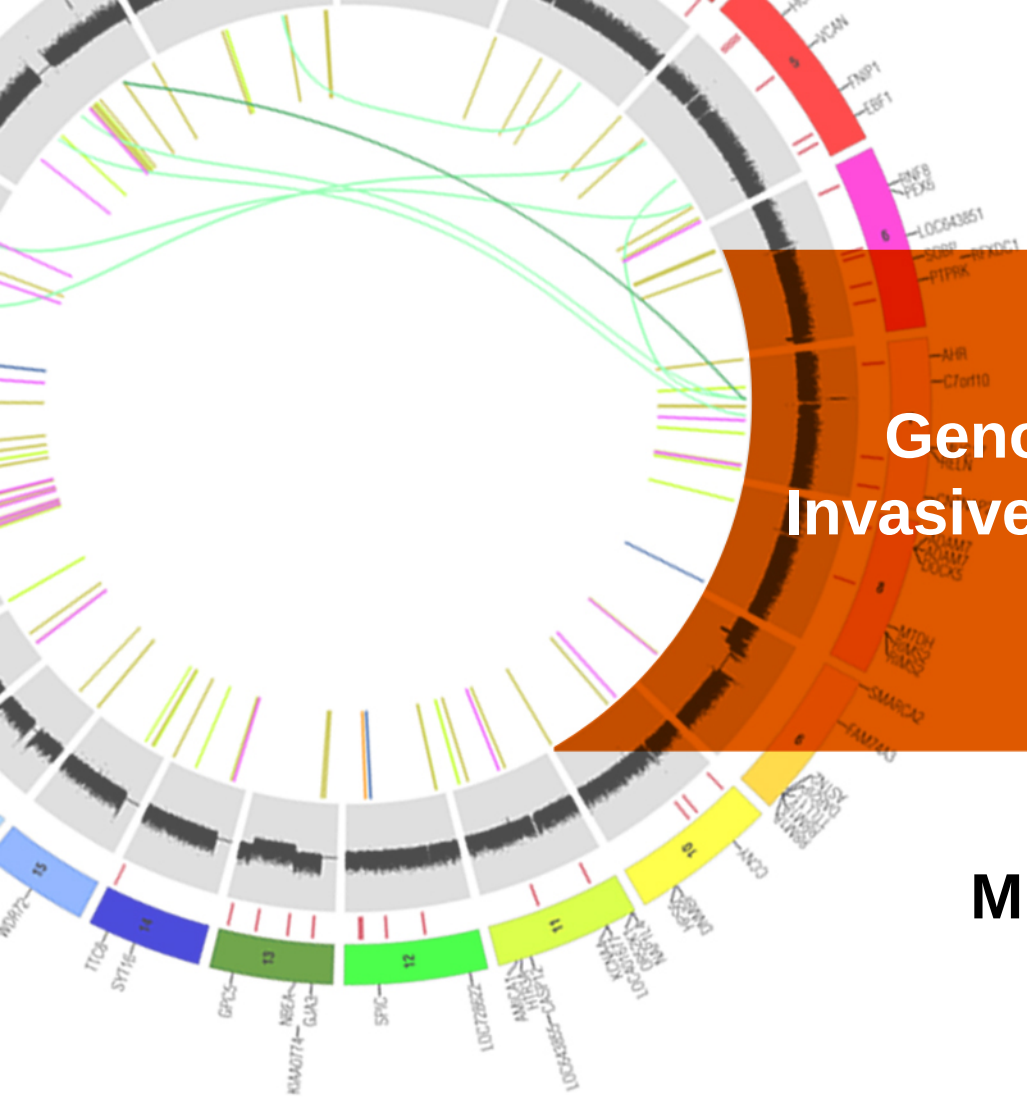


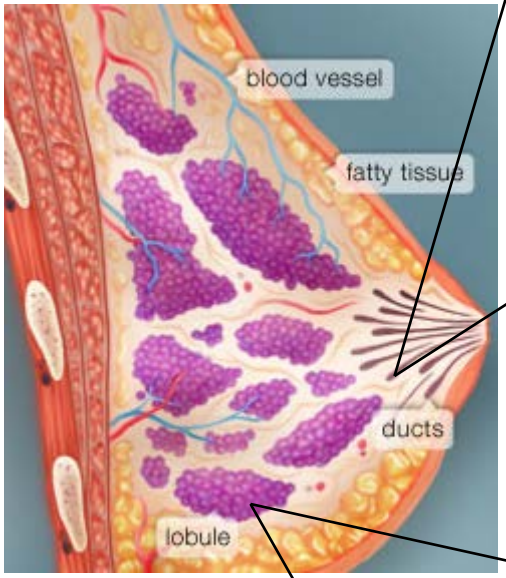
The Cancer Genome Atlas

Genomic Characterization of Invasive Lobular Breast Carcinoma

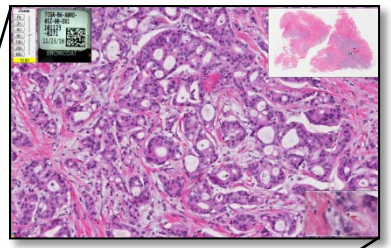
Michael L. Gatza, Ph.D.

TCGA Breast Cancer AWG

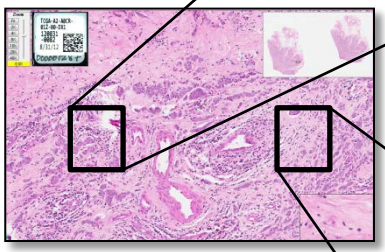
Invasive Breast Carcinoma



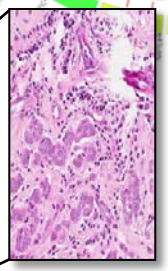
webmd.com



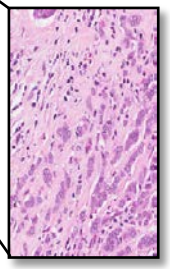
Invasive Ductal Carcinoma (IDC)
50-80%



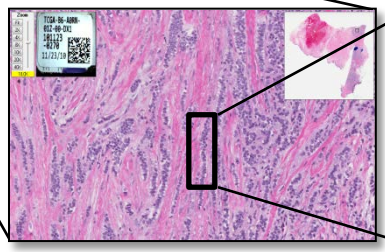
Mixed IDC.ILC
4-5%

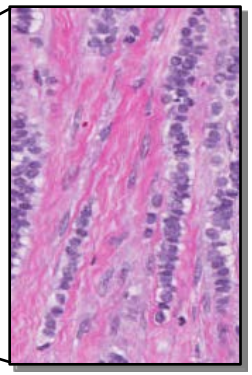


Ductal



Lobular





Invasive Lobular Carcinoma (ILC)
10-15%

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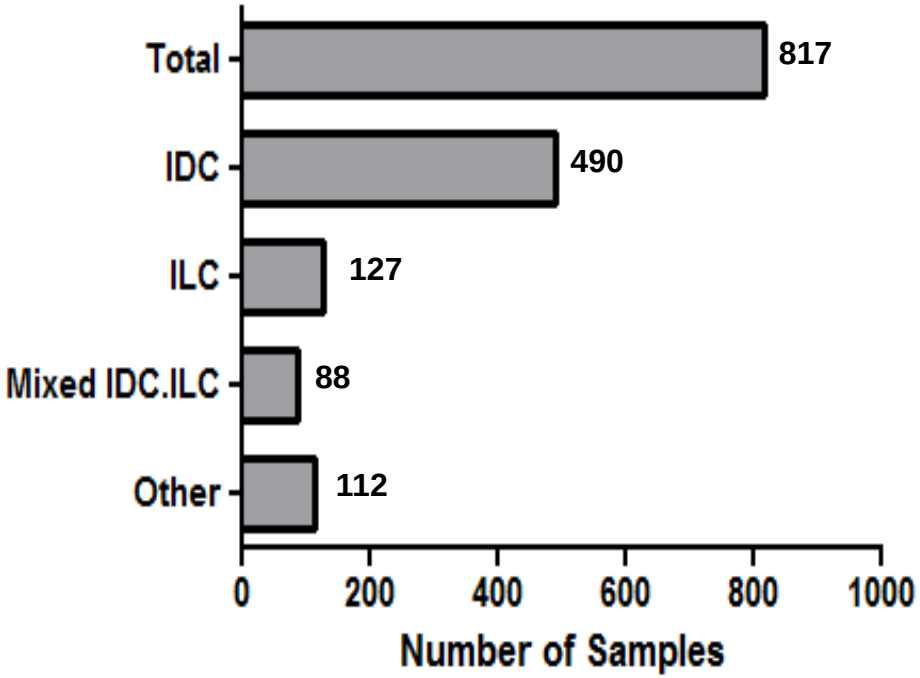
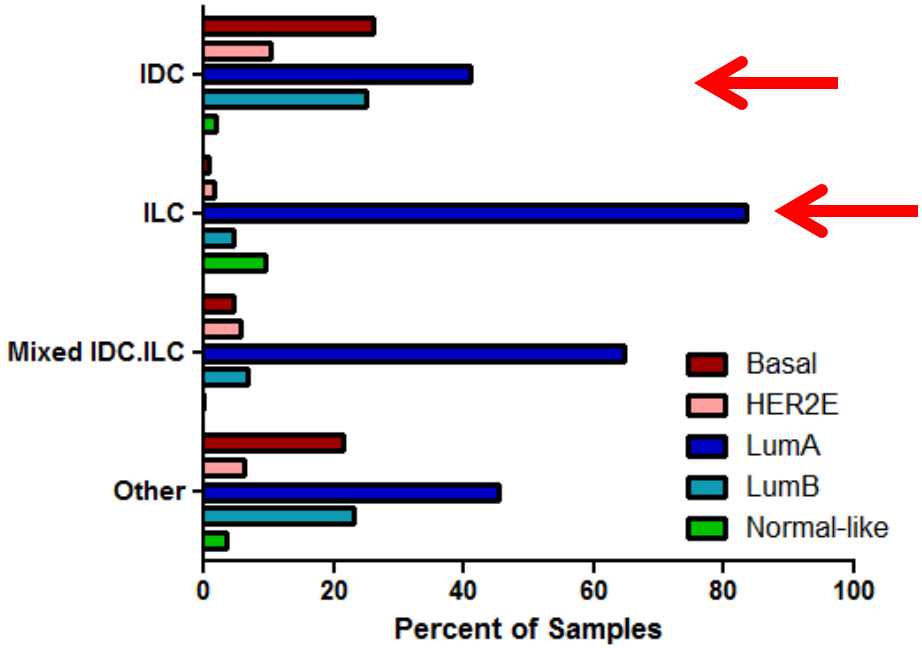
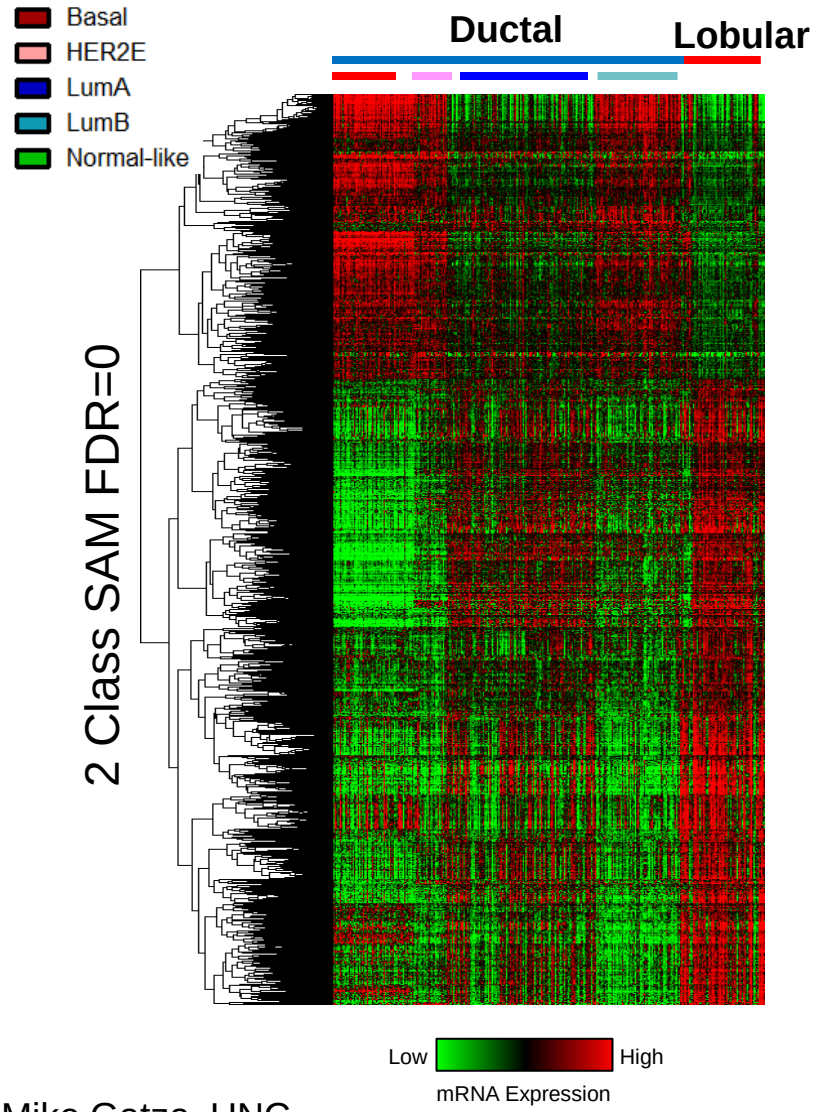
Summary of Data Freeze

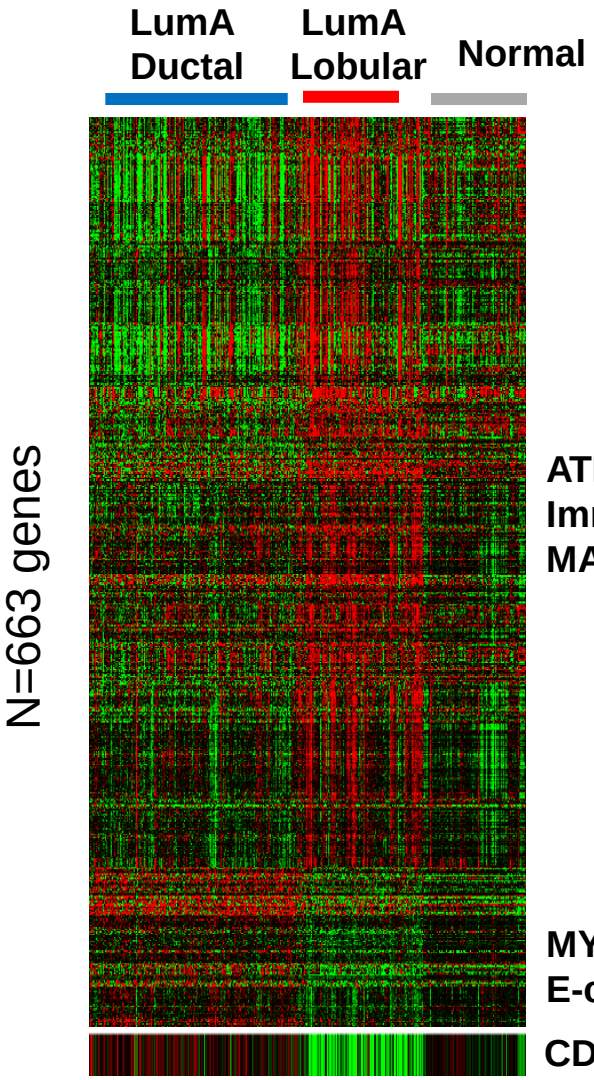
Pathology centrally re-reviewed
(Andy Beck, Harvard)





Identification of differentially expressed genes





ATM network
Immune signaling (multiple)
MAPK signaling

MYC targets (multiple)
E-cadherin stabilization

CDH1

Mike Gatza, UNC

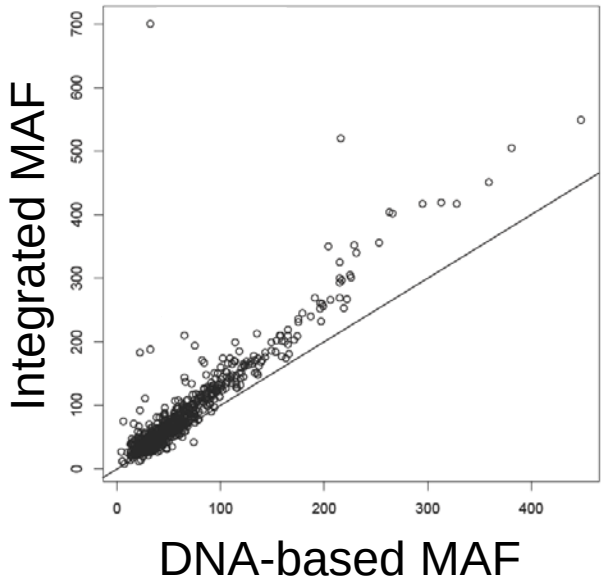
The Cancer Genome Atlas

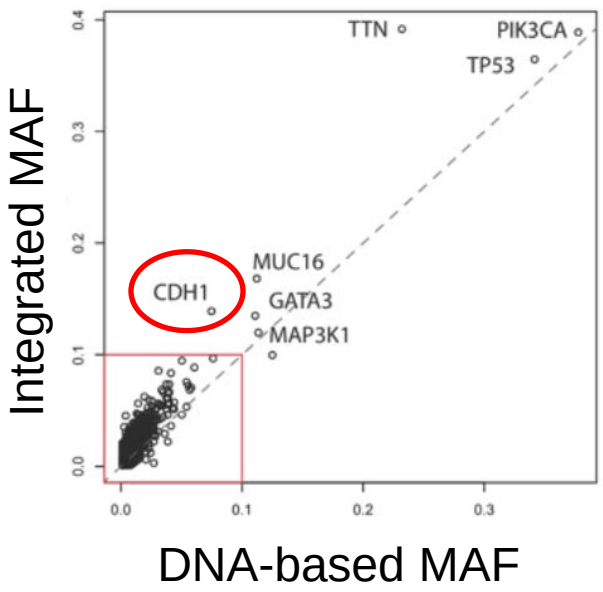
Development of Integrated MAF

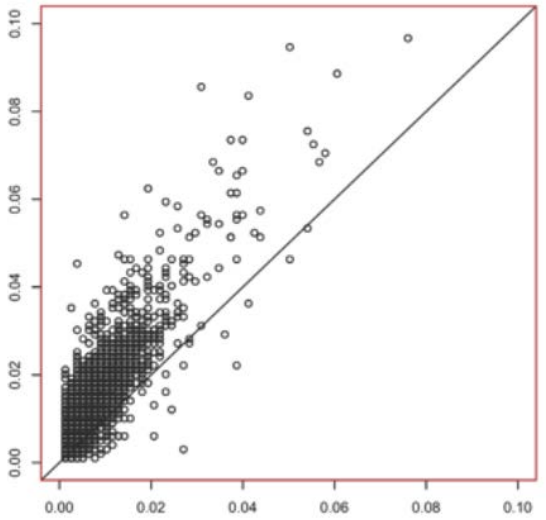
DNA Exome sequencing

UNCeqR (mRNAseq / DNAseq) → **Integrated MAF**

ABRA (CDH1, TP53, GATA3, PTEN, RB1)







Matt Wilkerson (UNC), Lisle Mose (UNC)
Giovanni Ciriello (MSKCC), Cyriac Kandoth (MSKCC)
Mike McLellan (Wash U)

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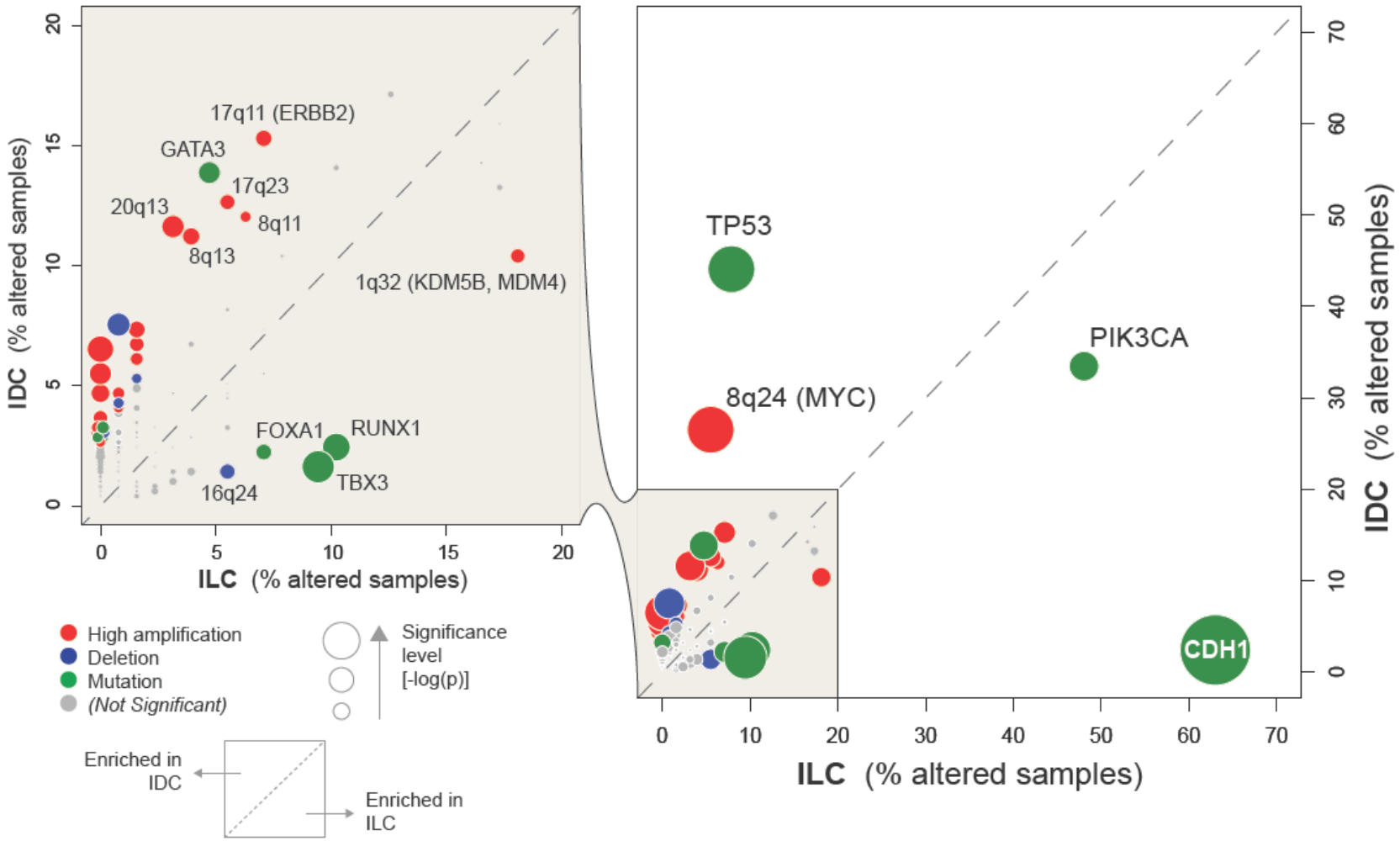
Comparison of significant alterations: IDC vs. ILC



Giovanni Ciriello, MSKCC

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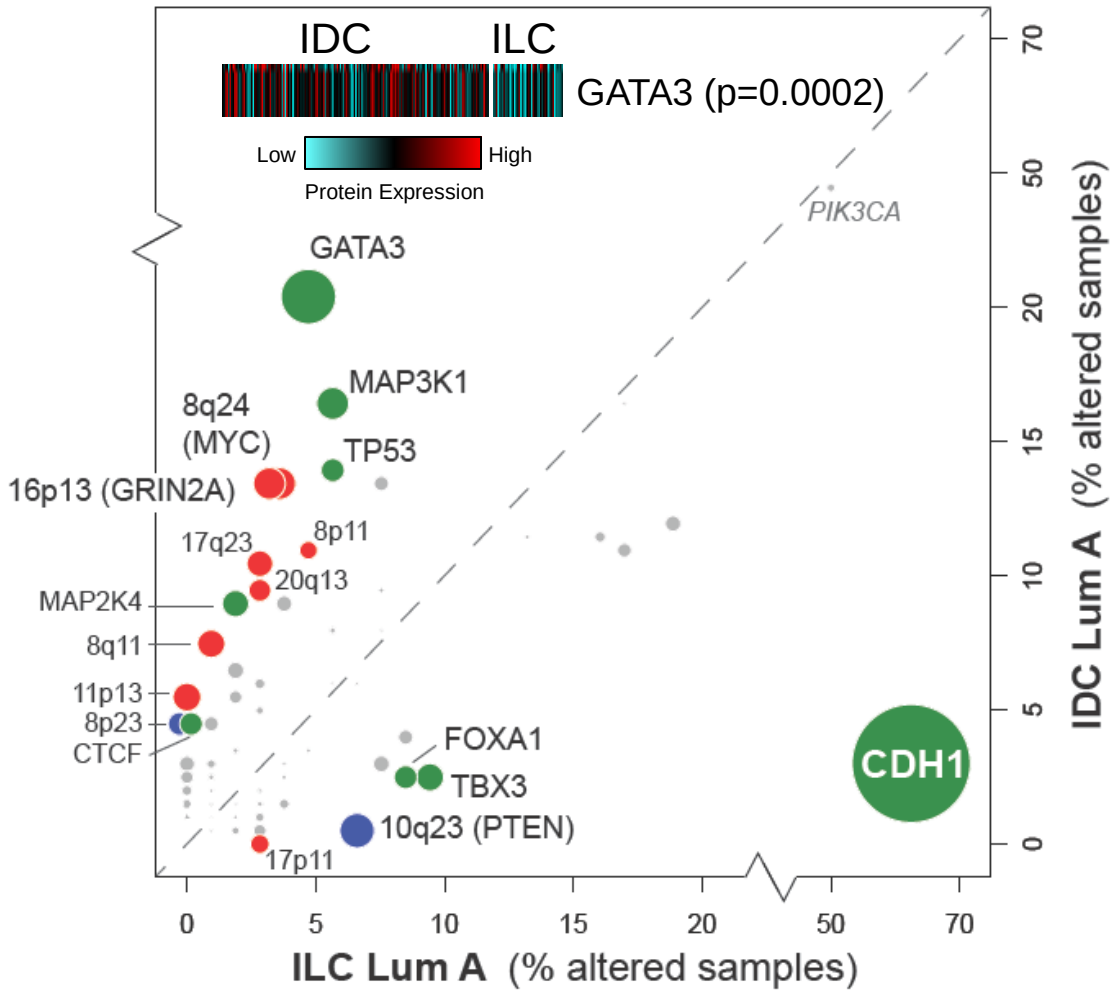
Identifying IDC LumA and ILC LumA-specific alterations



High amplification
Deletion
Mutation
(Not Significant)

* p ~ 0.05

Significance level [-log(p)]

Giovanni Ciriello, MSKCC

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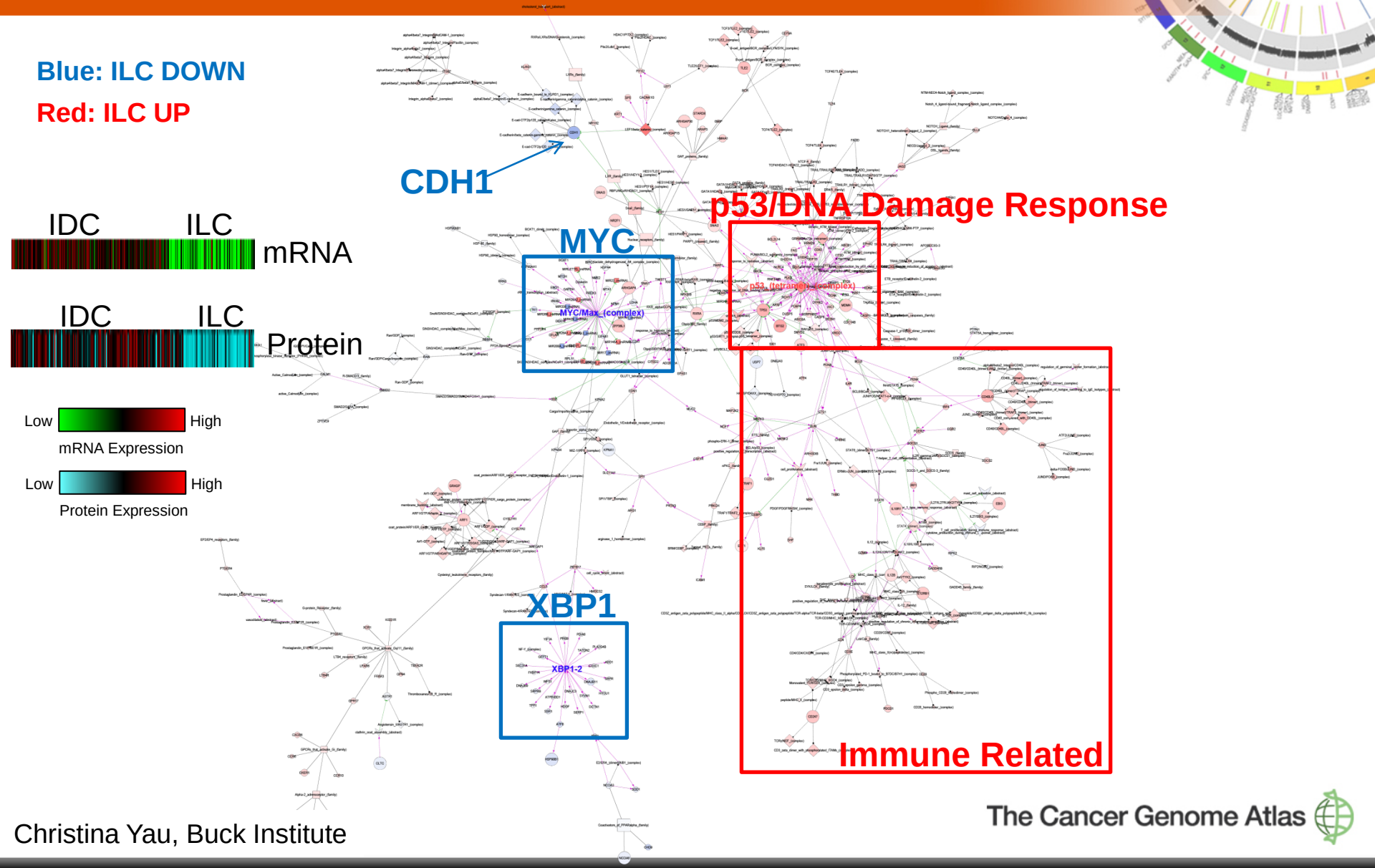
PARADIGM analysis identifies IDC and ILC-associated signaling pathways



Christina Yau, Buck Institute

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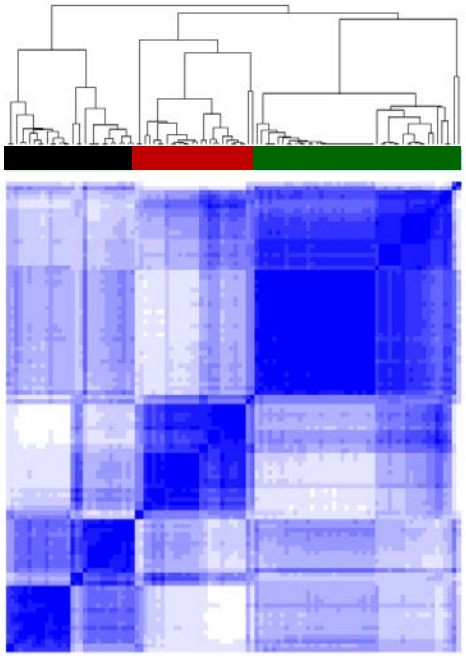
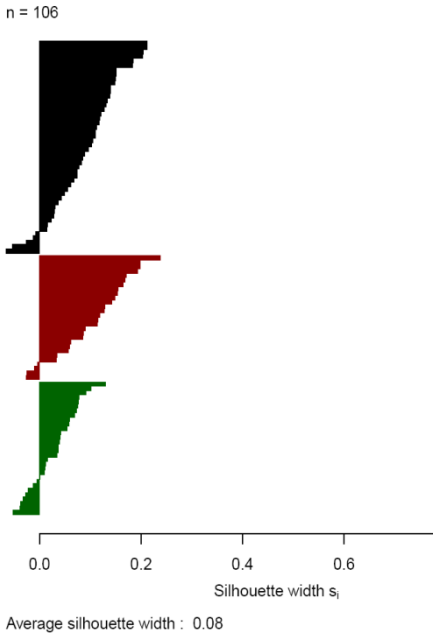
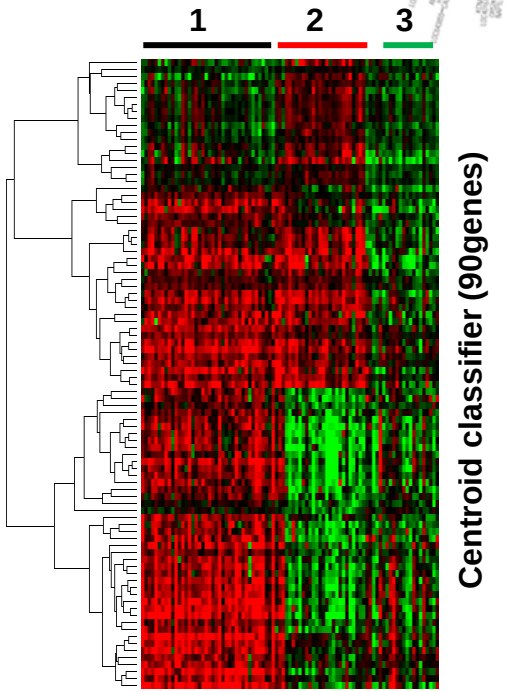
Development of mRNA-based ILC classes







ConsensusClusterPlus to ID 3 ILC classes

TCGA ILC LumA (n=106)

Identified samples with positive sil. width

TCGA ILC LumA (n=89)

ClaNC developed centroid predictor

TCGA ILC LumA (n=89)

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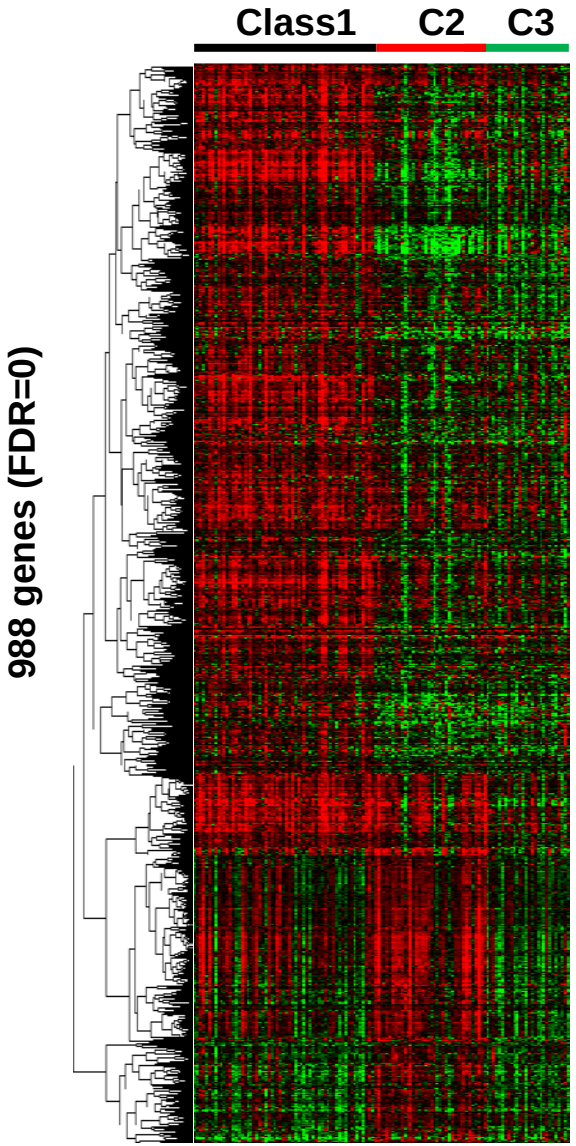
2 Class SAM identifies differentially expressed genes in ILC classes



N= 722 genes
EGFR
MET
GLI1
FGF17
WNT6
AREG
KIT

KRT 14, 15, 17, 32, 81
KRK 1, 6-8
CLDN 8,10,11, 19
PTCH2
TP63
VIT
ID4

N= 268 genes
Immune-related genes: >100

LCK
IFNG

Low High
mRNA Expression

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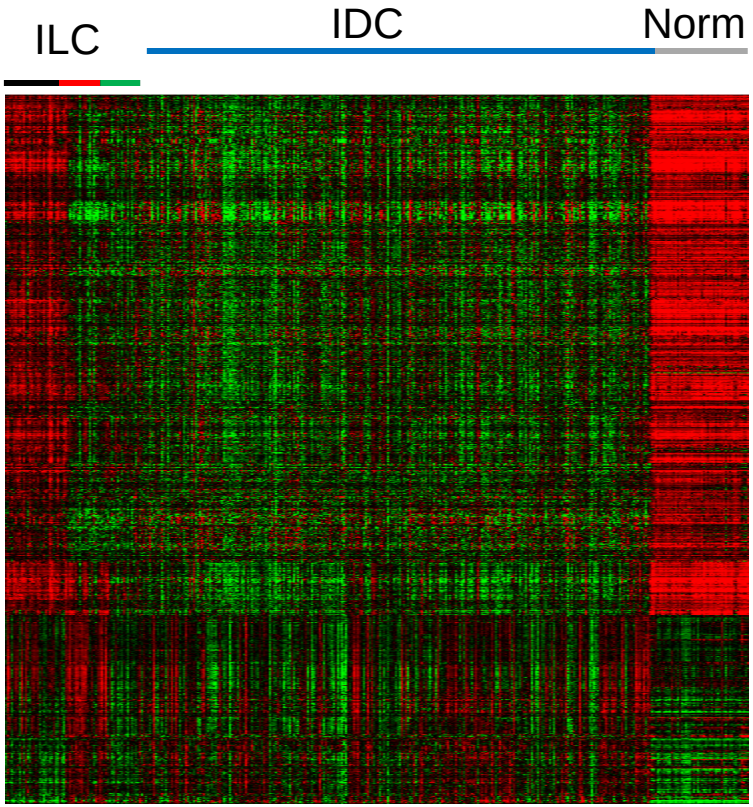
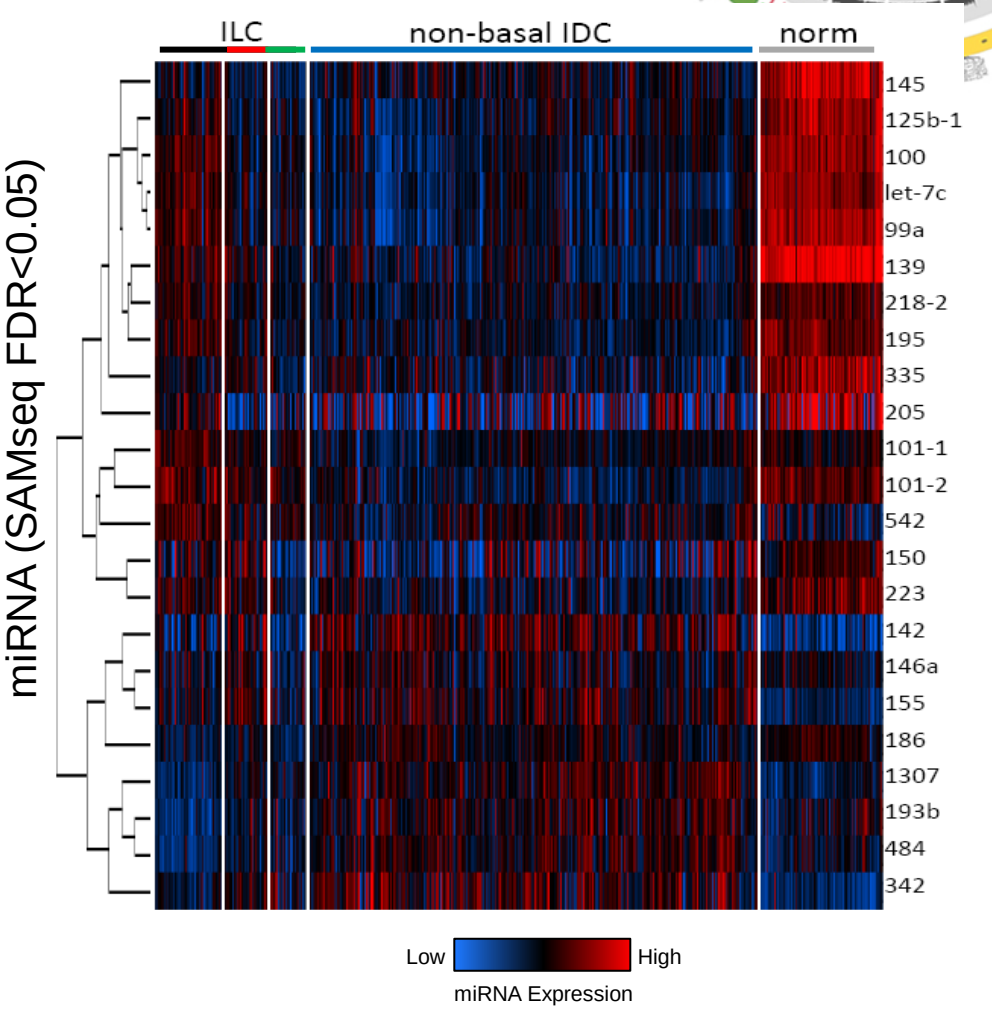
ILC class mRNA / miRNA expression patterns correspond with IDC and Adjacent Normal



	ILC	IDC	Normal
Class 1	61	49	94
Class 2	39	167	0
Class 3	27	274	0



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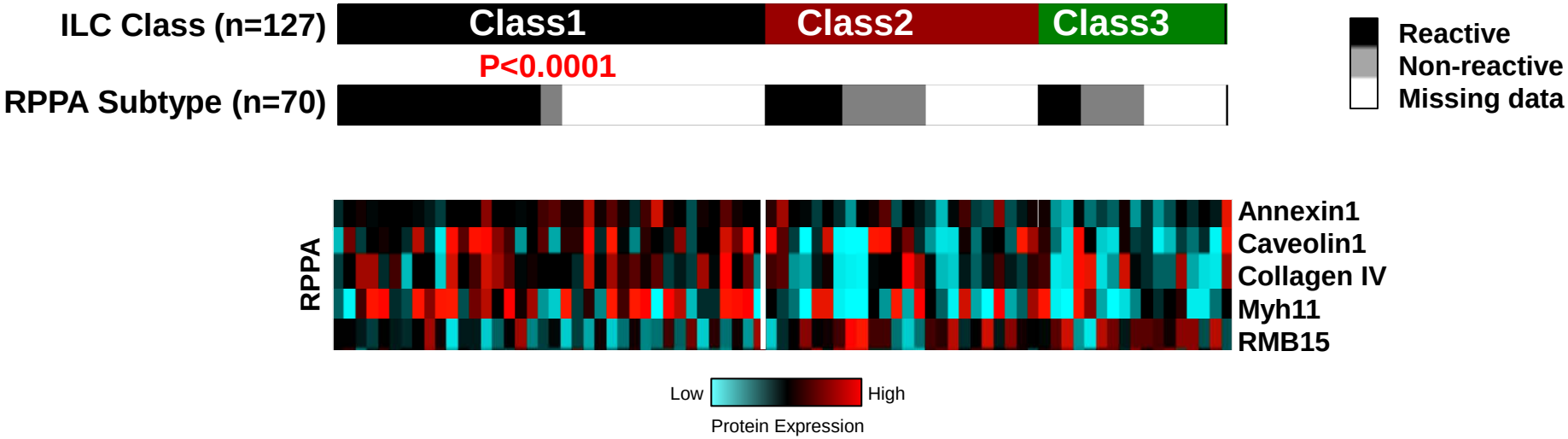
P<0.0001

Reanne Bowlby, BC Cancer Agency

ILC Class1 corresponds with RPPA Reactive Subtype



Mike Gatza, UNC
Gordon Mills, MDACC

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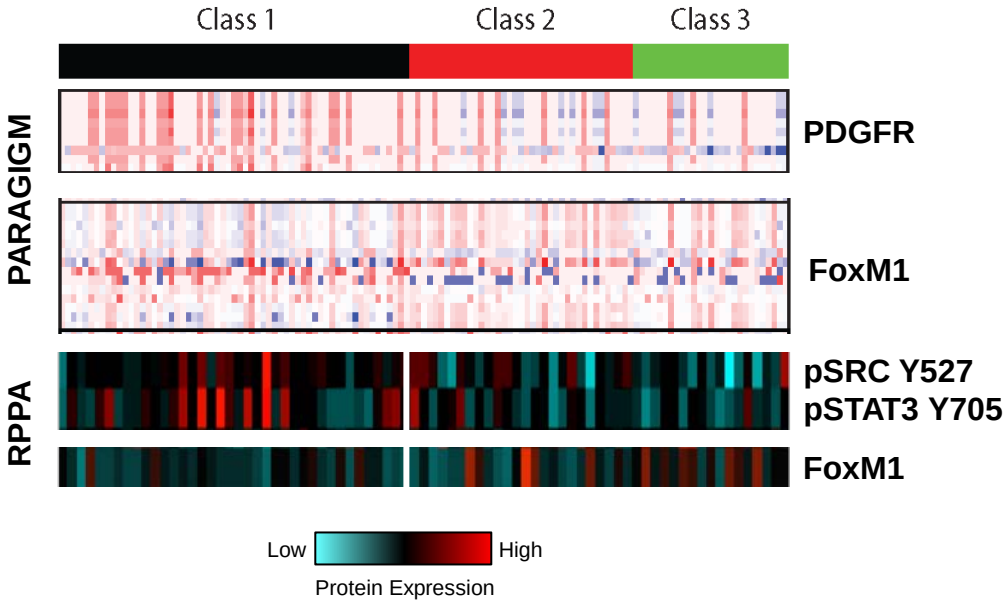
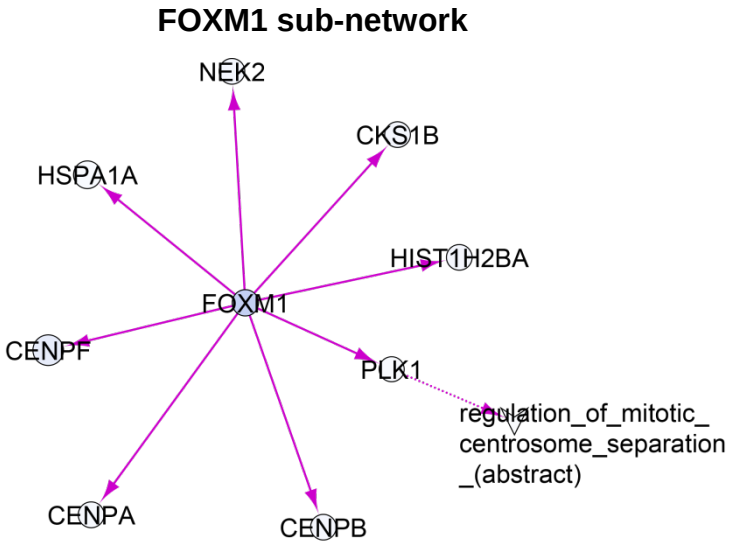
ILC Class1 tumors exhibit altered PDGFR/ STAT3 and FoxM1 signaling





Christina Yau, Buck Institute
Mike Gatza, UNC

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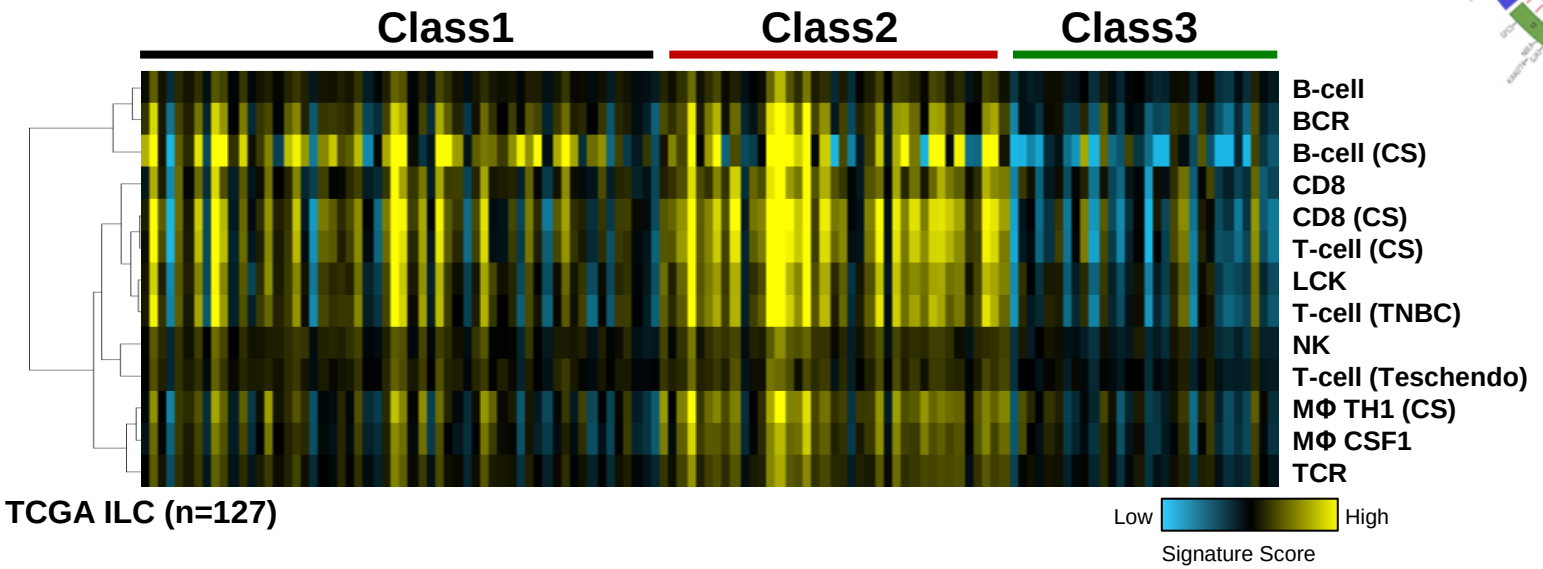
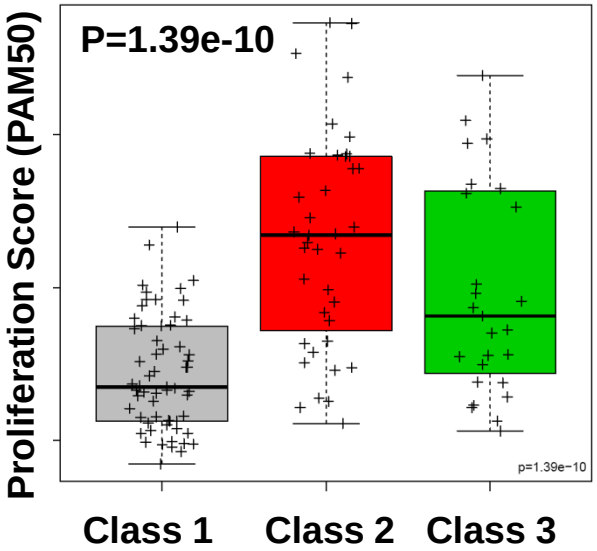
ILC class 2 defined by high immune signaling and proliferation





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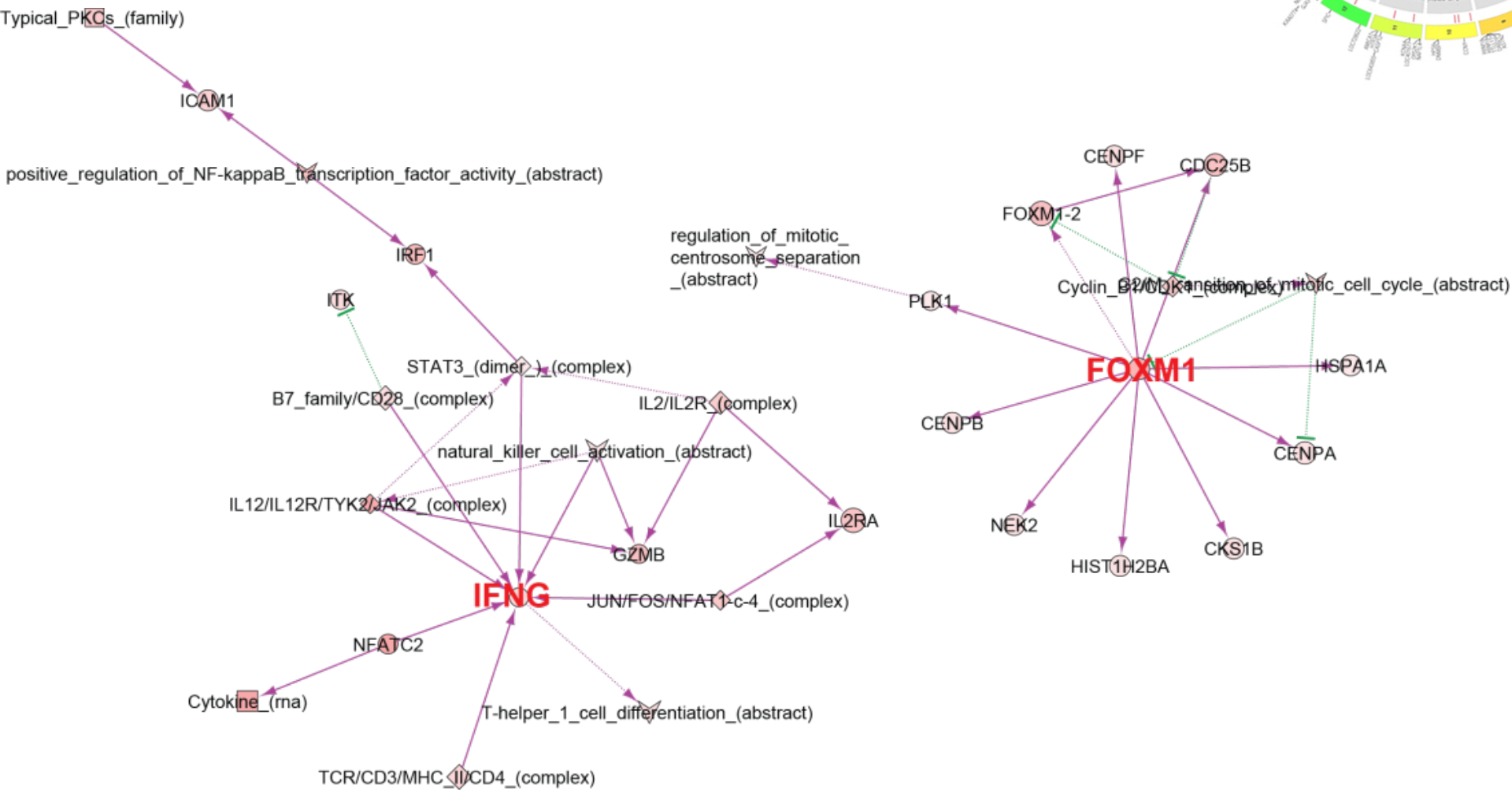
PARADIGM analysis identifies IFNG and FOXM1 a key pathways in ILC class 2 tumors



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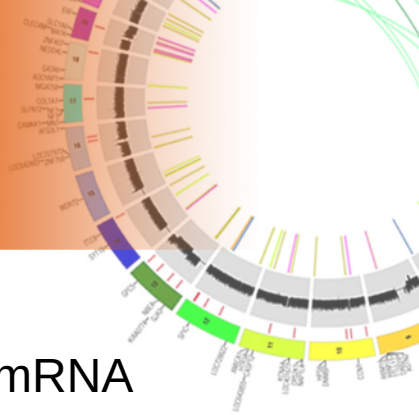
Summary

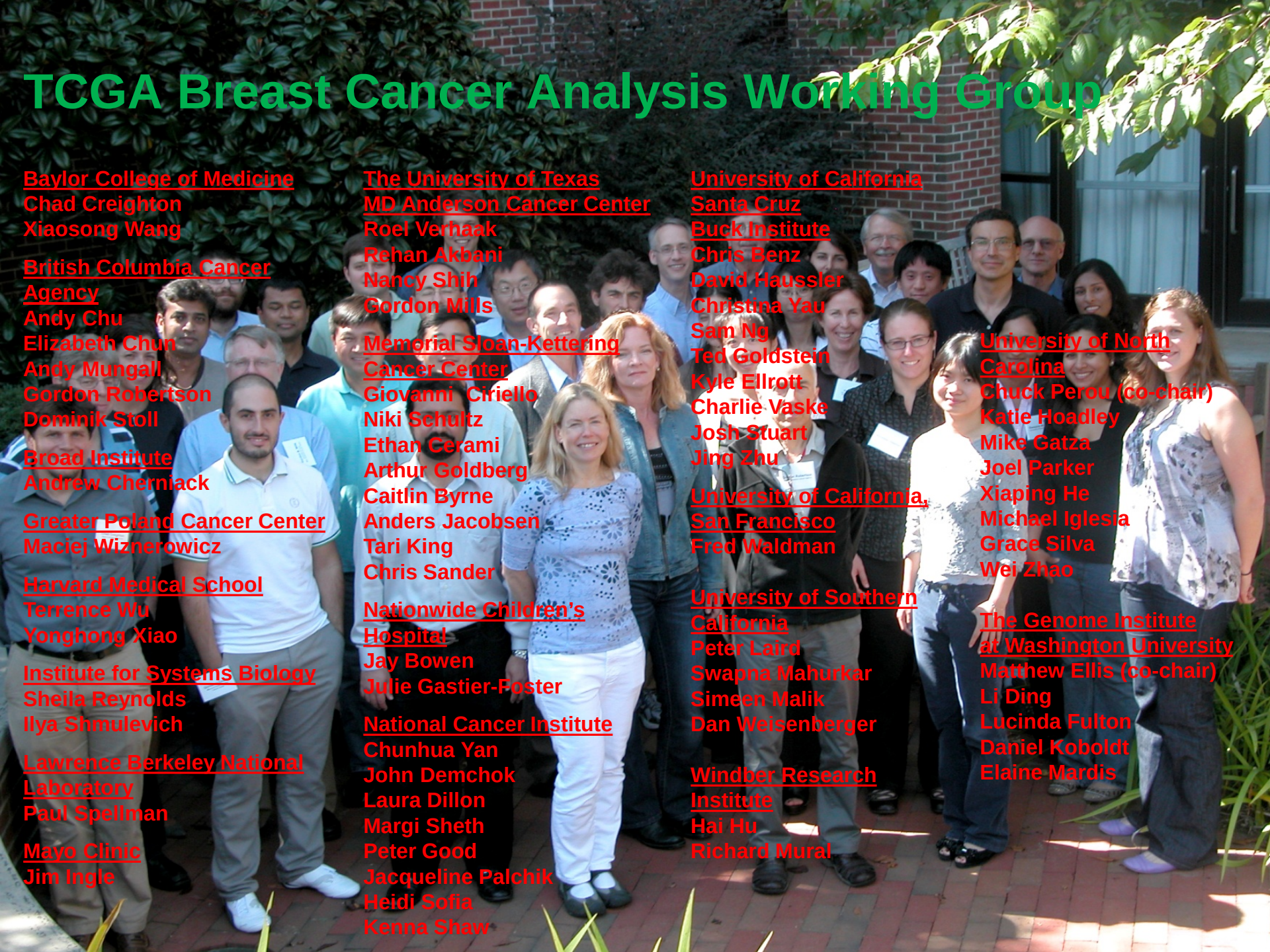


- Developed unique integrated MAF utilizing both DNA exome and mRNA sequencing

- ILC vs. IDC
  - FOXA1, CDH1 mutations associated with ILC
  - GATA3 mutation associated with IDC
  - Altered signaling: CDH1, Myc, p53/DNA damage, immune signaling
  - Identified differentially expressed miRNA and methylation

- ILC classes
  - Class 1 associated with Reactive subtype
  - Class 2 immune component and highly proliferative

TCGA Breast Cancer Analysis Working Group



Baylor College of Medicine
Chad Creighton
Xiaosong Wang

British Columbia Cancer Agency
Andy Chu
Elizabeth Chun
Andy Mungall
Gordon Robertson
Dominik Stoll

Broad Institute
Andrew Cherniack

Greater Poland Cancer Center
Maciej Wiznerowicz

Harvard Medical School
Terrence Wu
Yonghong Xiao

Institute for Systems Biology
Sheila Reynolds
Ilya Shmulevich

Lawrence Berkeley National Laboratory
Paul Spellman

Mayo Clinic
Jim Ingle

The University of Texas MD Anderson Cancer Center
Roel Verhaak
Rehan Akbani
Nancy Shih
Gordon Mills

Memorial Sloan-Kettering Cancer Center
Giovanni Ciriello
Niki Schultz
Ethan Cerami
Arthur Goldberg
Caitlin Byrne
Anders Jacobsen
Tari King
Chris Sander

Nationwide Children's Hospital
Jay Bowen
Julie Gastier-Foster

National Cancer Institute
Chunhua Yan
John Demchok
Laura Dillon
Margi Sheth
Peter Good
Jacqueline Palchik
Heidi Sofia
Kenna Shaw

University of California Santa Cruz
Buck Institute
Chris Benz
David Haussler
Christina Yau
Sam Ng
Ted Goldstein
Kyle Ellrott
Charlie Vaske
Josh Stuart
Jing Zhu

University of California, San Francisco
Fred Waldman

University of Southern California
Peter Laird
Swapna Mahurkar
Simeen Malik
Dan Weisenberger

Windber Research Institute
Hai Hu
Richard Mural

University of North Carolina
Chuck Perou (co-chair)
Katie Hoadley
Mike Gatza
Joel Parker
Xiaping He
Michael Iglesia
Grace Silva
Wei Zhao

The Genome Institute at Washington University
Matthew Ellis (co-chair)
Li Ding
Lucinda Fulton
Daniel Koboldt
Elaine Mardis