Current Concepts of Molecular Portraits of Human Breast Tumors

Katherine A. Hoadley
Department of Genetics
Lineberger Comprehensive Cancer Center
The University of North Carolina at Chapel Hill

Molecular portraits of human breast tumours

Charles M. Perou*†, Therese Sørlie†‡, Michael B. Eisen*, Matt van de Rijn§, Stefanie S. Jeffrey‖, Christian A. Rees*, Jonathan R. Pollack¶, Douglas T. Ross¶, Hilde Johnsen‡, Lars A. Akslen#, Øystein Fluge☆, Alexander Pergamenschikov*, Cheryl Williams*, Shirley X. Zhu§, Per E. Lønning, Anne-Lise Børresen-Dale‡, Patrick O. Brown¶†† & David Botstein***

** Department of Genetics, Stanford University School of Medicine, Stanford, California 94305, USA*
‡ Department of Genetics, The Norwegian Radium Hospital, N-0310 Montebello Oslo, Norway
§ Department of Pathology, Stanford University School of Medicine, Stanford, California 94305, USA
‖ Department of Surgery, Stanford University School of Medicine, Stanford, California 94305, USA
¶ Department of Biochemistry, Stanford University School of Medicine, Stanford, California 94305, USA
 # Department of Pathology, The Gade Institute, Haukeland University Hospital, N-5021 Bergen, Norway
☆ Department of Molecular Biology, University of Bergen, N-5020 Bergen, Norway
*** Department of Oncology, Haukeland University Hospital, N-5021 Bergen, Norway*
†† Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, California 94305, USA
† These authors contributed equally to this work

Perou et al., Nature, 2000 (PMID:10963602)

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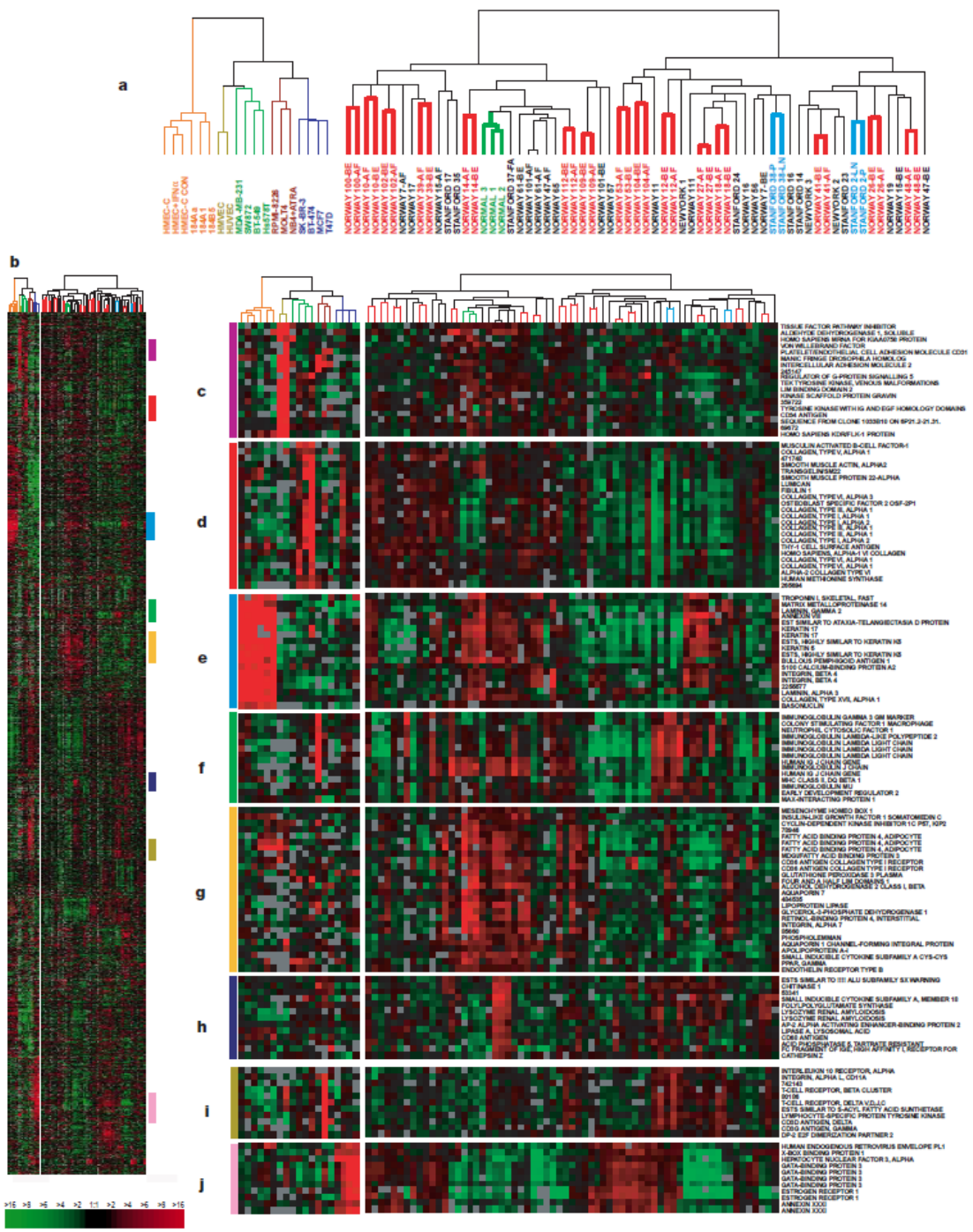


Endothelial

Stromal/fibroblasts

Breast Basal epithelial

B-cell

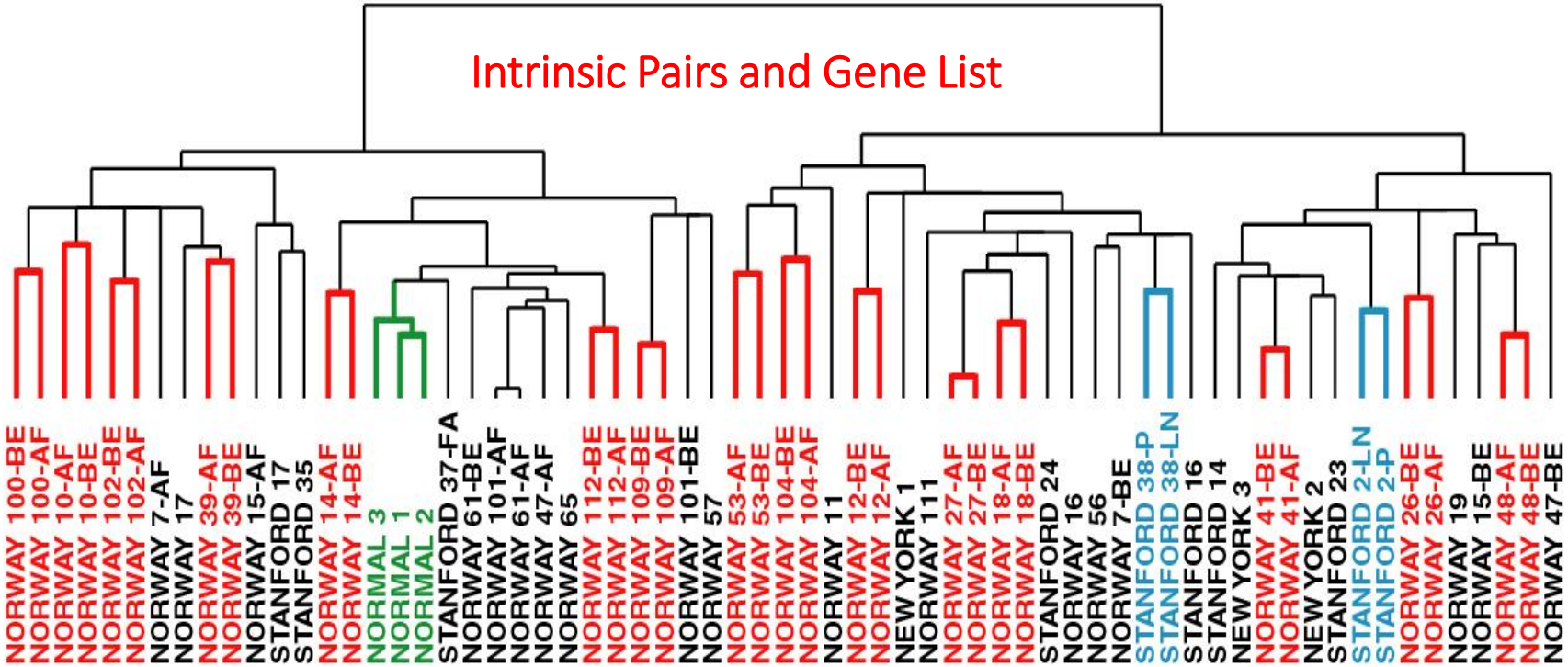
Adipose-enriched/normal breast

macrophage

T-cell

Breast luminal epithelial

Intrinsic Pairs and Gene List



22 tumor pairs tested (20 "before and after" doxorubicin pairs)

A. 15/20 "before and after" pairs were on the same terminal dendrogram branch

B. 2/2 tumor/lymph node metastasis pairs were on the same dendrogram branch

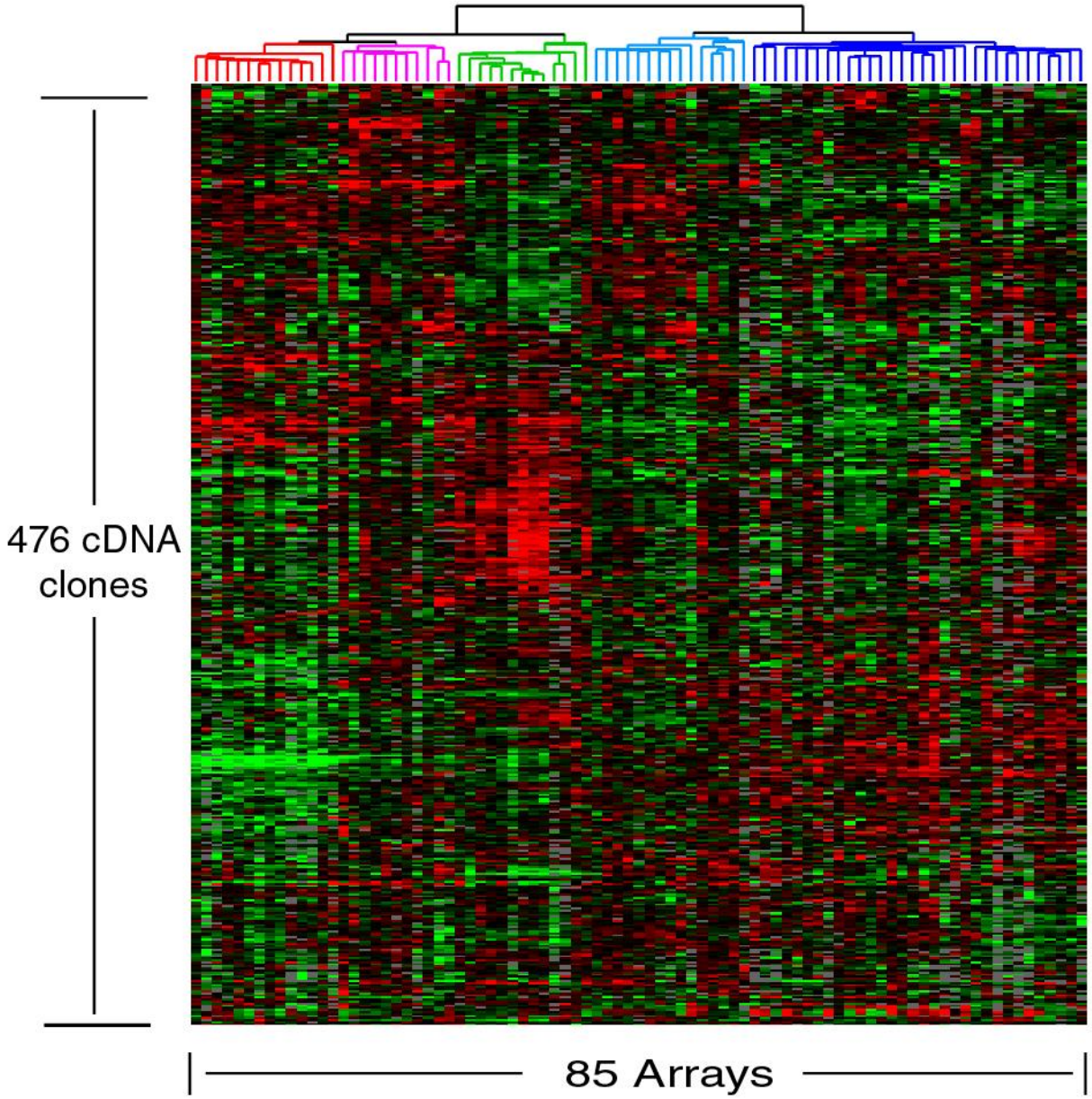
C. 3/20 "before and after" pairs had the "after" sample in the normal breast branch

D. 2/20 "before and after" pairs were not grouped together

E. 3/3 normal breast samples were on the same dendrogram branch

Perou et al., Nature, 2000 (PMID:10963602)

Sørlie et al., PNAS 19, 10869-74 (2001)



"Intrinsic" gene set on 78 single tumor samples

high variance across tumors

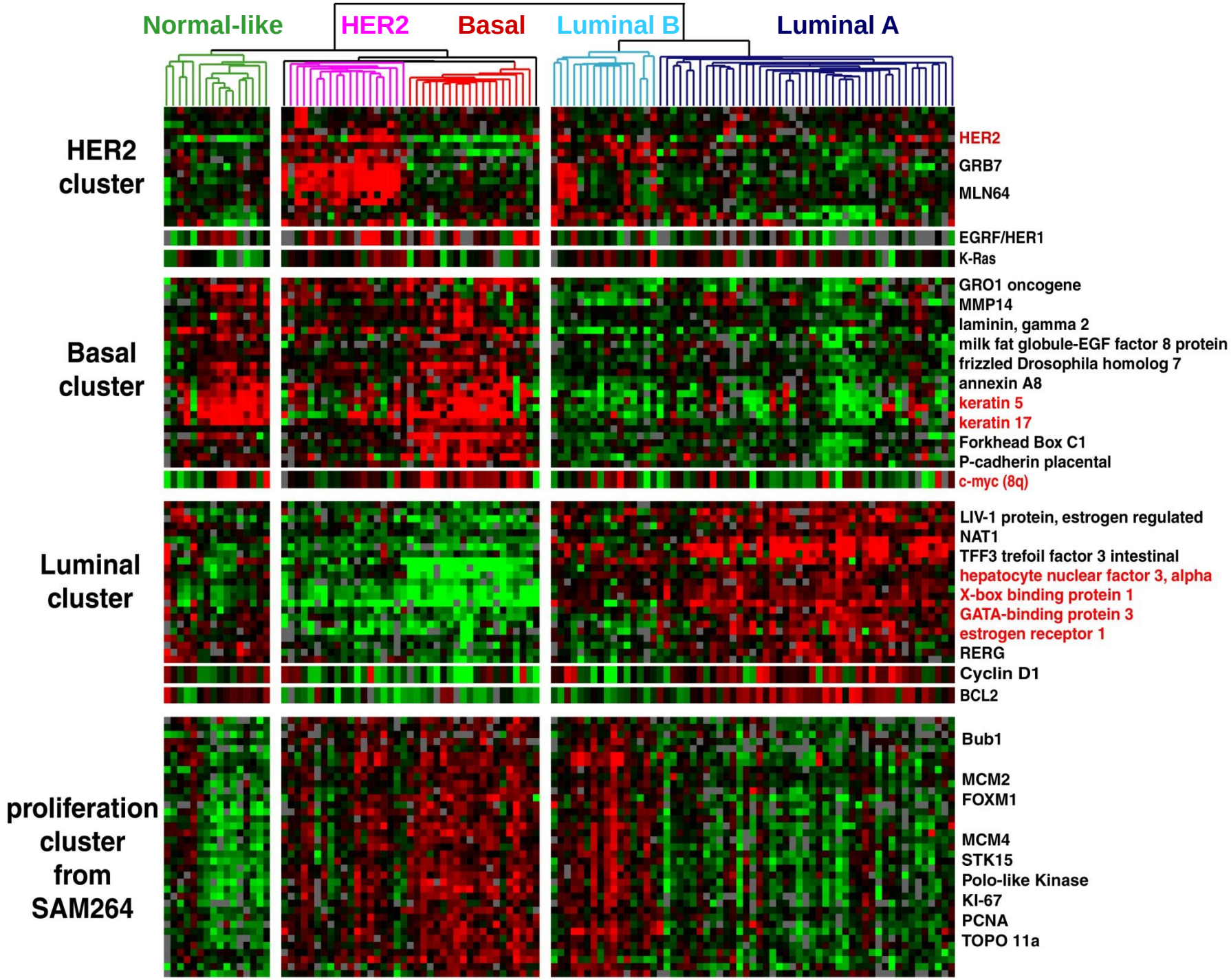
low variance across pairs

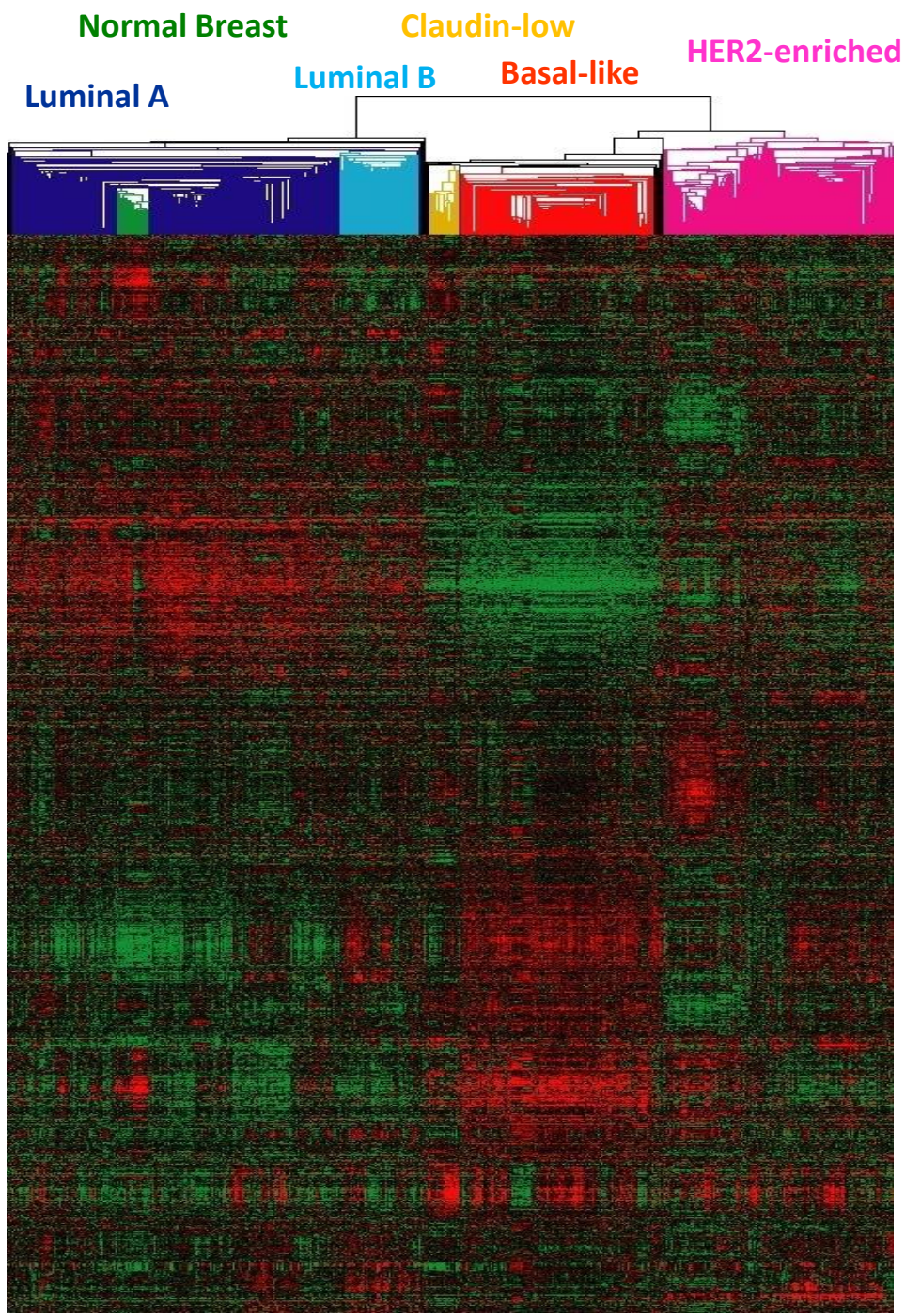
= above average

= average

= below average

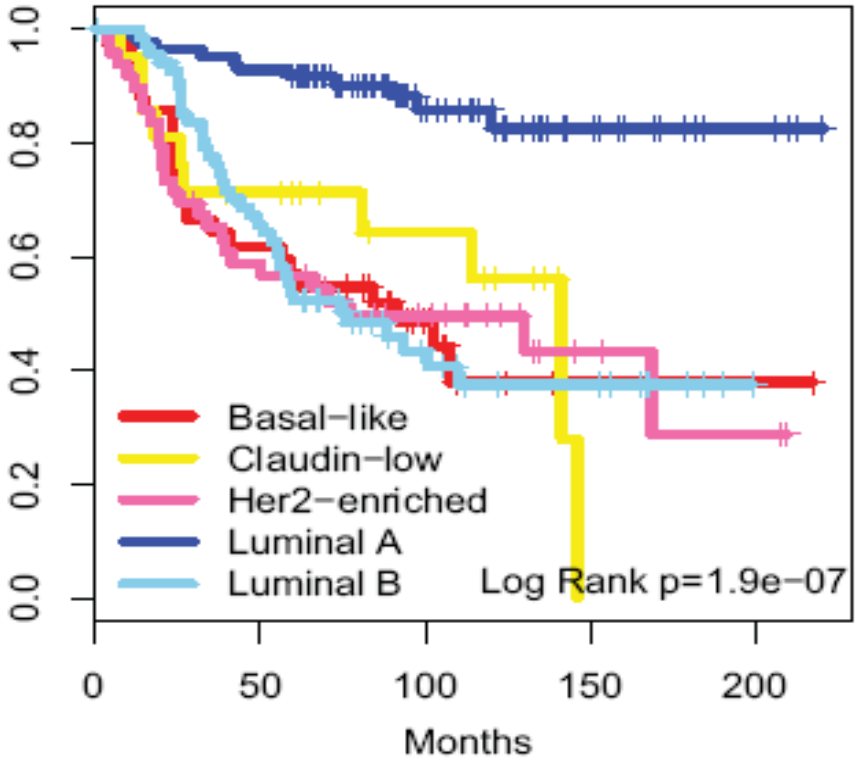
= missing or filtered data


Normal-like
HER2
Basal
Luminal B
Luminal A
HER2 cluster
HER2
GRB7
MLN64
EGRF/HER1
K-Ras
Basal cluster
GRO1 oncogene
MMP14
laminin, gamma 2
milk fat globule-EGF factor 8 protein
frizzled Drosophila homolog 7
annexin A8
keratin 5
keratin 17
Forkhead Box C1
P-cadherin placental
c-myc (8q)
Luminal cluster
LIV-1 protein, estrogen regulated
NAT1
TFF3 trefoil factor 3 intestinal
hepatocyte nuclear factor 3, alpha
X-box binding protein 1
GATA-binding protein 3
estrogen receptor 1
RERG
Cyclin D1
BCL2
proliferation cluster from SAM264
Bub1
MCM2
FOXM1
MCM4
STK15
Polo-like Kinase
KI-67
PCNA
TOPO 11a



Intrinsic Subtypes

Perou et al., Nature, 2000
Sorlie et al., PNAS, 2001
Sorlie et al., PNAS, 2003
Hu et al., BMC Genomics, 2006
Herschkowitz et al., GB, 2007
Parker et al., JCO, 2009



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ORIGINAL REPORT

Supervised Risk Predictor of Breast Cancer Based on Intrinsic Subtypes

Joel S. Parker, Michael Mullins, Maggie C.U. Cheang, Samuel Leung, David Voduc, Tammi Vickery, Sherri Davies, Christiane Fauron, Xiaping He, Zhiyuan Hu, John F. Quackenbush, Inge J. Stijleman, Juan Palazzo, J.S. Marron, Andrew B. Nobel, Elaine Mardis, Torsten O. Nielsen, Matthew J. Ellis, Charles M. Perou, and Philip S. Bernard

From the Lineberger Comprehensive Cancer Center and Departments of Genetics, Pathology and Laboratory Medicine, and Department of Statistics and Operations Research, Carolina Center for Genome Sciences, University of North Carolina at Chapel Hill, Chapel Hill, NC; Department of Pathology, University of Utah Health Sciences Center; ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, UT; Genetic Pathology Evaluation Centre, Department of Pathology, Vancouver Coastal Health Research Institute; Departments of Pathology and Radiation Oncology, British Columbia Cancer Agency; Department of Pathology, University of British Columbia, Vancouver, British Columbia, Canada; Genome Sequencing Facility and Division of Oncology, Department of Medicine, Washington University School of Medicine, St Louis, MO; and Department of Pathology, Thomas Jefferson University, Philadelphia, PA.

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Supported by the Huntsman Cancer Institute/Foundation (P.S.B.), the ARUP Institute for Clinical and Experimental Pathology (P.S.B.), a National Cancer Institute (NCI) Strategic Partnering to Evaluate Cancer Signatures Grant No. U01 CA114722-01 (M.J.E.), an NCI Breast SPORE Grant No. P50-CA58223-09A1 (C.M.P.), a St Louis Affiliate of the Susan G. Komen Foundation CRAFT grant (M.J.E.), and the Breast Cancer Research Foundation (C.M.P. and M.J.E.). Additional support provided by the TRAC facility and Informatics at the Huntsman Cancer Center, supported in part by the NCI Cancer Center Support Grant No. P30 CA42014-19, and the tissue procurement facility at the Alvin J. Siteman Cancer

ABSTRACT

Purpose
To improve on current standards for breast cancer prognosis and prediction of chemotherapy benefit by developing a risk model that incorporates the gene expression–based "intrinsic" subtypes luminal A, luminal B, HER2-enriched, and basal-like.

Methods
A 50-gene subtype predictor was developed using microarray and quantitative reverse transcriptase polymerase chain reaction data from 189 prototype samples. Test sets from 761 patients (no systemic therapy) were evaluated for prognosis, and 133 patients were evaluated for prediction of pathologic complete response (pCR) to a taxane and anthracycline regimen.

Results
The intrinsic subtypes as discrete entities showed prognostic significance (P = 2.26E-12) and remained significant in multivariable analyses that incorporated standard parameters (estrogen receptor status, histologic grade, tumor size, and node status). A prognostic model for node-negative breast cancer was built using intrinsic subtype and clinical information. The C-index estimate for the combined model (subtype and tumor size) was a significant improvement on either the clinicopathologic model or subtype model alone. The intrinsic subtype model predicted neoadjuvant chemotherapy efficacy with a negative predictive value for pCR of 97%.

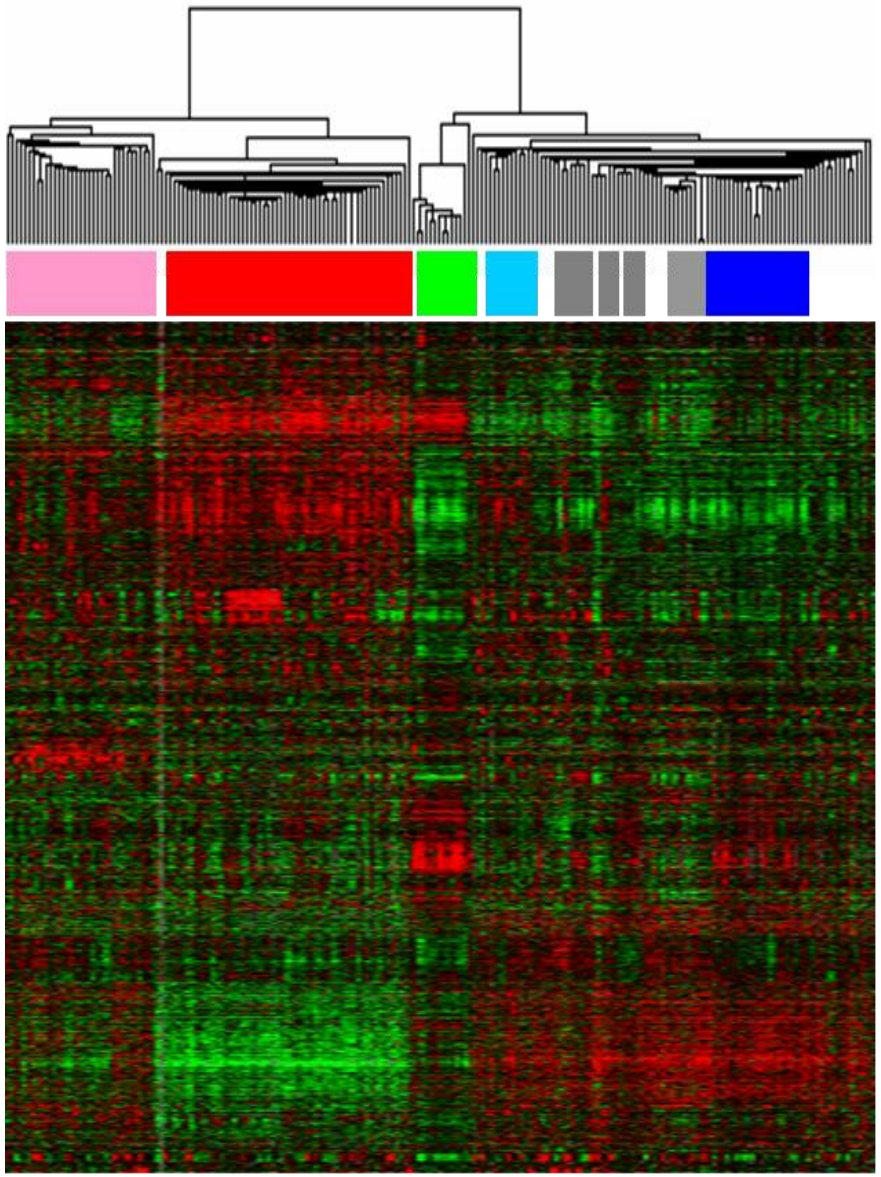
Conclusion
Diagnosis by intrinsic subtype adds significant prognostic and predictive information to standard parameters for patients with breast cancer. The prognostic properties of the continuous risk score will be of value for the management of node-negative breast cancers. The subtypes and risk score can also be used to assess the likelihood of efficacy from neoadjuvant chemotherapy.

J Clin Oncol 27:1160-1167. © 2009 by American Society of Clinical Oncology

Intrinsic Subtype Clinical Assay Development

Parker et al., JCO, February 9, 2009

1. Assayed 191 patients/tumors with
    A. full-genome microarrays using RNA from frozen tumor materials (~25,000 genes)
    B. qRT-PCR using RNA from FFPE materials for ~160 genes
2. Objectively identified “prototypical” samples
    A. Hierarchical clustering analysis using 4 intrinsic lists combined (~2000 genes) and the 191 tumors
    B. Ran “SigClust” (Liu et al., JASA 2008) to identify statistically significant groups/subtypes of tumors, thereby assigning subtype labels and identifying prototypical samples



Intrinsic Subtype Clinical Assay Development

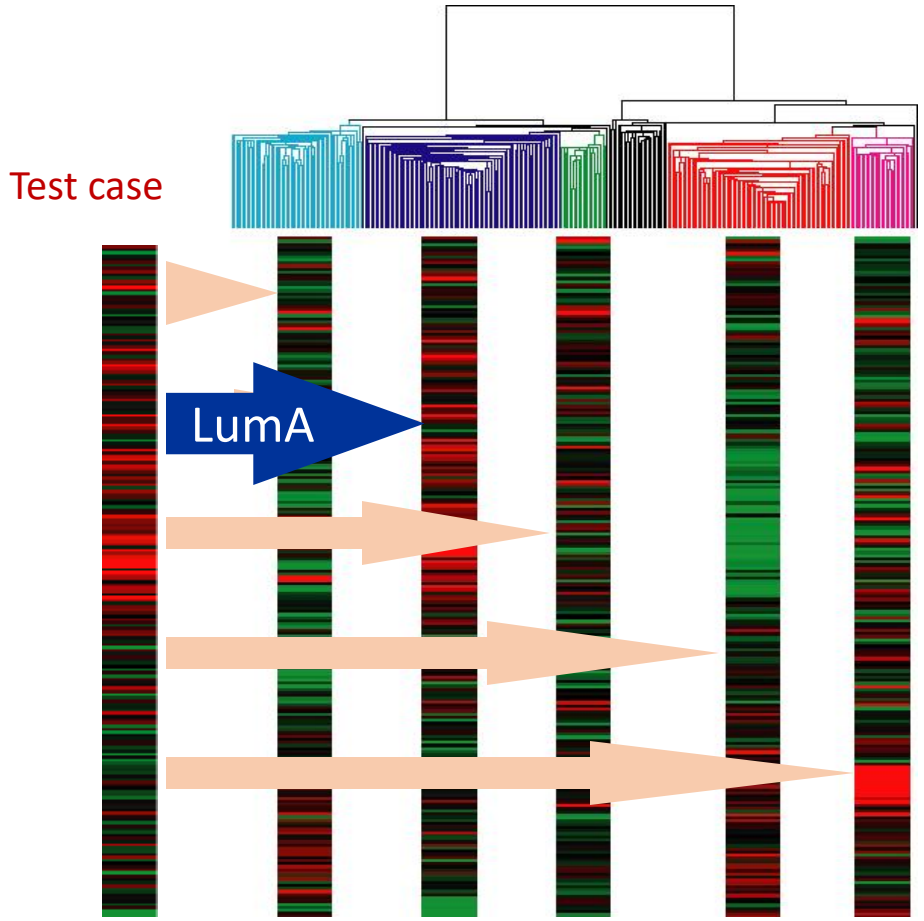
Parker et al., JCO, February 9, 2009

3. **Constructed classification model in qRT-PCR (FFPE) data using prototypical samples**

   A. **Calculate each subtype's average centroid/profile using the 161 genes measured by qRT-PCR with the subtype assignment provided by the microarray data**

   B. **Compare a test case to each centroid and assign a label to the test case based upon the most similar centroid**

   C. **Perform multiple cycles of cross-validation over ever decreasing numbers of genes to find the smallest gene list with highest concordance to the 2000 gene list microarray-based classifications**



Dudoit & Fridlyand JASA 2002
Storey et al. Bioinformatics 2006
Tibshirani et al. PNAS 2002

Intrinsic Subtype Clinical Assay Development

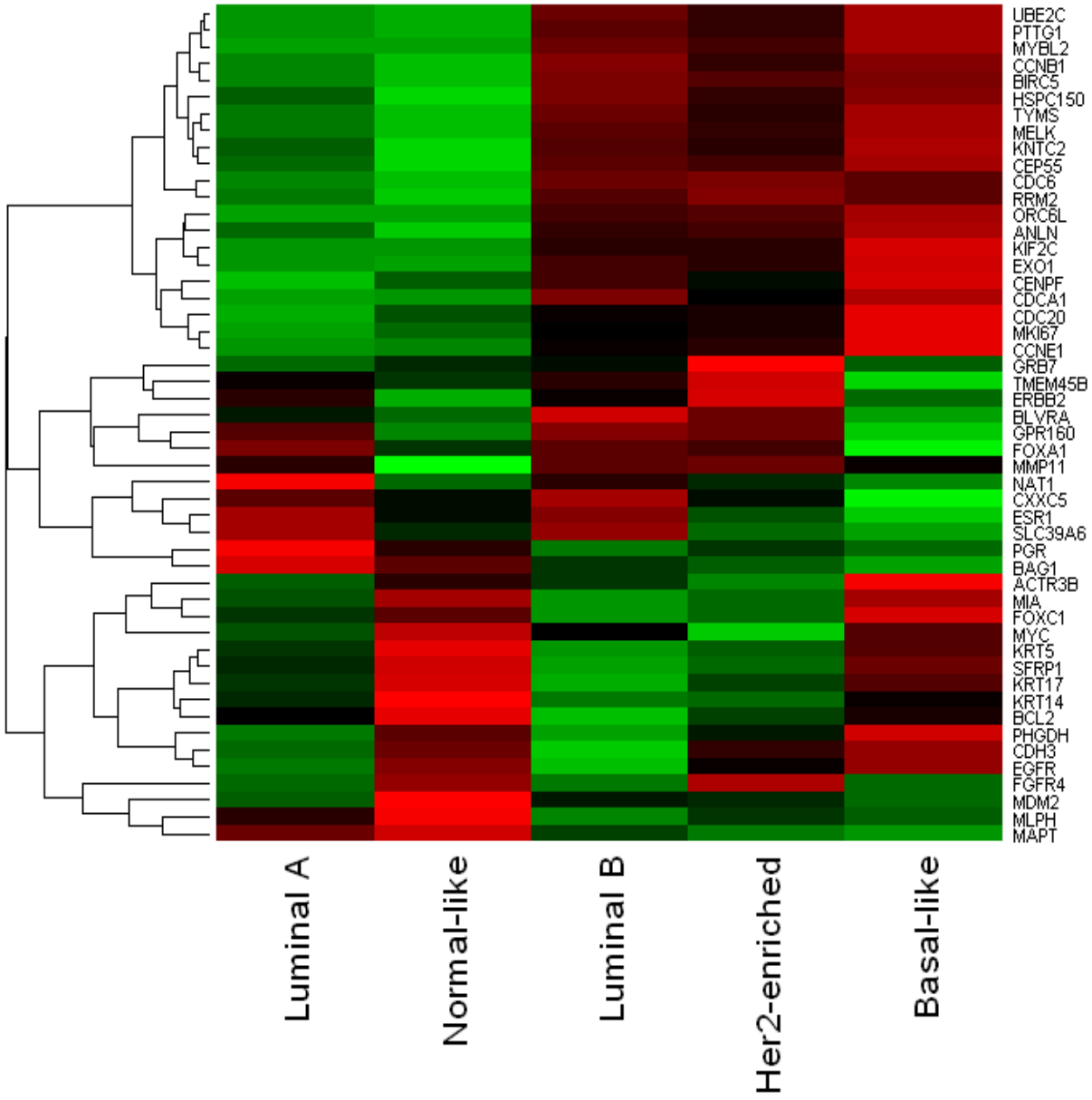
Parker et al., JCO, February 9, 2009

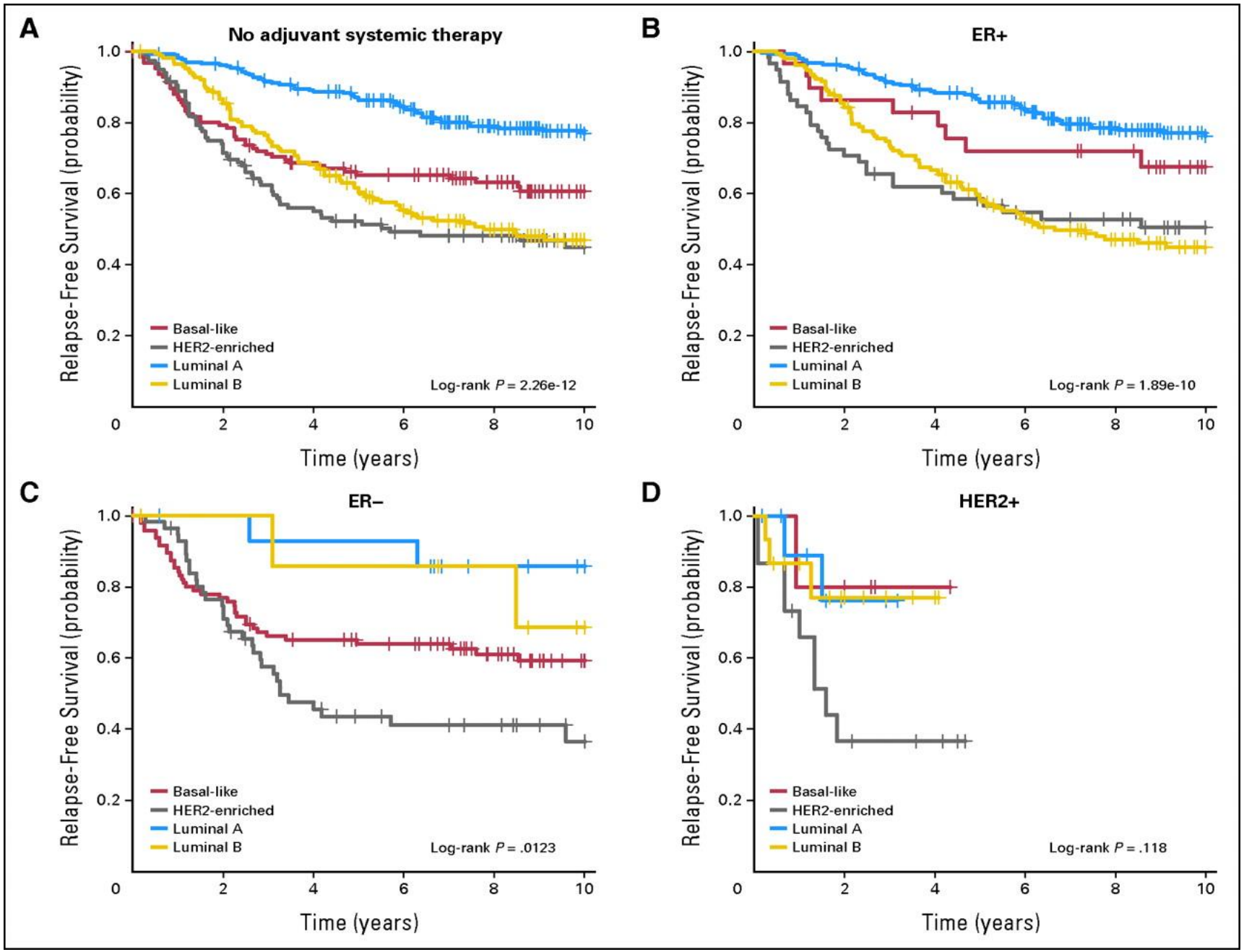
4. **The final classifier consists of 50 genes and 5 centroids.**
   (provided at https://genome.unc.edu/)

5. **The CV classification accuracy of the 50 genes versus the 2000 genes was 93%.**

6. **The assay is called the**

“PAM50”

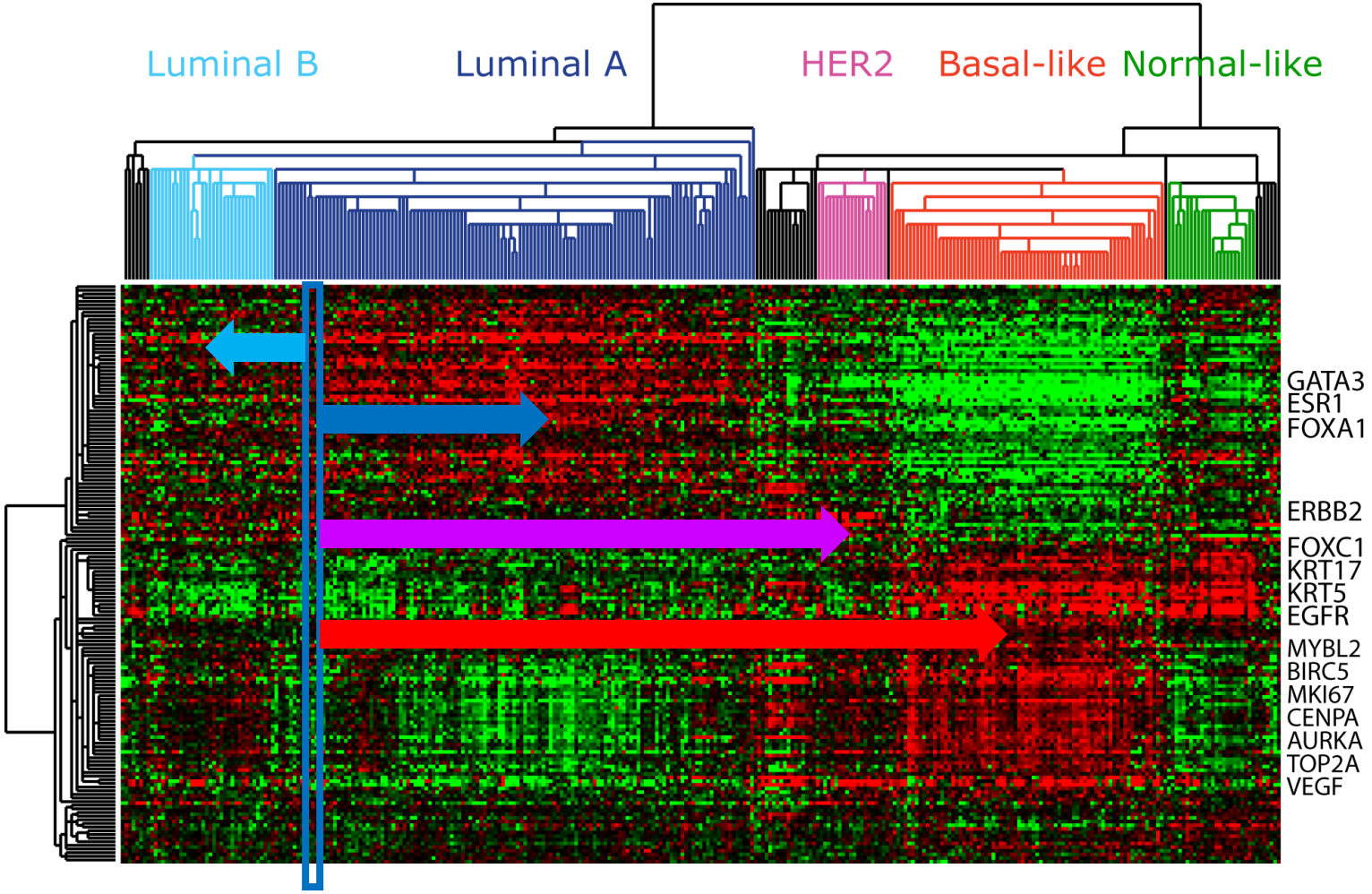




Parker et al. J Clin Oncol; 27:1160-1167 2009

JOURNAL OF CLINICAL ONCOLOGY

Diversity Within Subtypes



Distance of a tumor to each centroid/subtype as a genomic summary

Prognostic Risk Classification Strategy (ROR)

- **Similarity to the subtypes are used as variables in the prognostic model where the outcome is Risk of Relapse (ROR):**

(Model 1) ROR-S = β_1*Basal + β_2*HER2 + β_3*LumA + β_4*LumB

(Model 2) ROR-C = β_1*Basal + β_2*HER2 + β_3*LumA + β_4*LumB + β_5*Tumor Size

(Model 3) ROR-X = β_1*Basal + β_2*HER2 + β_3*LumA + β_4*LumB + β_5*Size + β_6*Node

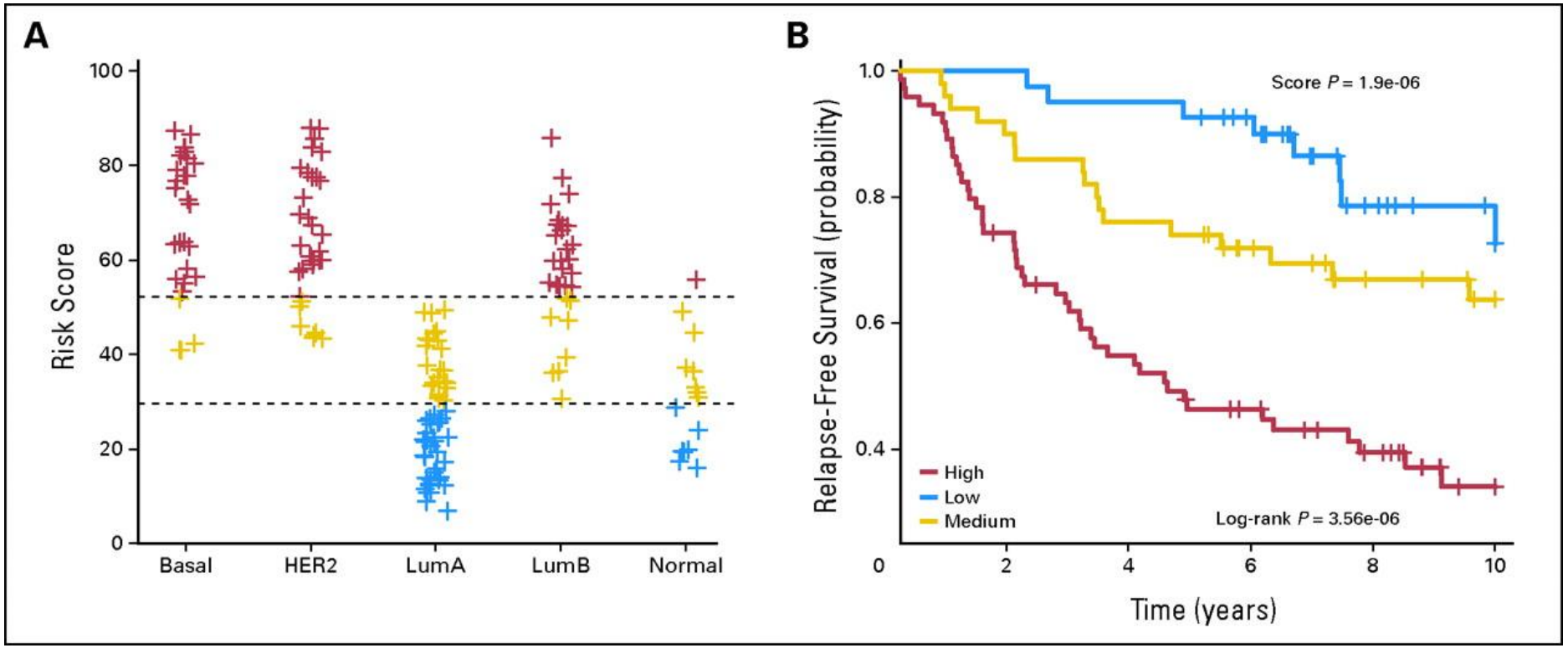
- **Weights for each term are learned from a training data set using a Cox model with Ridge Regression**

- **The weighted sum is assigned as the ROR score for a test case and a threshold may be applied for class assignment**

Ridge regression with Cox model: Tibshirani, Statistics in Medicine 1997
Comparative study: Bovelstad et al. Bioinformatics 2007

Parker et al. J Clin Oncol; 27:1160-1167 2009

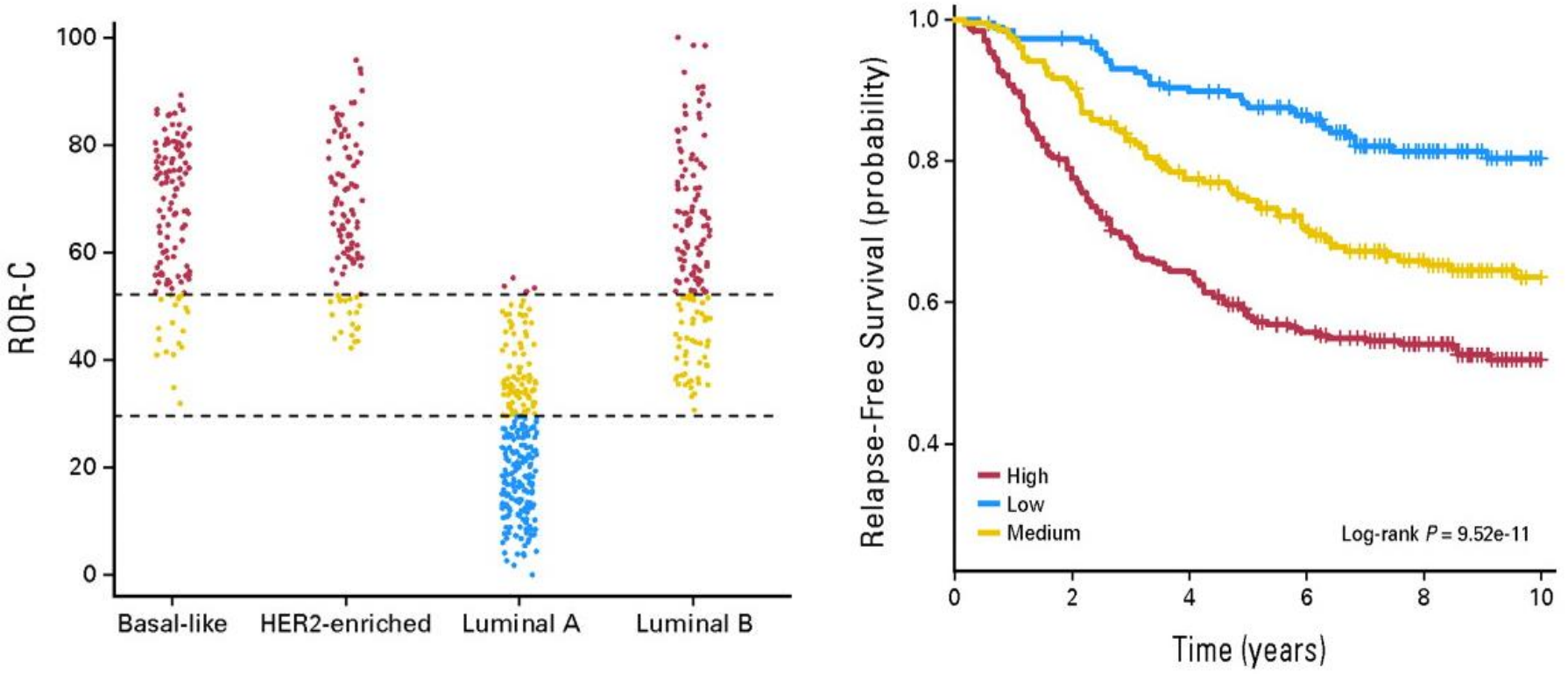
Risk Classification on the Training Set



Model trained on NKI no adjuvant systemic therapy and node negative patient subset with relapse free survival as the outcome and using the ROR-C (subtype+tumor size) model

Parker et al. J Clin Oncol; 27:1160-1167 2009

Risk Classification on a Test set

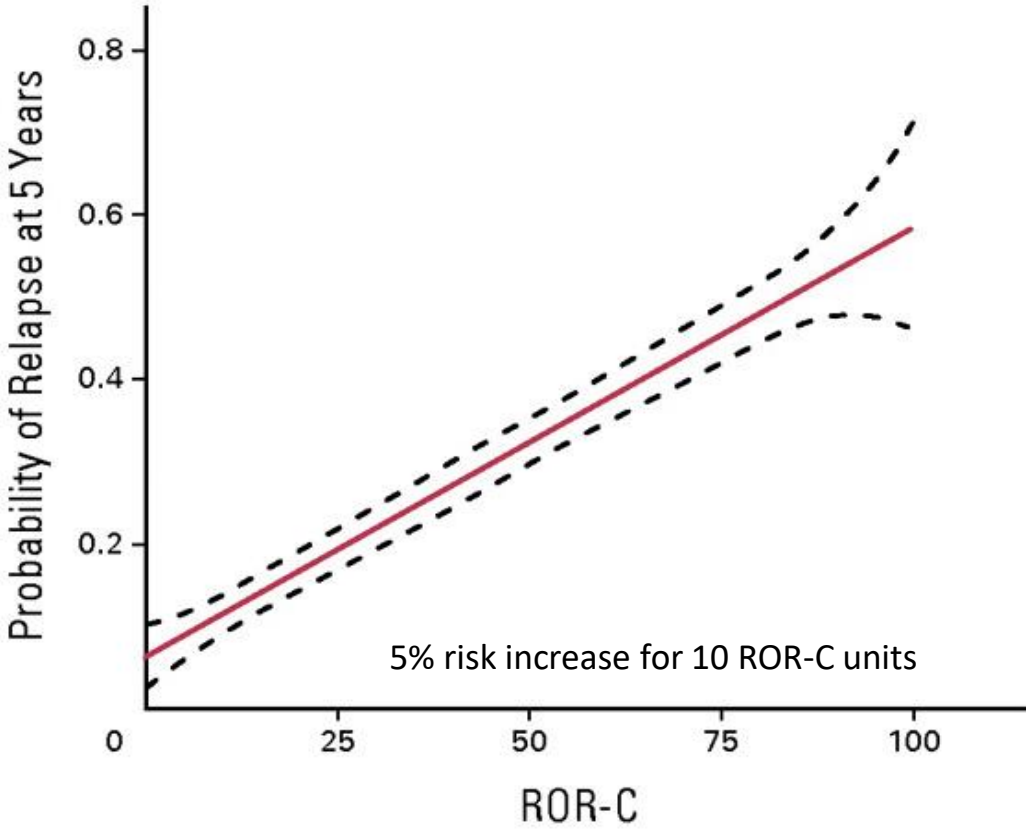


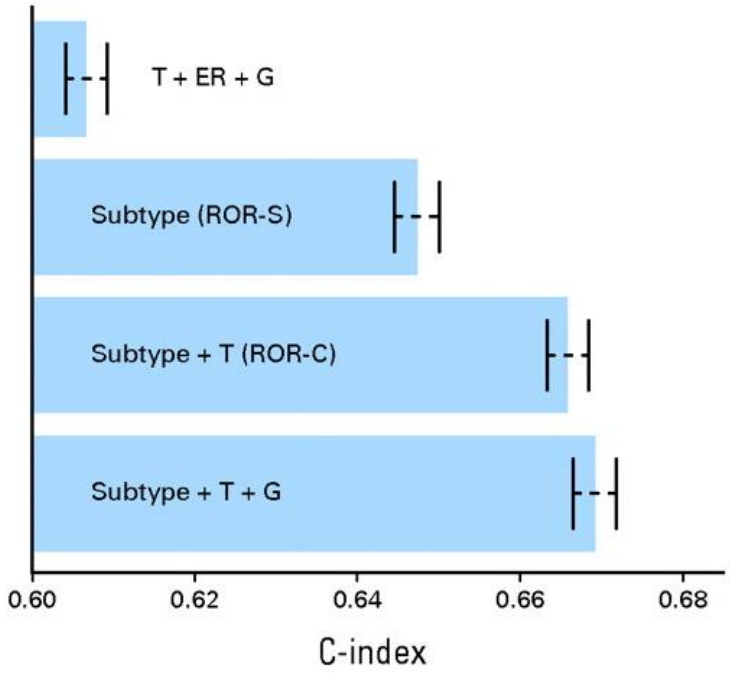
N=558 no adjuvant systemic therapy and node negative test cases

ROR-C thresholds determined from training set

Parker et al. J Clin Oncol; 27:1160-1167 2009

Risk Classification by PAM50 ROR





N=558 no adjuvant systemic therapy and node negative test cases

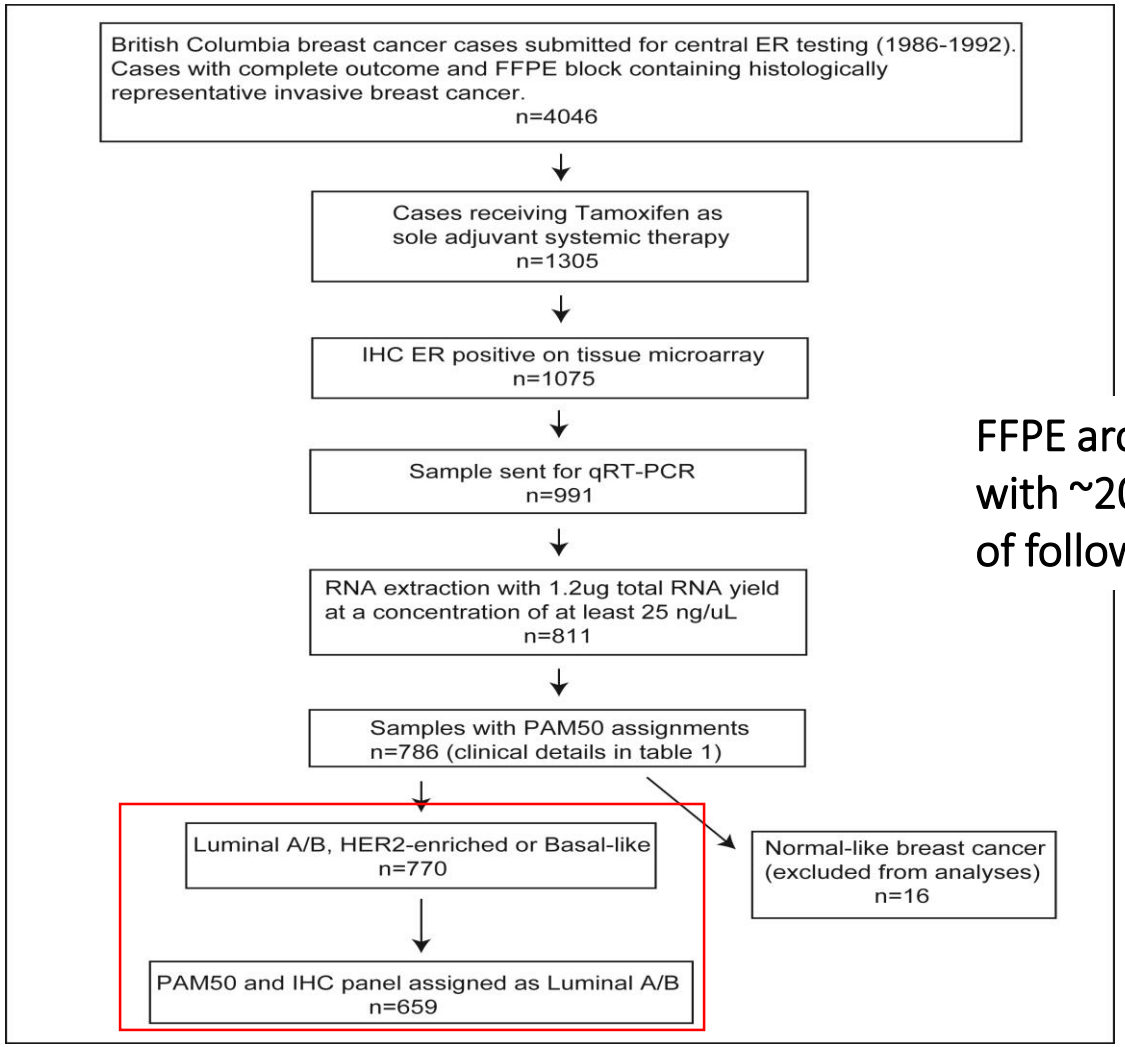
C-index: FE Harrell et al., *JAMA* 1982; 247(18).

"The c-index is the proportion of all pairs of subjects whose survival time can be ordered such that the subject with the higher predicted survival is the one who survived longer" (taken from Harrell, Regression Modeling Strategies, Springer Series in Statistics).

Parker et al. J Clin Oncol; 27:1160-1167 2009

A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in tamoxifen-treated estrogen receptor positive breast cancer

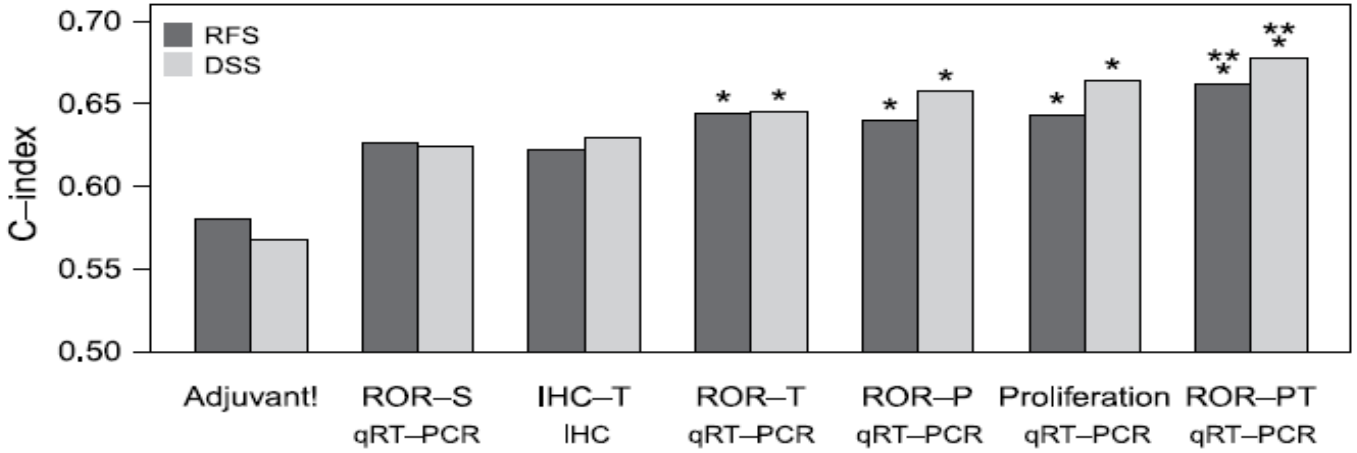
Torsten O. Nielsen, Joel S Parker, Samuel Leung, David Voduc, Mark Ebbert, Tammi Vickery,
Sherri R. Davies, Jacqueline Snider, Inge J. Stijleman, Jerry Reed, Maggie C.U. Cheang,
Elaine R. Mardis, Charles M. Perou, Philip S. Bernard, Matthew J. Ellis, Clinical Cancer Research 2010

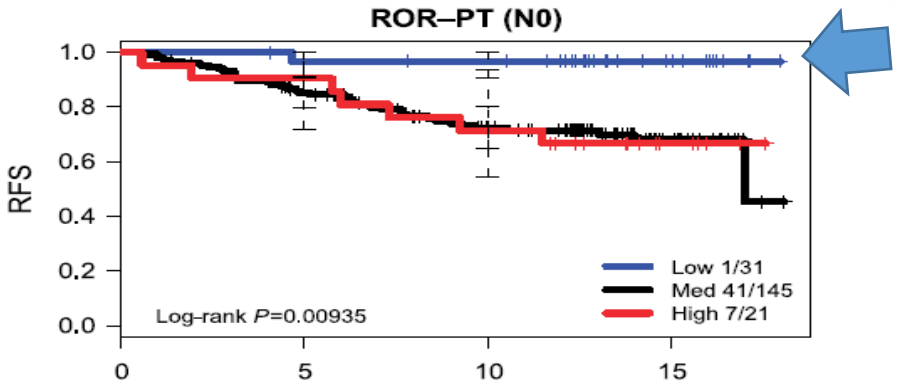


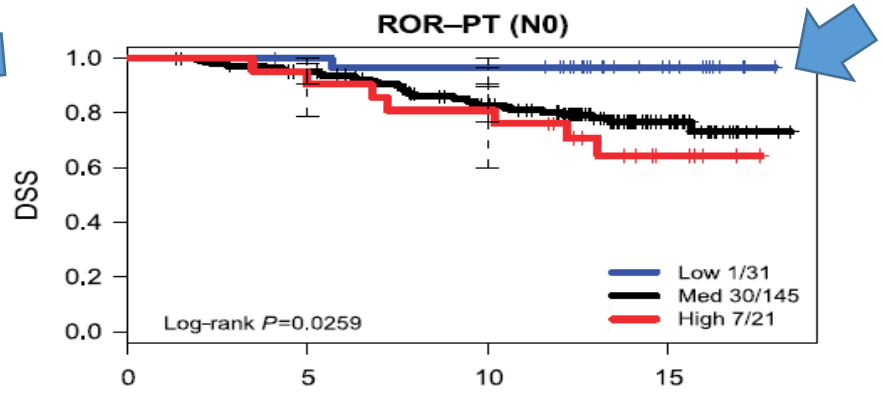
FFPE archive with ~20 years of follow up

Nielsen et al., CCR 2010 (PMID:20837693)

ER+, tamoxifen treated, node-negative patient subset







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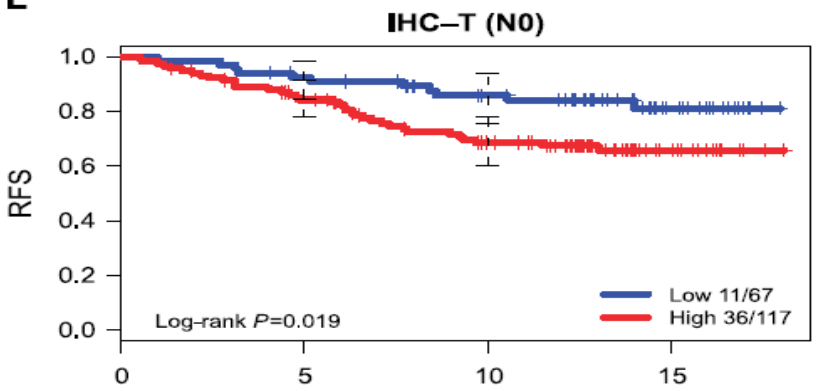
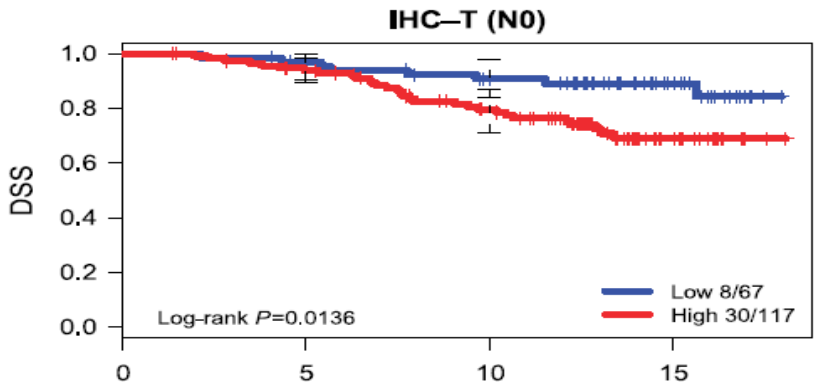
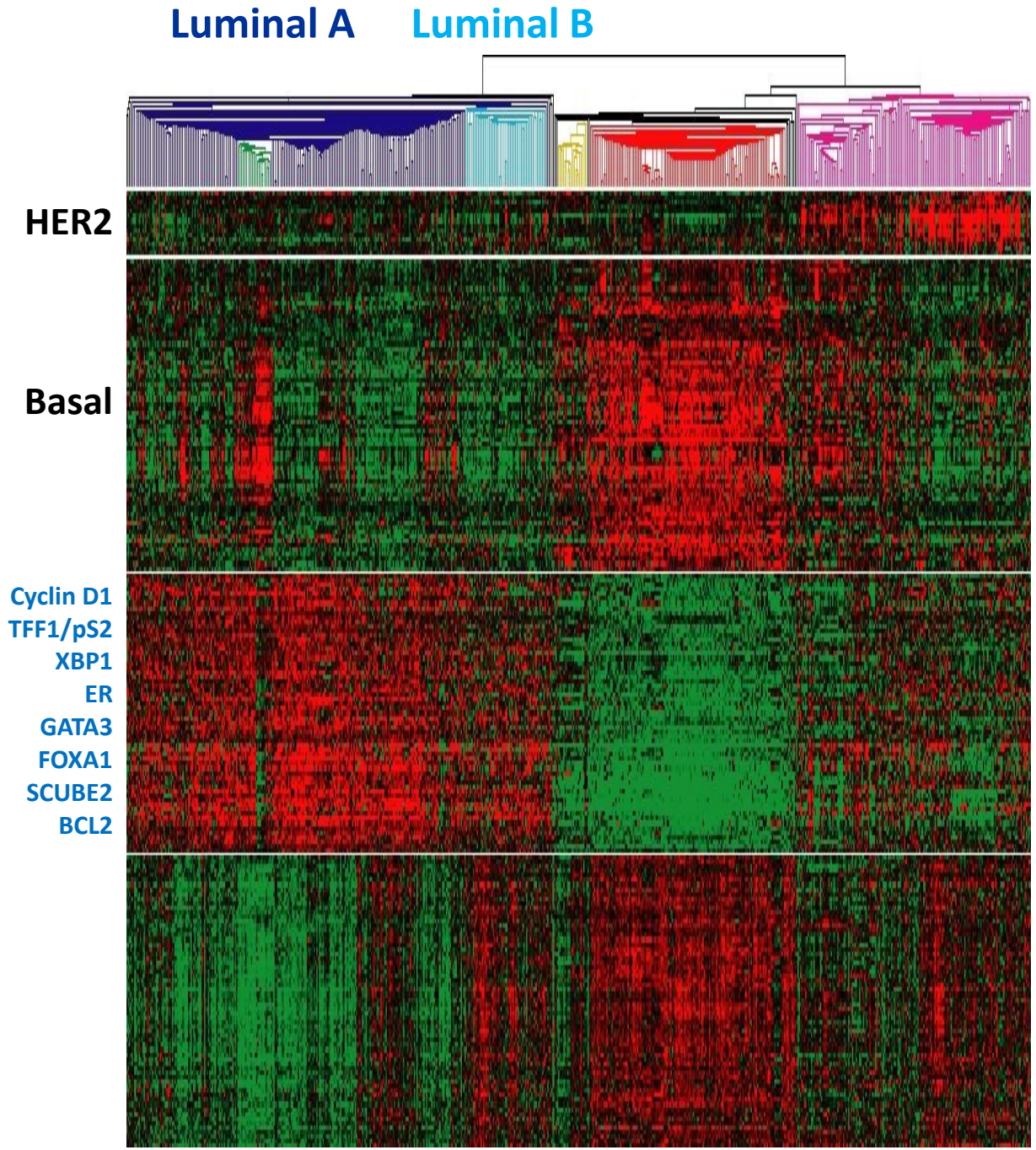




Nielsen et al., CCR 2010 (PMID:20837693)

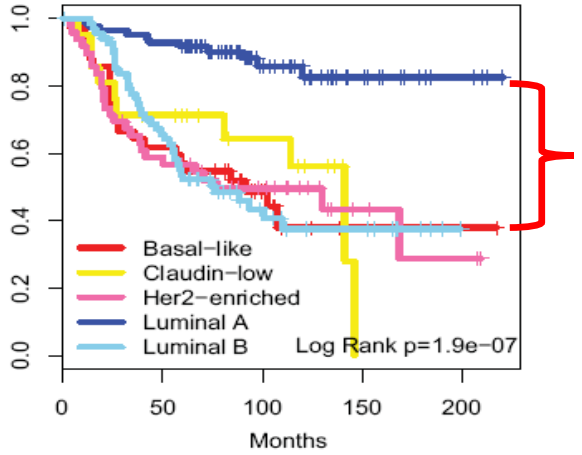


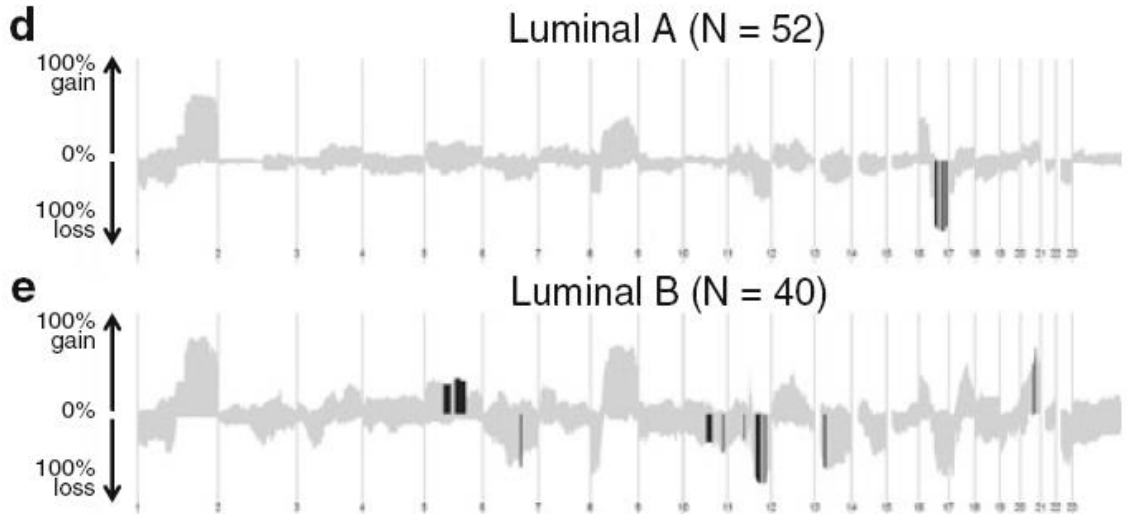
Luminal A and B

1. ~70% of Breast Cancers
2. Most are ER+ and/or PR+
3. ER-GATA3-FOXA1-XBP1 signaling

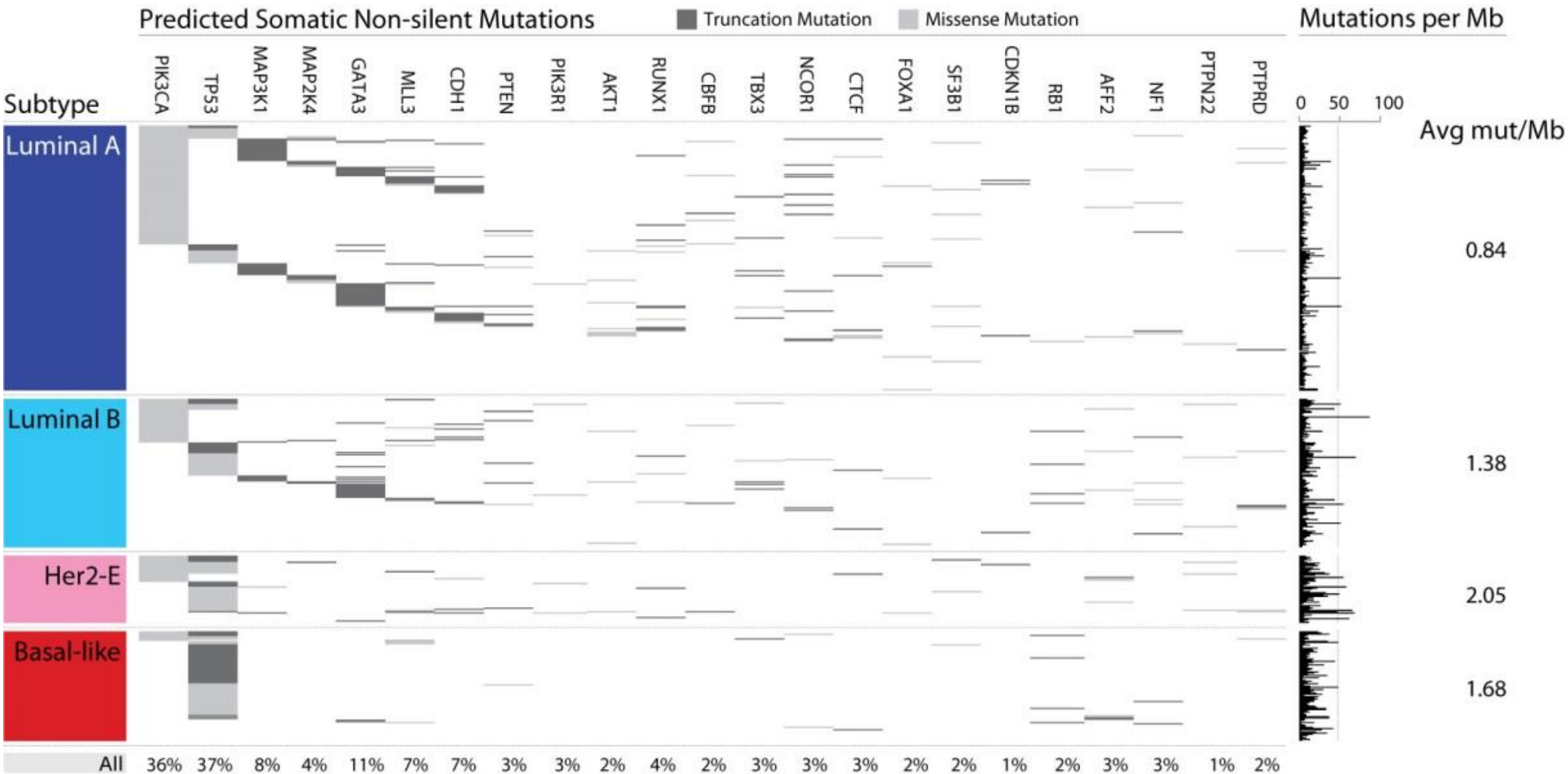
Differences between A and B

1. Levels of Luminal genes including ER and GATA3
2. proliferation rate
3. histological grade
4. p53 mutations
5. DNA amplifications
6. Survival Differences





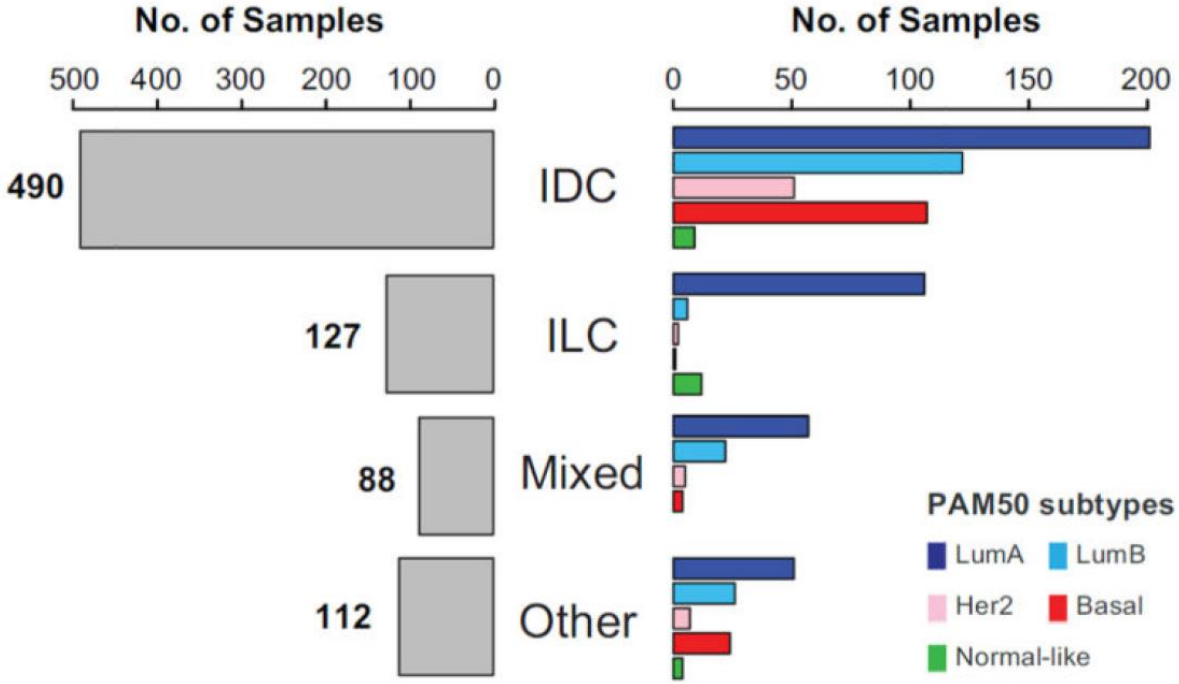
Weigman VJ et aBreast Cancer Res Treat 2011

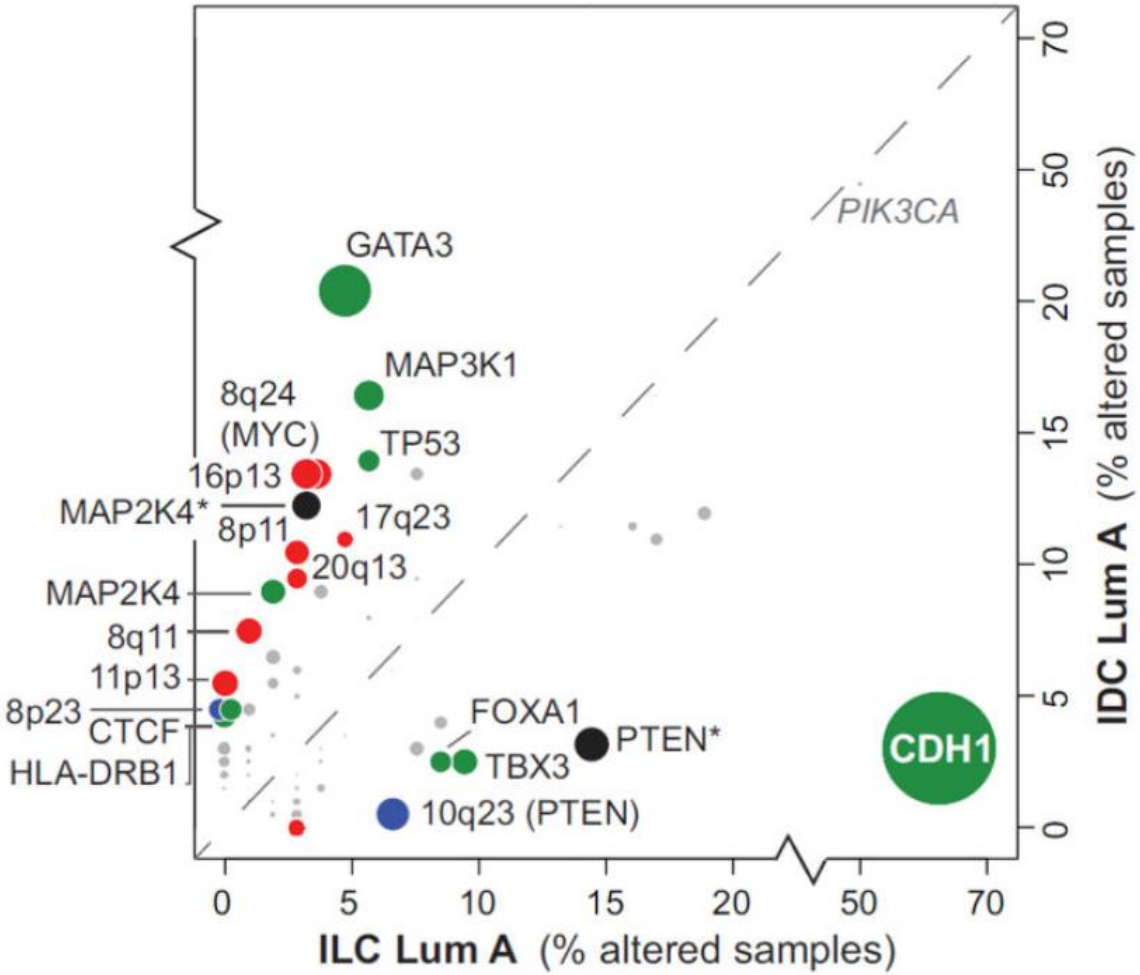


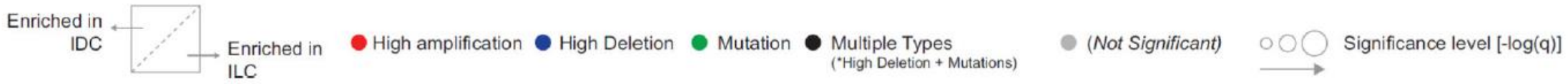
TCGA Network et al., Nature, 2012. (PMID:2300089)

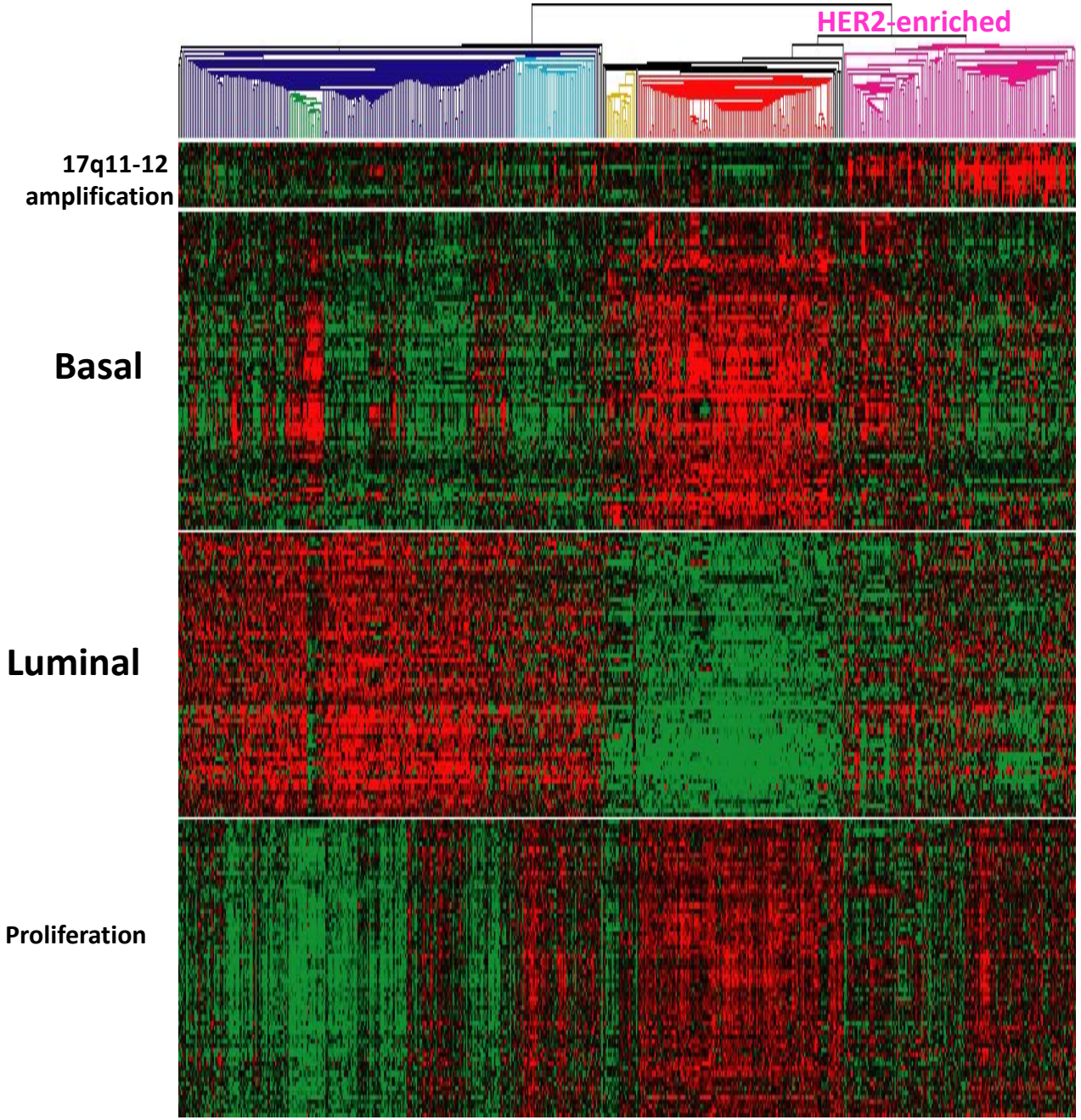
Comprehensive Molecular Portraits of Invasive Lobular Breast Cancer.

Ciriello et al. TCGA Cell 2015 (PMID: 26451490)



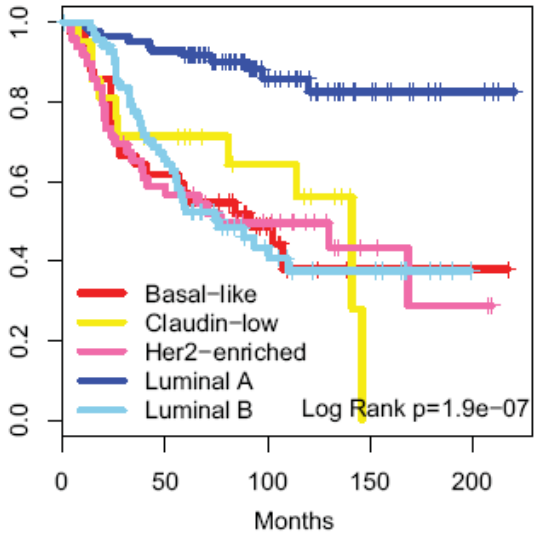




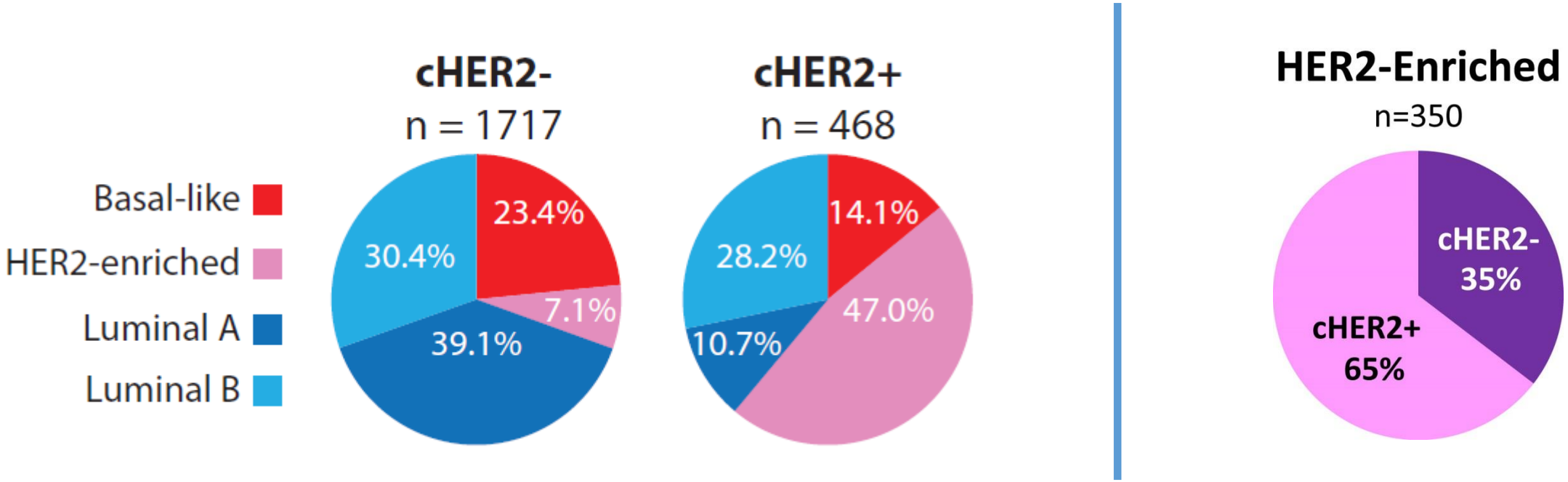


HER2-enriched subtype

1. 10-15% of tumors
2. at least 2 types of clinically defined HER2+ tumors that are the HER2-enriched and some Luminal B
3. Within HER2-enriched, not all are clinically HER2+



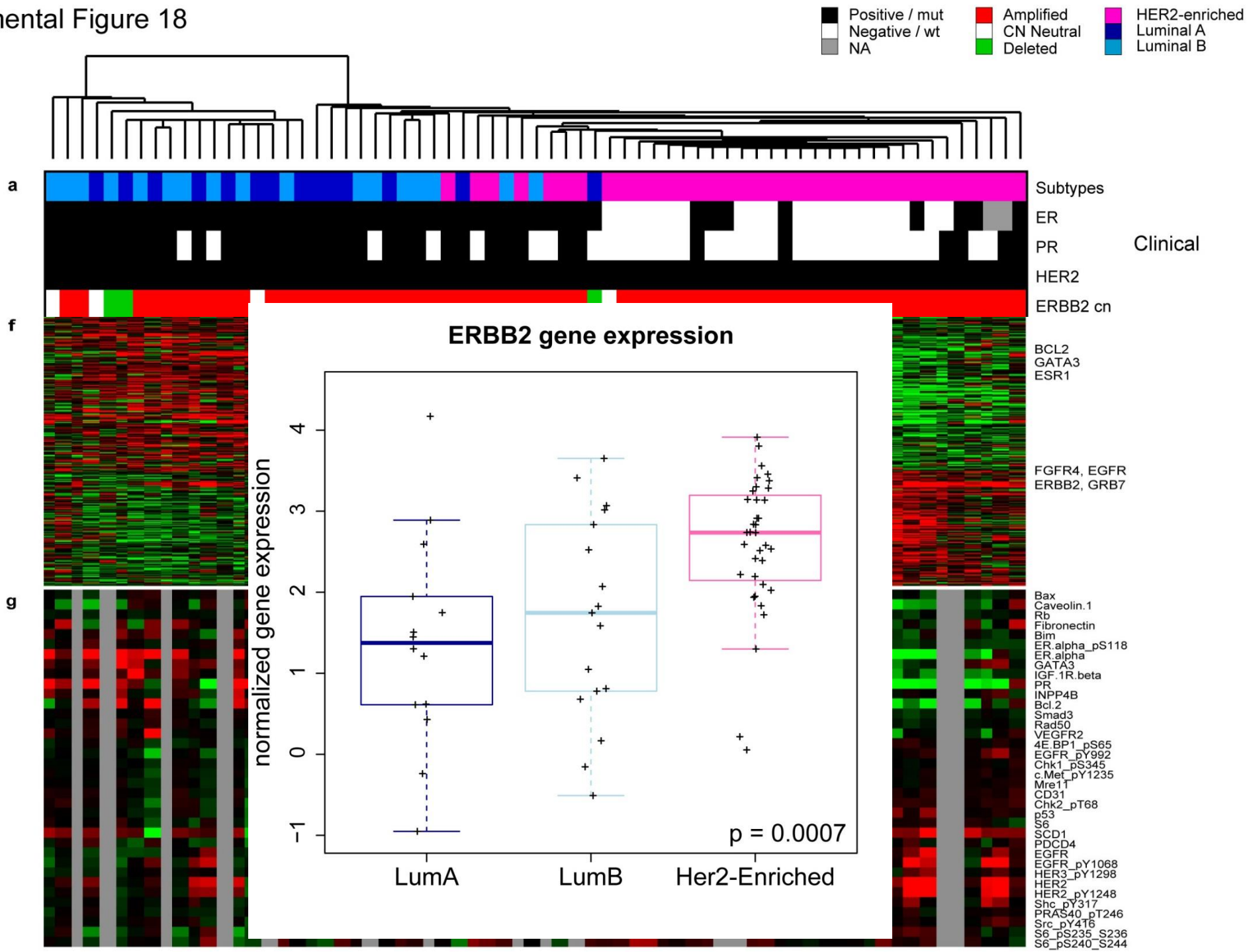
HER2-positive Breast Cancer



Clinical HER2 Status

Prat et al. JNCI (2014) PMID: 25139534

Supplemental Figure 18



Comprehensive Molecular Portraits of Human Breast Tumors. TCGA Network et al., Nature, 2012. (PMID:2300089)

Molecular Heterogeneity and Response to Neoadjuvant HER2 Targeting in CALGB 40601, a Randomized Phase III Trial of Paclitaxel Plus Trastuzumab With or Without Lapatinib.

Carey et al., JCO 2015 (PMID:26527775)

Stage II-III HER2+

N=300

- **Paclitaxel + Lapatinib x 16 weeks** → **32%**
- **Paclitaxel + Trastuzumab x 16 weeks** → **46%**
- **Paclitaxel + Trastuzumab + Lapatinib x 16 weeks** → **56%**

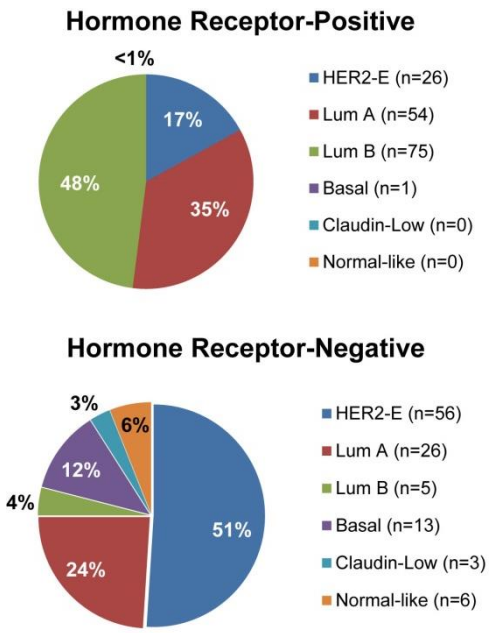
SURGERY

pCR Rate

Pretreatment Research biopsy

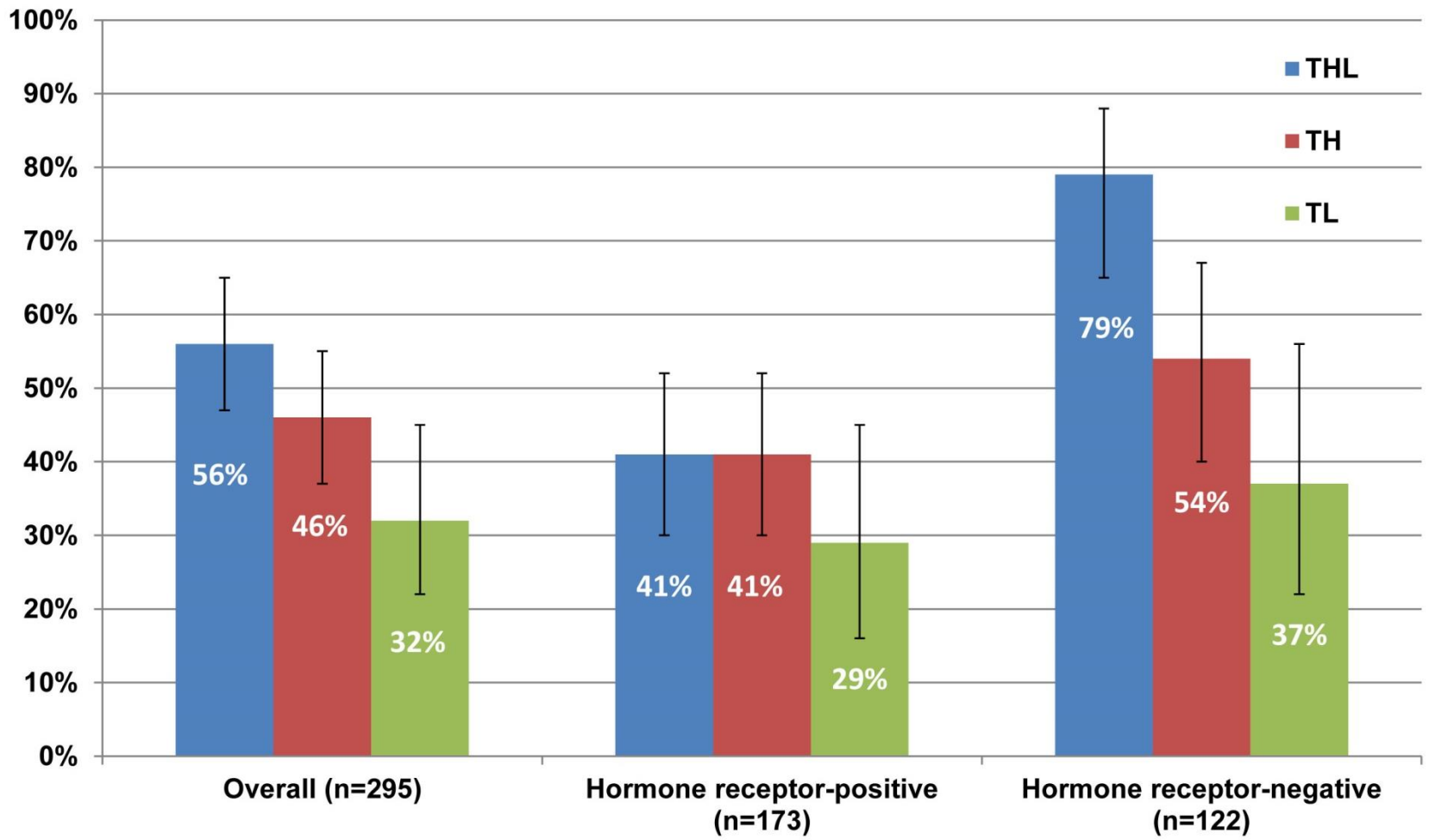
Post-treatment Research biopsy

59% Hormone Receptor-Positive

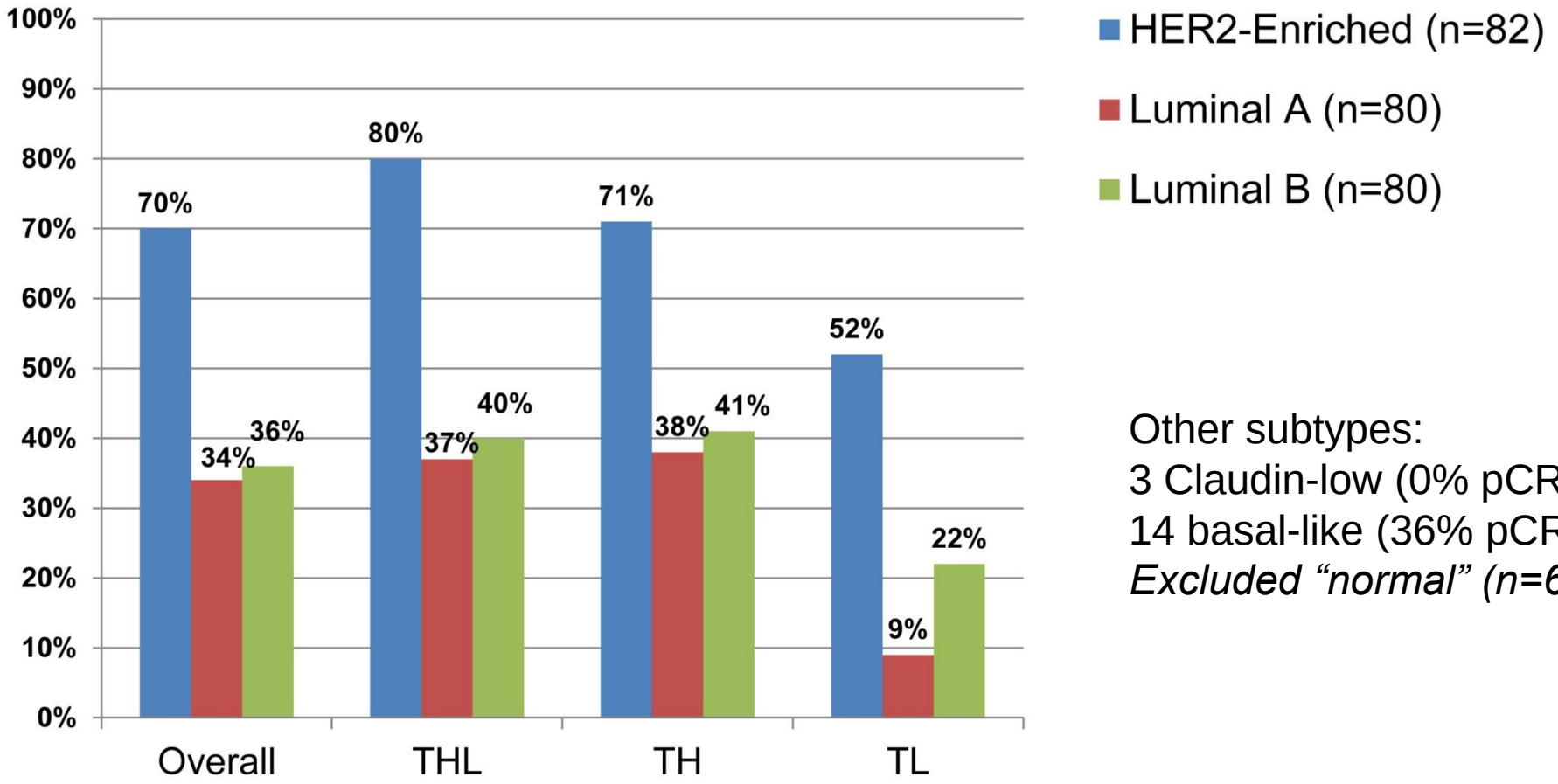


ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

pCR Rate in CALGB by Clinical Classification



pCR Rate in CALGB by Subtype



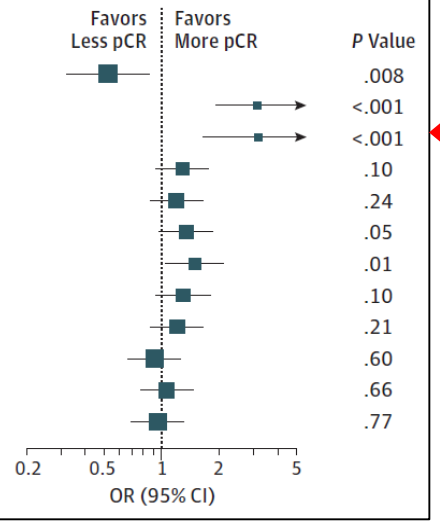
Other subtypes:
3 Claudin-low (0% pCR)
14 basal-like (36% pCR)
Excluded "normal" (n=6)

NeoALTTO

Paclitaxel + (Lapatinib, trastuzumab, or Lapatinib/Trastuzumab)

B Adjusted for clinicopathological parameters and treatment arm

Parameter	OR (95% CI)	FDR
ESR1	0.53 (0.33-0.86)	0.016
ERBB2/HER2	3.1 (1.9-5.1)	2.1×10^{-7}
HER2 enriched (PAM50)	3.2 (1.7-6.0)	9.9×10^{-4}
Immune1	1.3 (0.95-1.8)	0.085
Immune2	1.2 (0.89-1.6)	0.16
Immune3	1.3 (0.99-1.8)	0.065
Genomic Grade Index	1.5 (1.1-2.1)	0.021
Aurka	1.3 (0.95-1.8)	0.085
AKT/mTOR	1.2 (0.89-1.6)	0.16
Stroma1	0.92 (0.68-1.2)	0.36
Stroma2	1.1 (0.79-1.5)	0.36
AR	0.96 (0.70-1.3)	0.39



Fumagalli et al., JAMA Oncology 2017 (PMID:27684533)

PAMELA

Lapatinib + Trastuzumab, No Chemo

	n (%)	Univariate analysis		Multivariate analysis	
		OR (95% CI)	p value	OR (95% CI)	p value
Age (continuous variable)	NA	1 (0·97–1·02)	0·86	..	..
Tumour size (continuous variable)	NA	1 (0·96–1·01)	0·24	..	..
Tumour size					
T1	60 (35%)	1	..	..	..
T2	79 (33%)	1·19 (0·58–2·46)	0·63	..	..
T3	12 (17%)	0·48 (0·10–2·40)	0·37	..	..
Menopausal status					
Premenopausal	61 (33%)	1	..	..	..
Postmenopausal	90 (29%)	0·80 (0·40–1·62)	0·53	..	..
Nodal status					
0	98 (35%)	1	..	..	..
1–2	53 (23%)	0·55 (0·26–1·19)	0·13	..	..
Histological grade					
1	23 (74%)	1	..	1	..
2	27 (33%)	0·18 (0·05–0·60)	0·0056	0·24 (0·06–0·94)	0·041
3	101 (20%)	0·09 (0·03–0·25)	<0·0001	0·10 (0·03–0·32)	<0·0001
Histological type					
Others	21 (10%)	1	..	1	..
Ductal	130 (34%)	4·86 (1·08–21·82)	0·039	3·54 (0·66–18·86)	0·14
Hormone receptor status					
Positive	77 (18%)	1	..	1	..
Negative	74 (43%)	3·42 (1·64–7·2)	0·0011	2·27 (0·93–5·55)	0·26
Intrinsic molecular subtype					
Non-HER2-enriched	50 (10%)	1	..	1	..
HER2-enriched	101 (41%)	6·15 (2·25–16·81)	0·0004	4·04 (1·30–12·50)	0·016

OR=odds ratio. NA=not applicable.

Table 3: Logistic regression analyses of pathological complete response

Llombart-Cussac et al., Lancet Oncology, 2017 (PMID: 28238593)

VOLUME 27 · NUMBER 33 · NOVEMBER 20 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

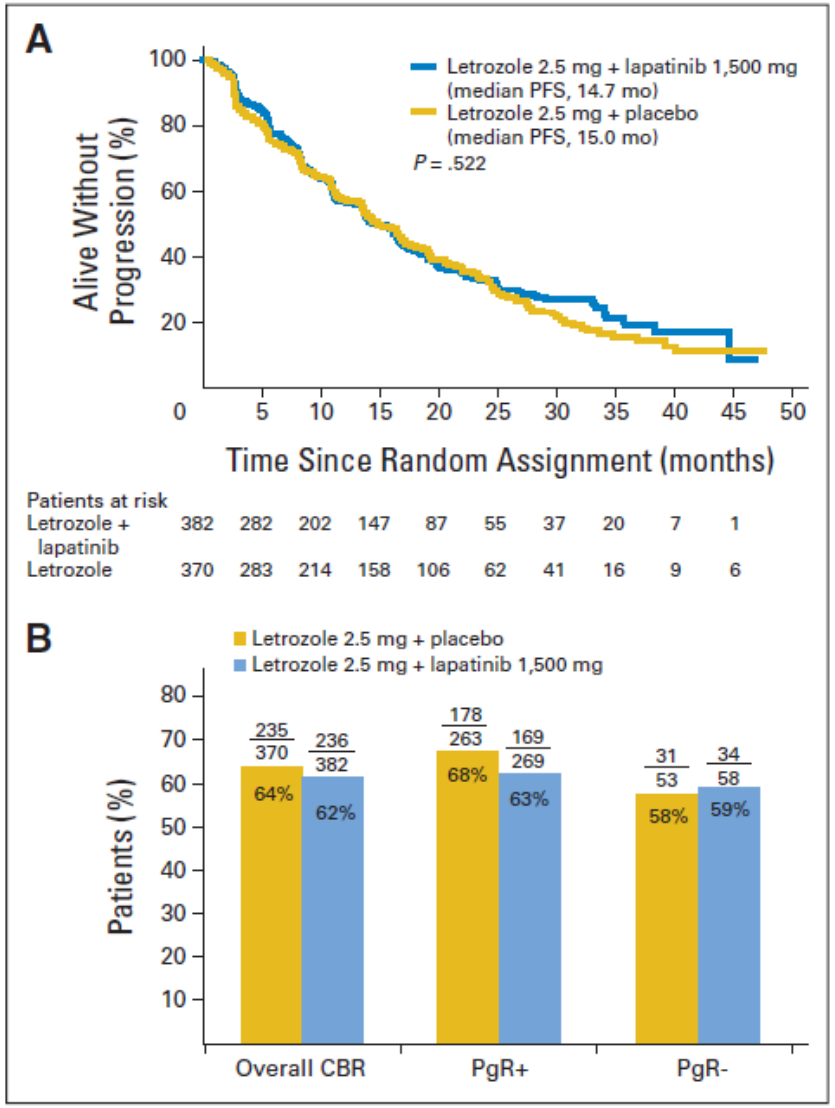
Lapatinib Combined With Letrozole Versus Letrozole and Placebo As First-Line Therapy for Postmenopausal Hormone Receptor–Positive Metastatic Breast Cancer

Stephen Johnston, John Pippen Jr, Xavier Pivot, Mikhail Lichinitser, Saeed Sadeghi, Veronique Dieras, Henry Leonidas Gomez, Gilles Romieu, Alexey Manikhas, M. John Kennedy, Michael F. Press, Julie Maltzman, Allison Florance, Lisa O'Rourke, Cristina Oliva, Steven Stein, and Mark Pegram

Phase III clinical trial
1,286 patients with HR+ metastatic disease

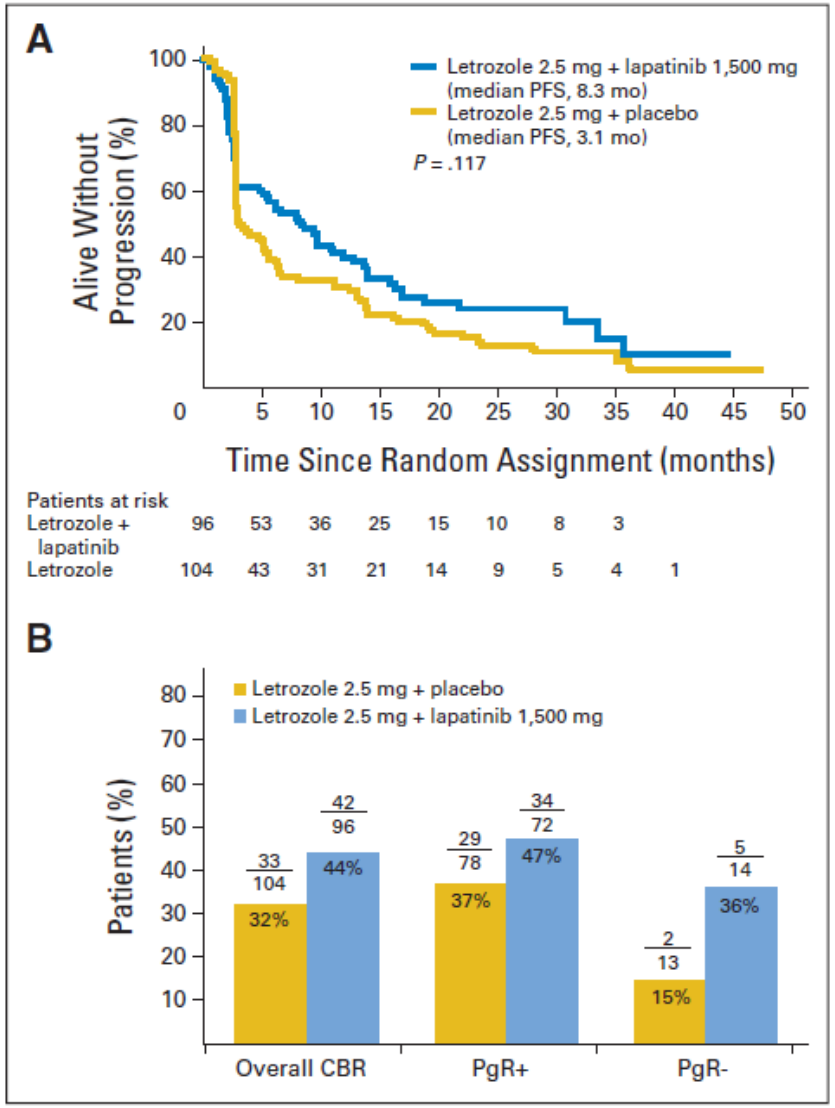
(PMID:19786658)

HR+/HER2-negative



No benefit of lapatinib

HR+/HER2-positive



Survival benefit of lapatinib

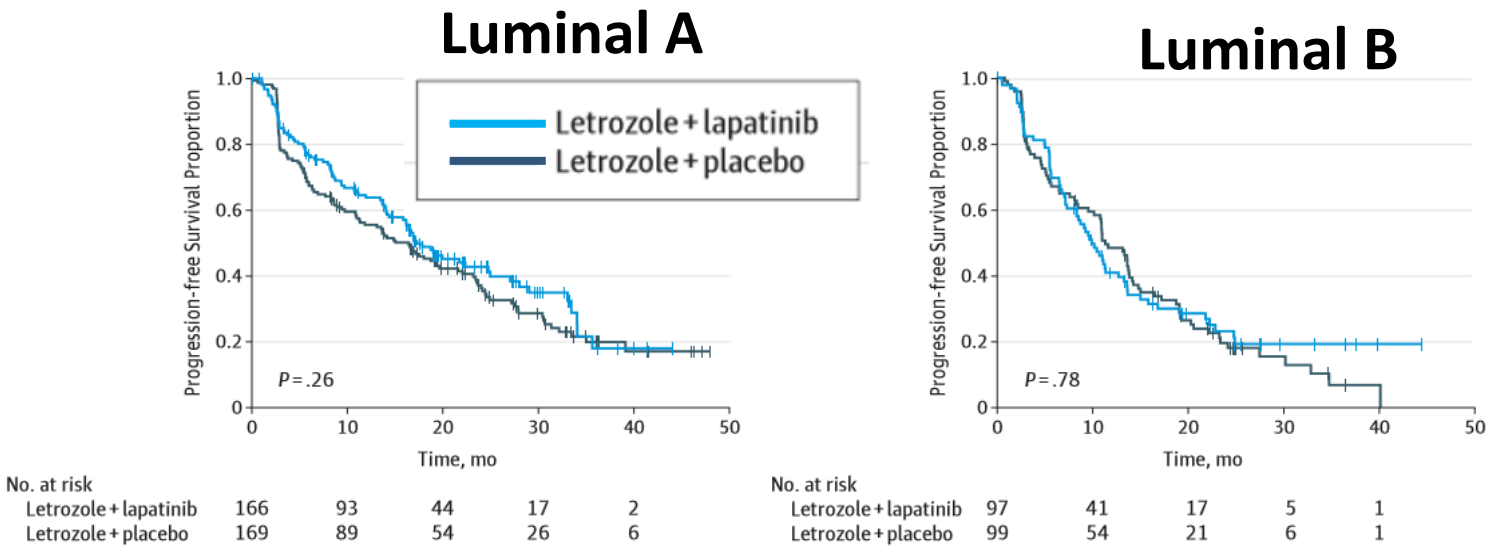
Johnson et al., JCO 2009 (PMID:19786658)

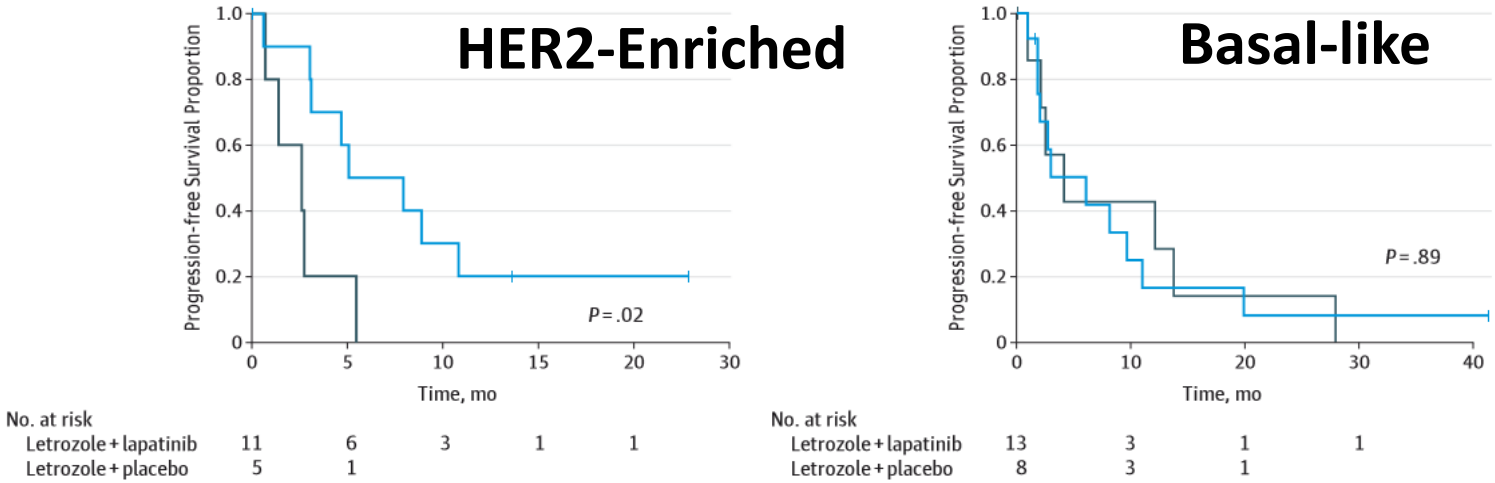
Prognostic Value of Intrinsic Subtypes in Hormone Receptor–Positive Metastatic Breast Cancer Treated With Letrozole With or Without Lapatinib

Prat et al., JAMA Oncology 2016 (PMID:27281556)

HR+/ HER2-negative

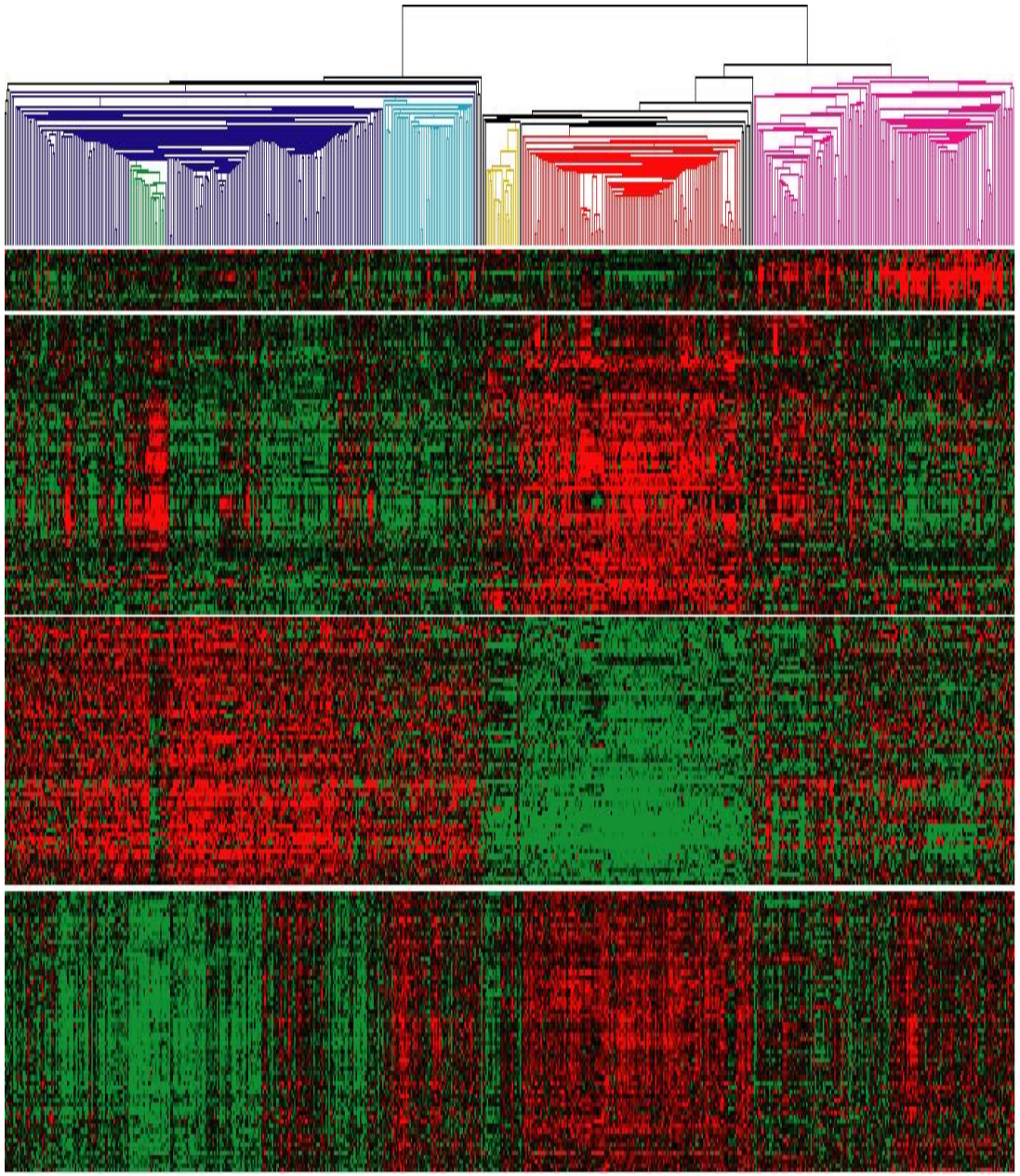
Clinically HER2-negative, HER2-Enriched subtype benefit from lapatinib

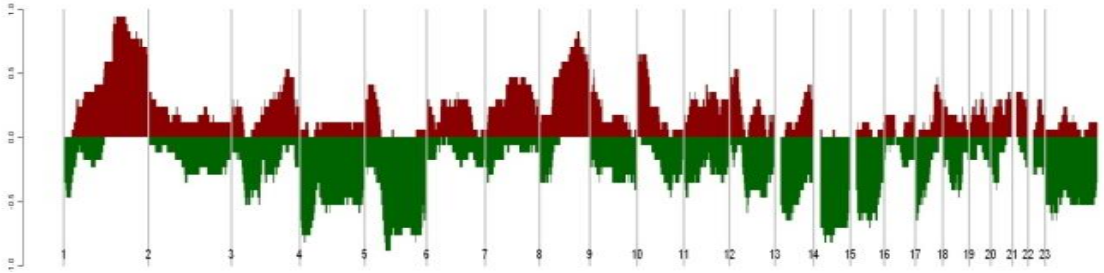


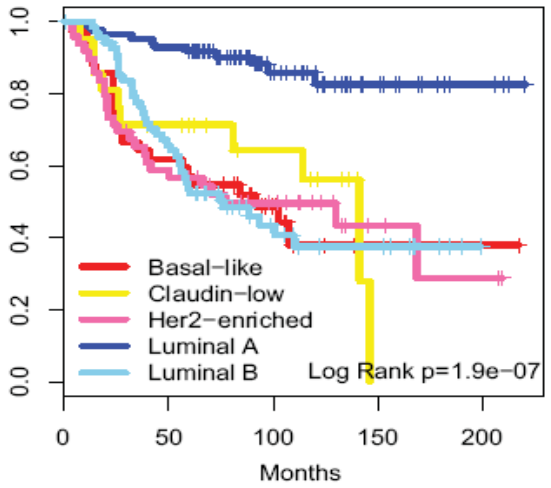


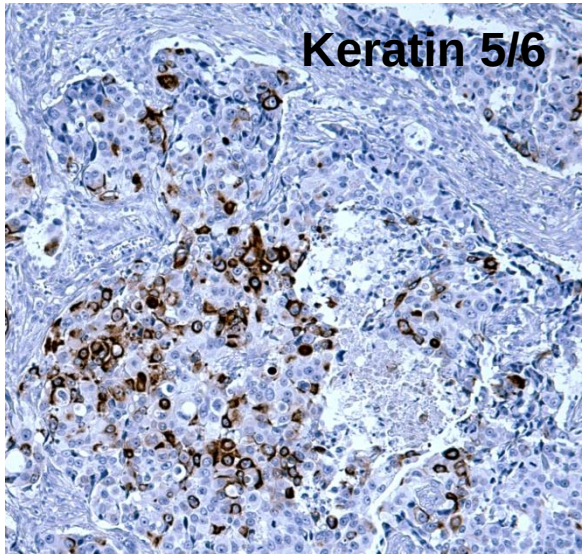
Basal-like subtype

1. 10-25% of tumors
2. distinct cell type of origin
3. >80% TP53 mutant
4. BRCA1 associated
5. highly proliferative (RB null)
6. Typically ER-, PR-, and HER2-not amplified (Triple-negative), so treatment options are limited - mostly chemotherapy only

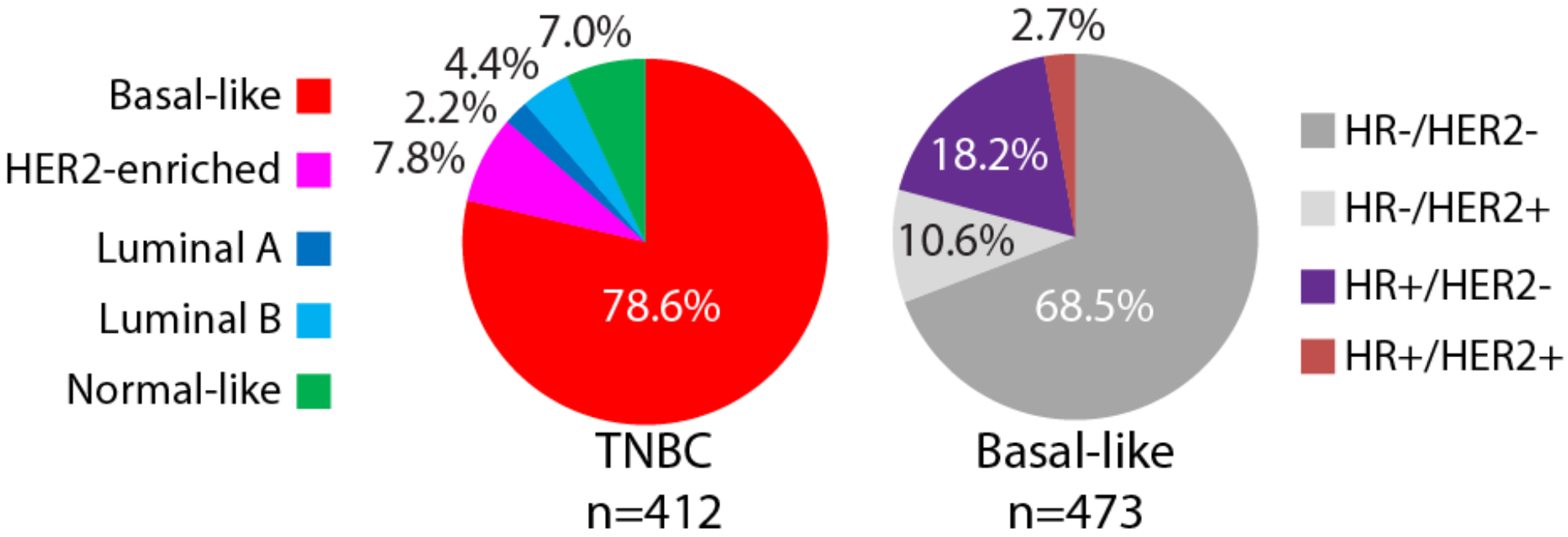








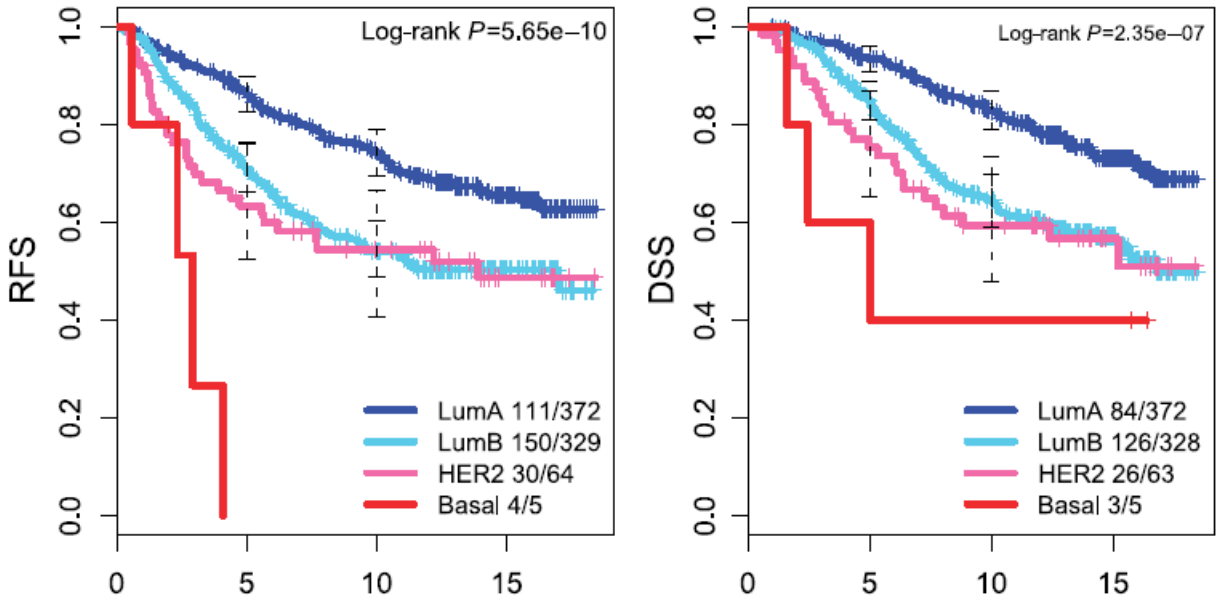
Basal-like and Triple Negative Classifications



Prat et al., The Oncologist, 2013 (PMID:23404817)

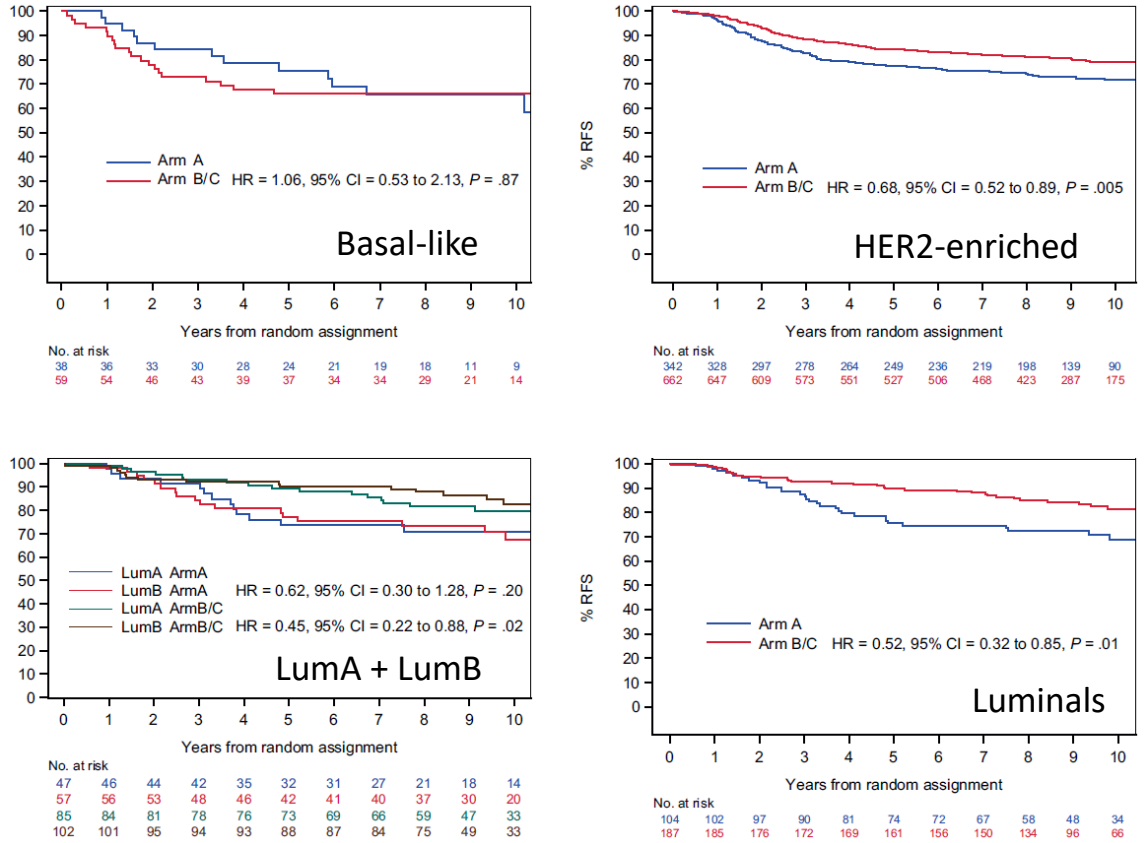
Potential Clinical Utility of Knowing a Tumor is Basal-like Subtype

ER+ patients receiving endocrine therapy only



A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in tamoxifen-treated estrogen receptor positive breast cancer
Nielsen et al., Clinical Cancer Research, 2010 (PMID:20837693)

HER2+ patients receiving adjuvant ACT (Arm A) or ACT + trastuzumab (Arms B/C)



Intrinsic Subtype and Therapeutic Response Among HER2-Positive Breast Tumors from the NCCTG (Alliance) N9831 Trial, Perez et al., JNCI, 2016 (PMID:27794124)

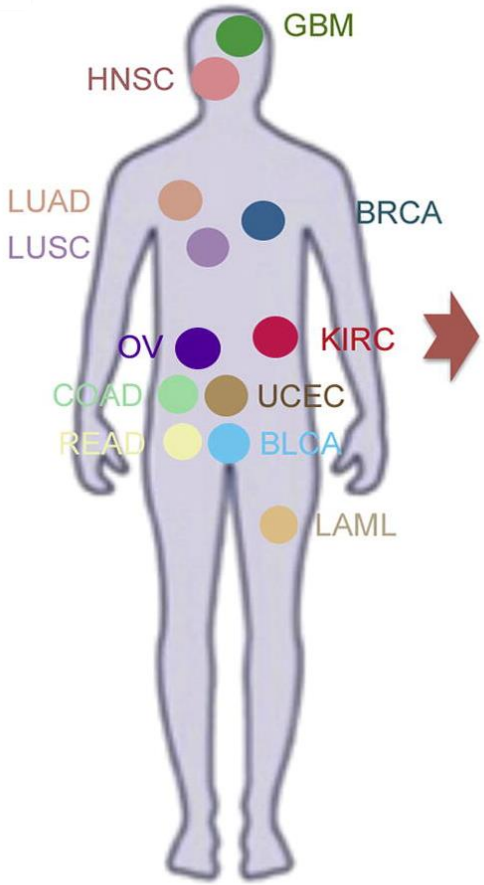
Resource

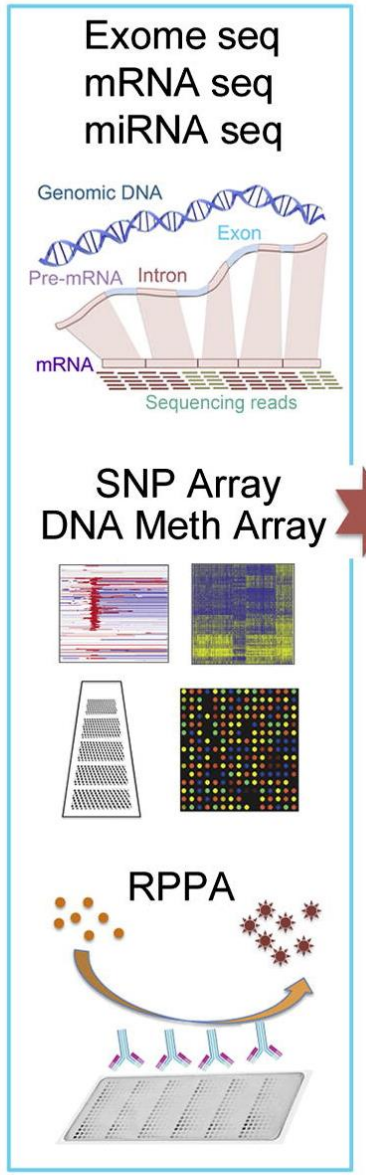
Cell

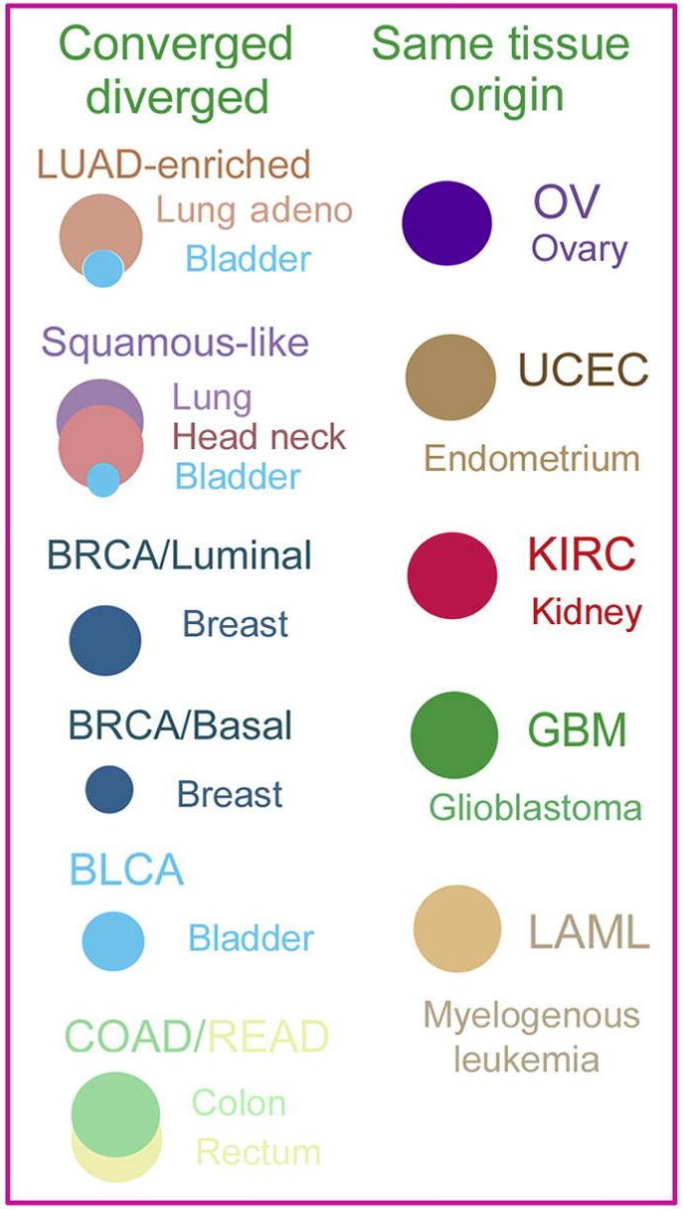
Multiplatform Analysis of 12 Cancer Types Reveals Molecular Classification within and across Tissues of Origin

Katherine A. Hoadley,[1,20] Christina Yau,[2,20] Denise M. Wolf,[3,20] Andrew D. Cherniack,[4,20] David Tamborero,[5] Sam Ng,[6] Max D.M. Leiserson,[7] Beifang Niu,[8] Michael D. McLellan,[8] Vladislav Uzunangelov,[6] Jiashan Zhang,[9] Cyriac Kandoth,[8] Rehan Akbani,[10] Hui Shen,[11,22] Larsson Omberg,[12] Andy Chu,[13] Adam A. Margolin,[12,21] Laura J. van't Veer,[3] Nuria Lopez-Bigas,[5,14] Peter W. Laird,[11,22] Benjamin J. Raphael,[7] Li Ding,[8] A. Gordon Robertson,[13] Lauren A. Byers,[10] Gordon B. Mills,[10] John N. Weinstein,[10] Carter Van Waes,[18] Zhong Chen,[19] Eric A. Collisson,[15] The Cancer Genome Atlas Research Network, Christopher C. Benz,[2,*] Charles M. Perou,[1,16,17,*] and Joshua M. Stuart[6,*]

Cell *158*, 929–944, August 14, 2014 ©2014 Elsevier Inc.

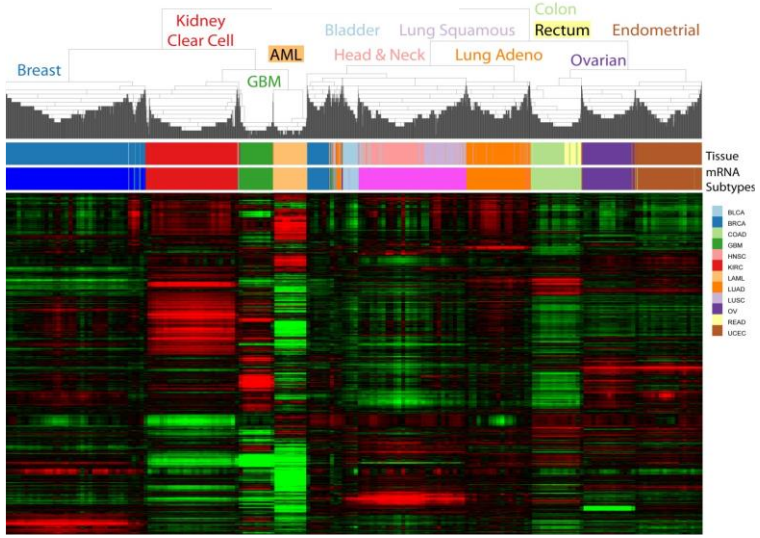




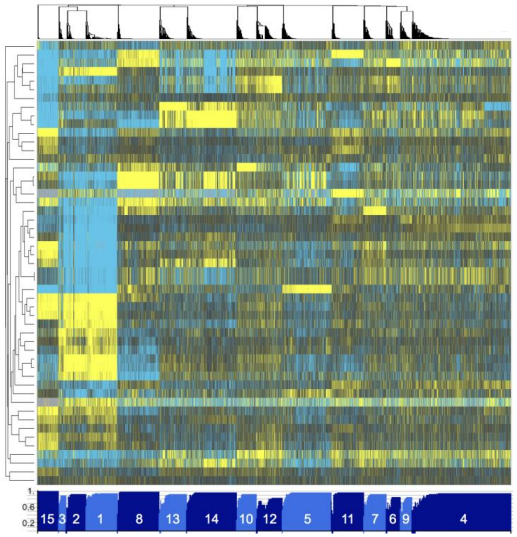


PMID:25109877

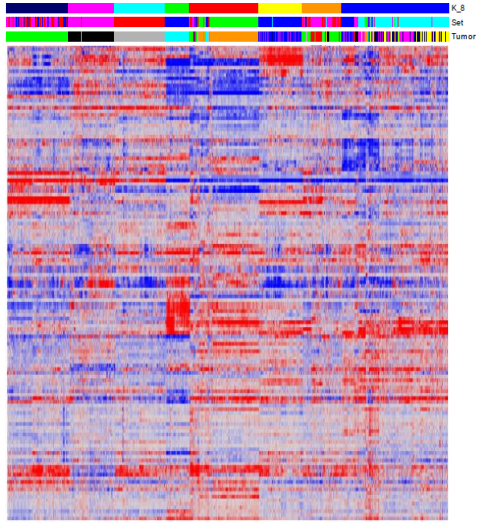
mRNA



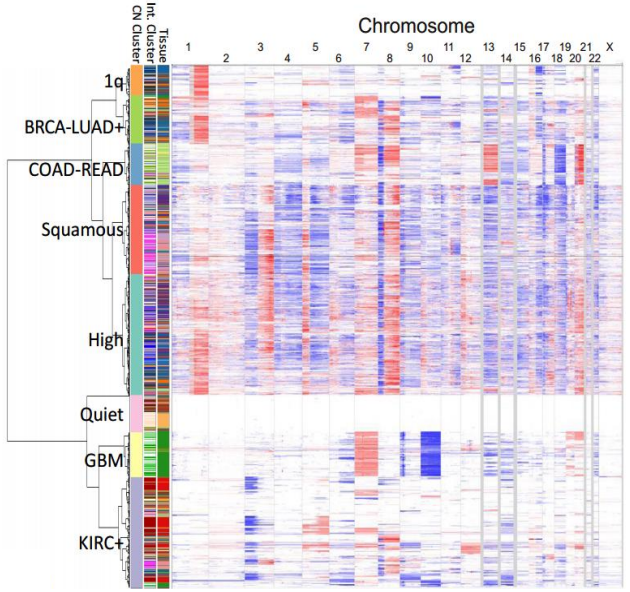
microRNA



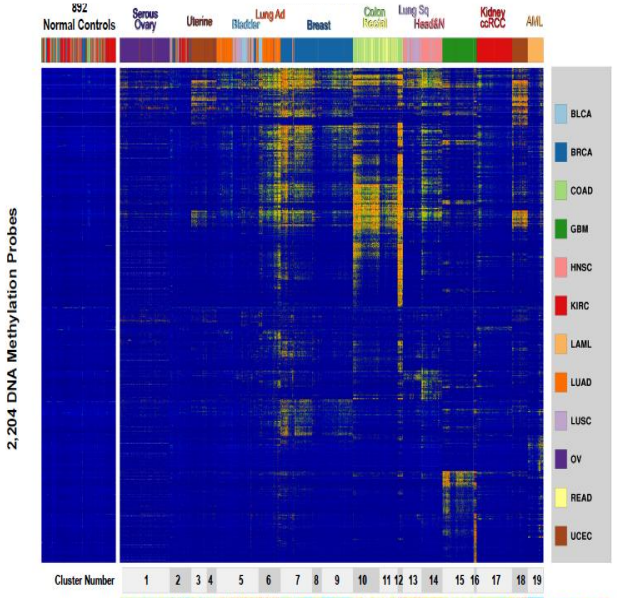
Protein/RPPA



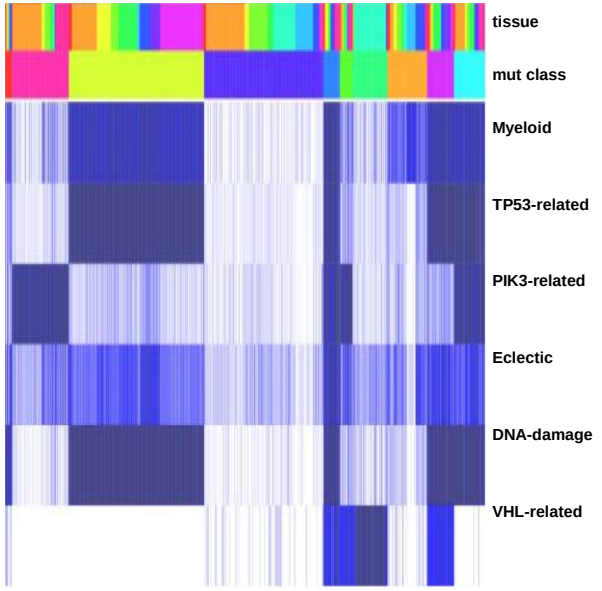
DNA Copy Number



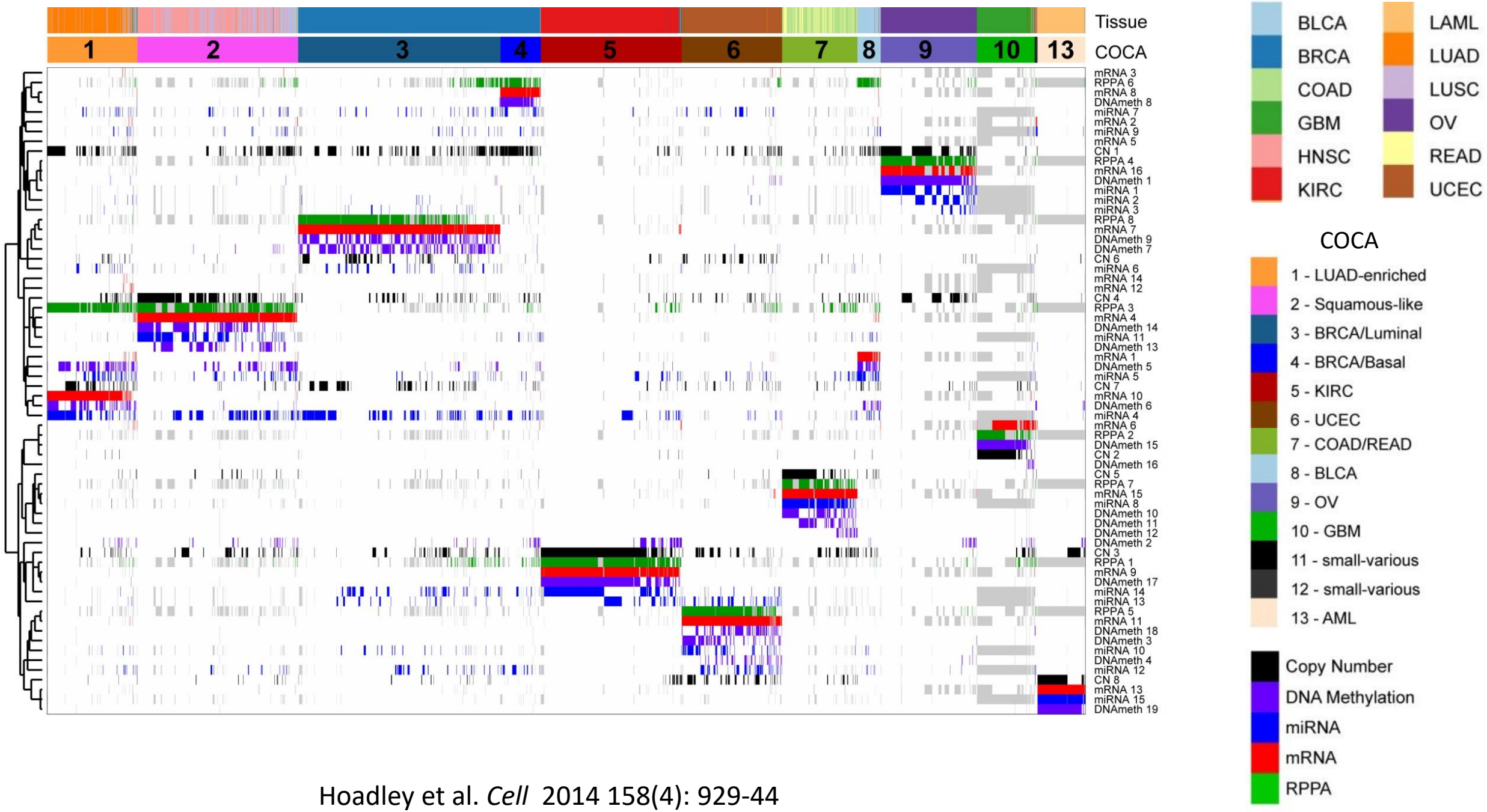
DNA Methylation



Mutations/Exomes

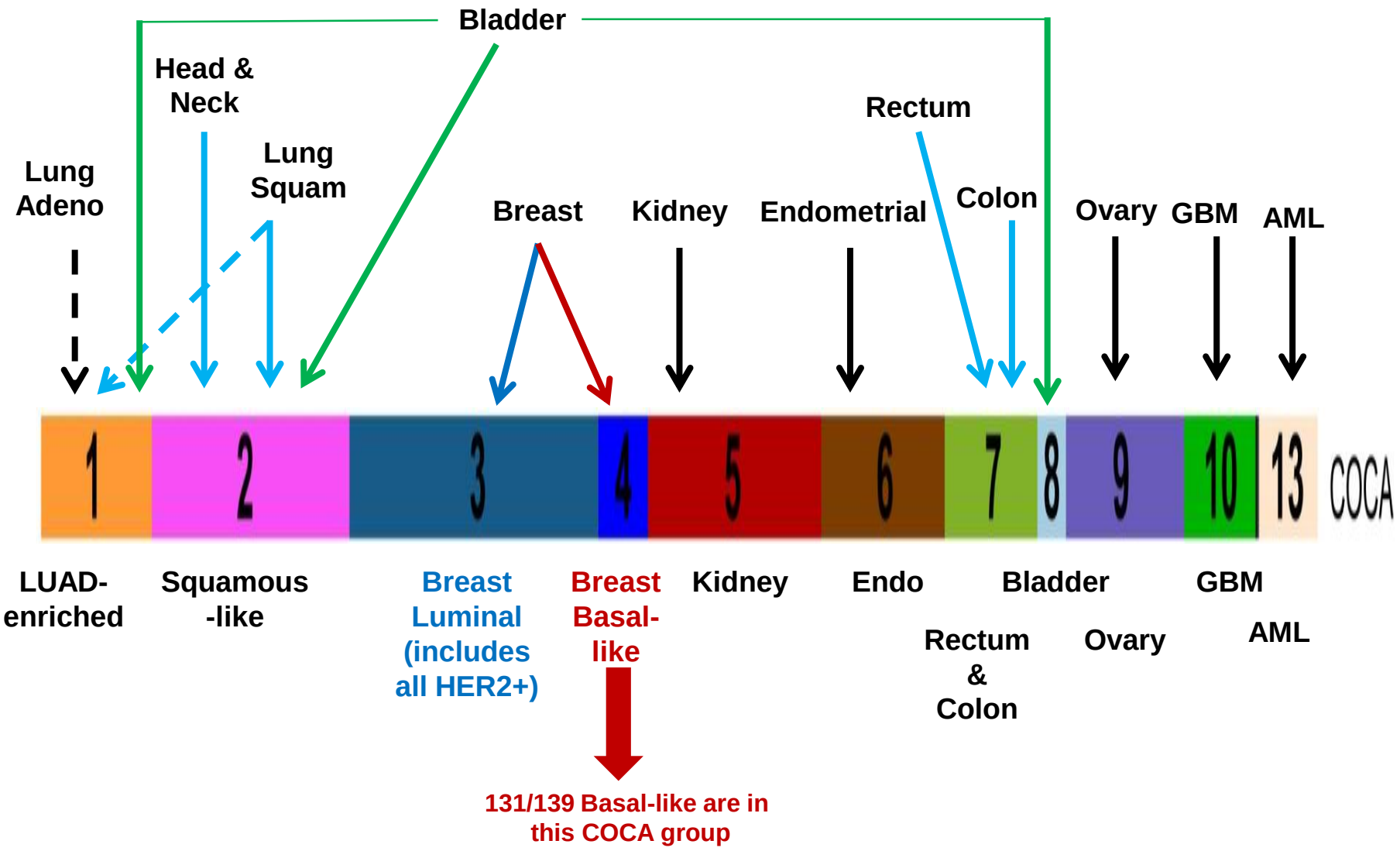


Hoadley et al., Cell, 2014. (PMID:25109877)



Hoadley et al. *Cell* 2014 158(4): 929-44

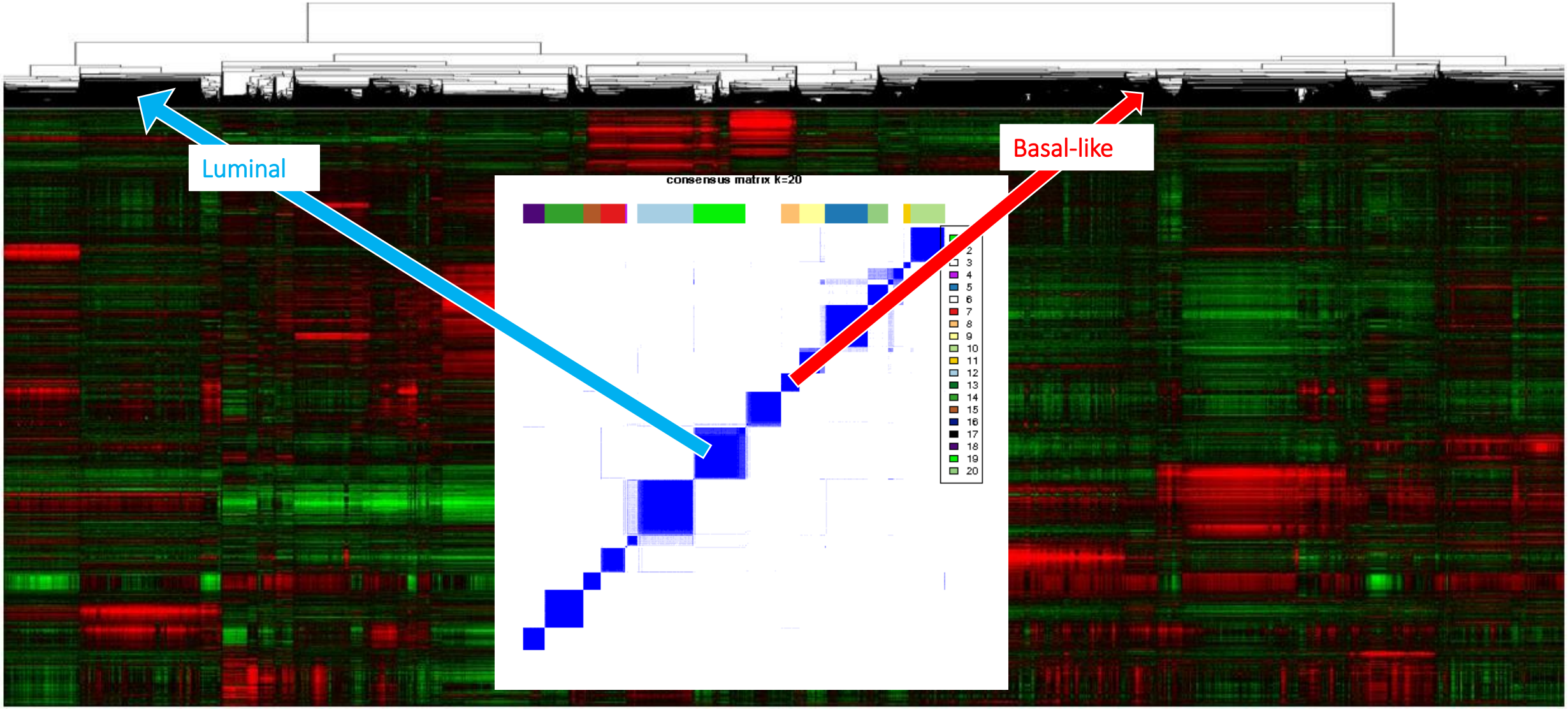
12 Tissue of Origin Sites Translate into 11 COCA Subtypes



Hoadley et al., Cell, 2014. PMID:25109877

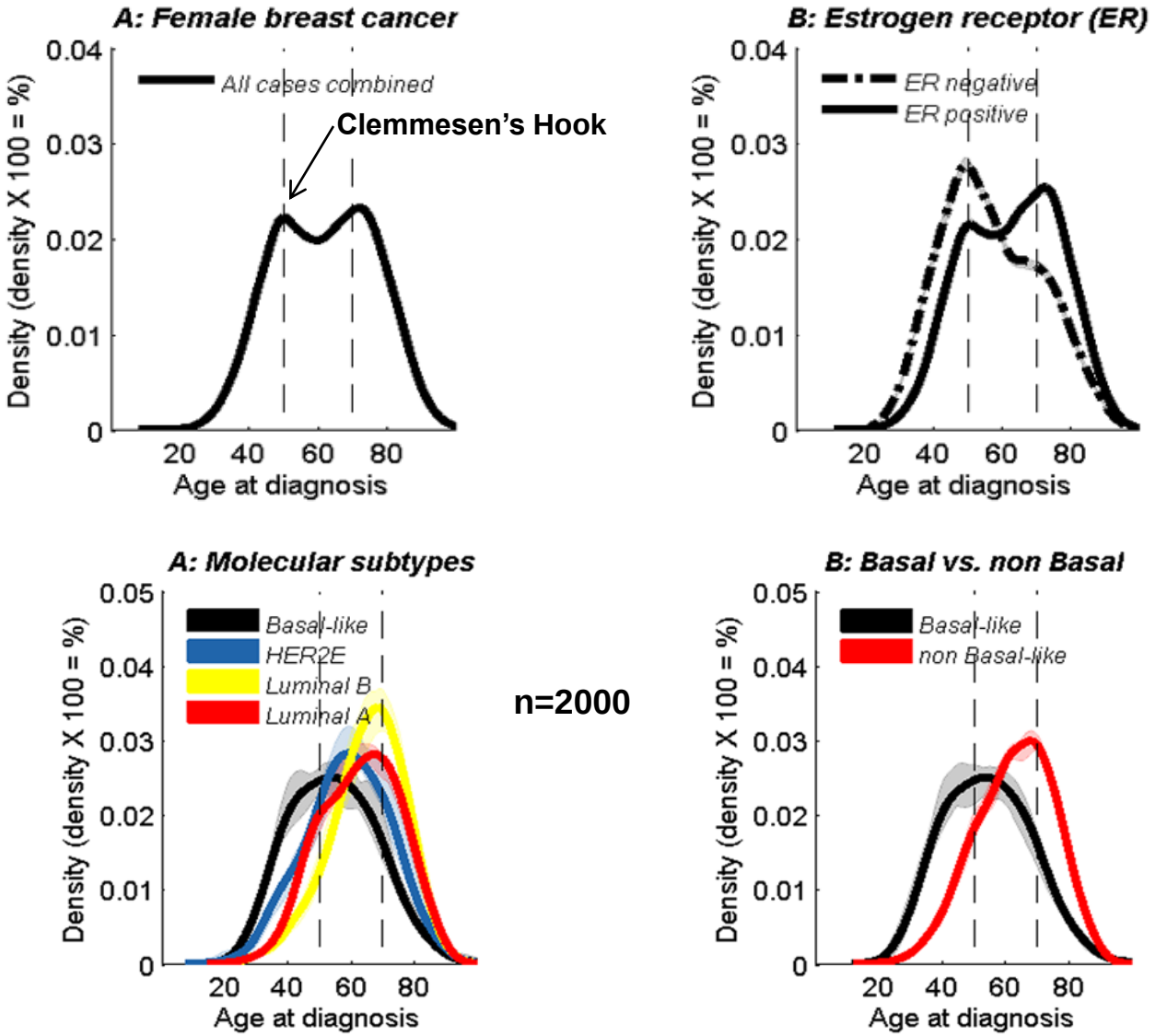
TCGA Cluster Analysis of 10,000 tumors x 5000 genes

33 tumor types studied including breast (n=1100), bladder, colon, rectum, head & neck, gastric, lung squamous & adenocarcinoma, melanoma, **renal clear cell & chromophobe, ovarian,** glioblastoma, prostate, endometrial, thyroid, pancreas, testicular and others

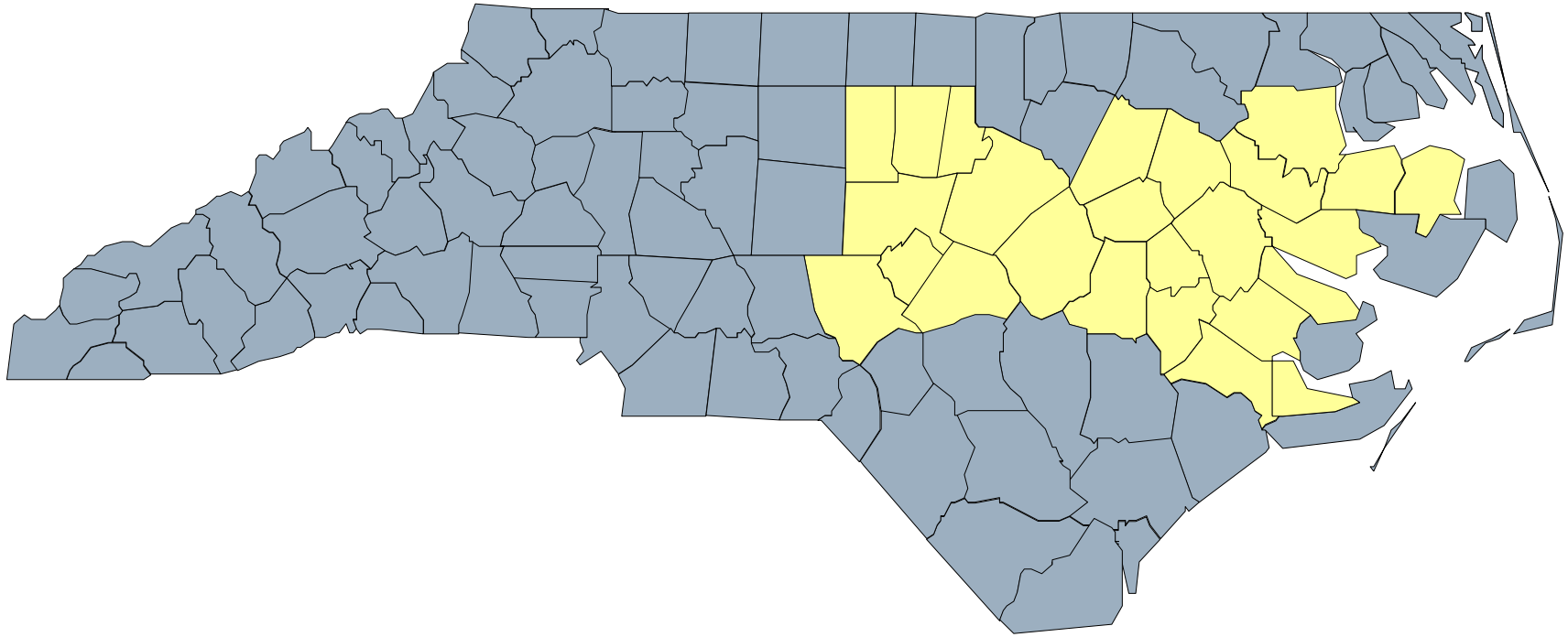


HOW MANY ETIOLOGICAL SUBTYPES OF BREAST CANCER: TWO, THREE, OR MORE?

William F. Anderson, Philip S. Rosenberg, Aleix Prat, Charles M. Perou,
and Mark E. Sherman JNCI, (2014). PMID:25118203



Carolina Breast Cancer Study (CBCS)
Population-based case-control study



40% African-American / 60% Caucasian

50% under the age of 50 at diagnosis

1424 cases with FFPE materials/tumors

Epidemiology of basal-like breast cancer

Millikan et al., Breast Cancer Research and Treatment, 2008 (PMID:17578664)

	Luminal A N=796	Basal-like N=225
Menarche < 13	1.1 (0.9-1.3)	1.4 (1.1-1.9)
≥ 3 children	0.7 (0.5-0.9)	1.9 (1.1-3.3)
First birth < 26	0.7 (0.5-0.9)	1.9 (1.2-3.2)
Breastfeeding ≥ 4m	0.9 (0.7-1.1)	0.7 (0.4-0.9)
Parity ≥ 3 and No breastfeeding	0.7 (0.4-0.9)	1.9 (1.1-3.3)
Waist:Hip ≥ 0.84	1.5 (1.1-1.9)	2.3 (1.4-3.6)

Adjusted ORs (95% CI)
N = 1424 cases and 2022 controls

Epidemiology of basal-like breast cancer

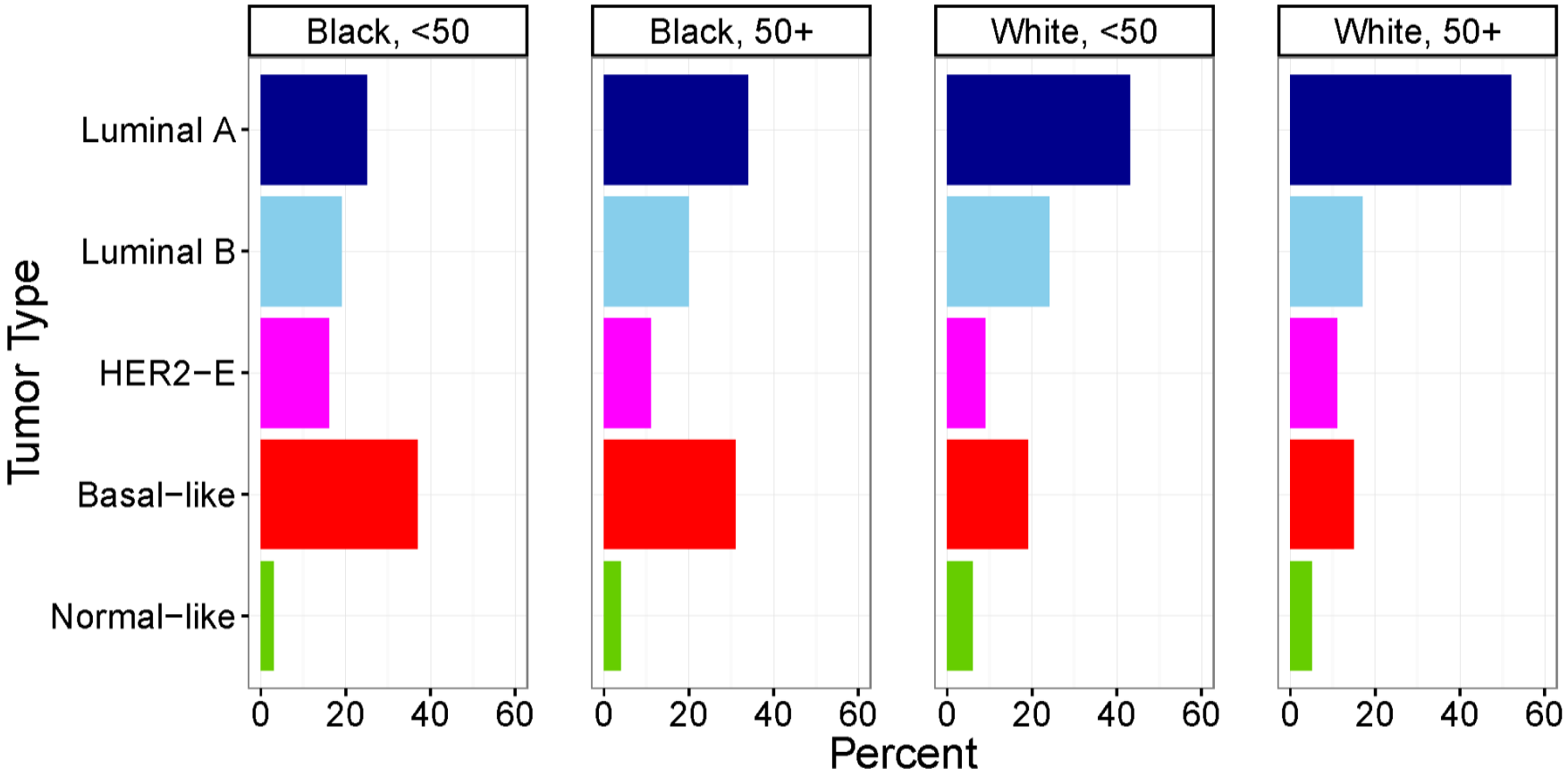
Millikan et al., Breast Cancer Research and Treatment, 2008 (PMID:17578664)

Distribution of breast cancer subtypes according to race and menopausal status using 1424 cases: invasive (1000) and *in-situ* (424) breast cancers

Breast cancer subtype	African-American Premenopausal N (%)	African-American Postmenopausal N (%)	Caucasian Premenopausal N (%)	Caucasian Postmenopausal N (%)
Luminal A N = 796	108 (41.4%)	179 (56.3%)	216 (57.4%)	293 (66.5%)
Basal-like N = 225	70 (27.2%)	52 (16.0%)	54 (14.5 %)	49 (9.3%)
HER2+/ER- N = 116	22 (8.4%)	26 (7.7%)	24 (5.6%)	44 (6.0%)
Luminal B N = 137	19 (7.3%)	26 (8.7%)	46 (12.4%)	46 (10.7%)
Unclassified N = 150	41 (15.7%)	38 (11.3%)	38 (10.1%)	33 (7.5%)
Total: 1424 P < 0.0001	260 (100%)	321 (100%)	378 (100%)	465 (100%)

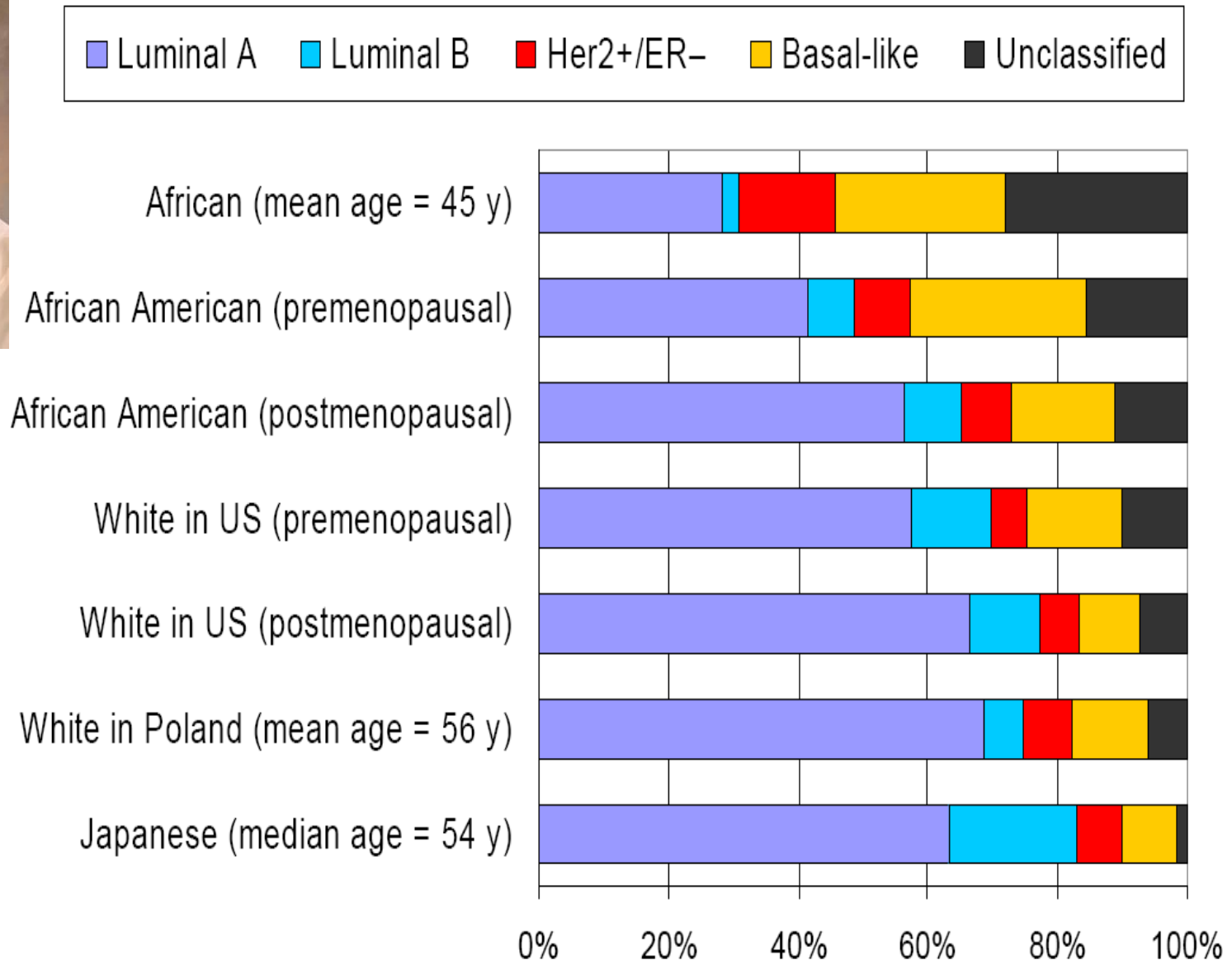
Melissa Troester, University of North Carolina,

Race and Age Differences in PAM50 Biomarker status in in the Carolina Breast Cancer Study (PD8-01), SABCS 2016



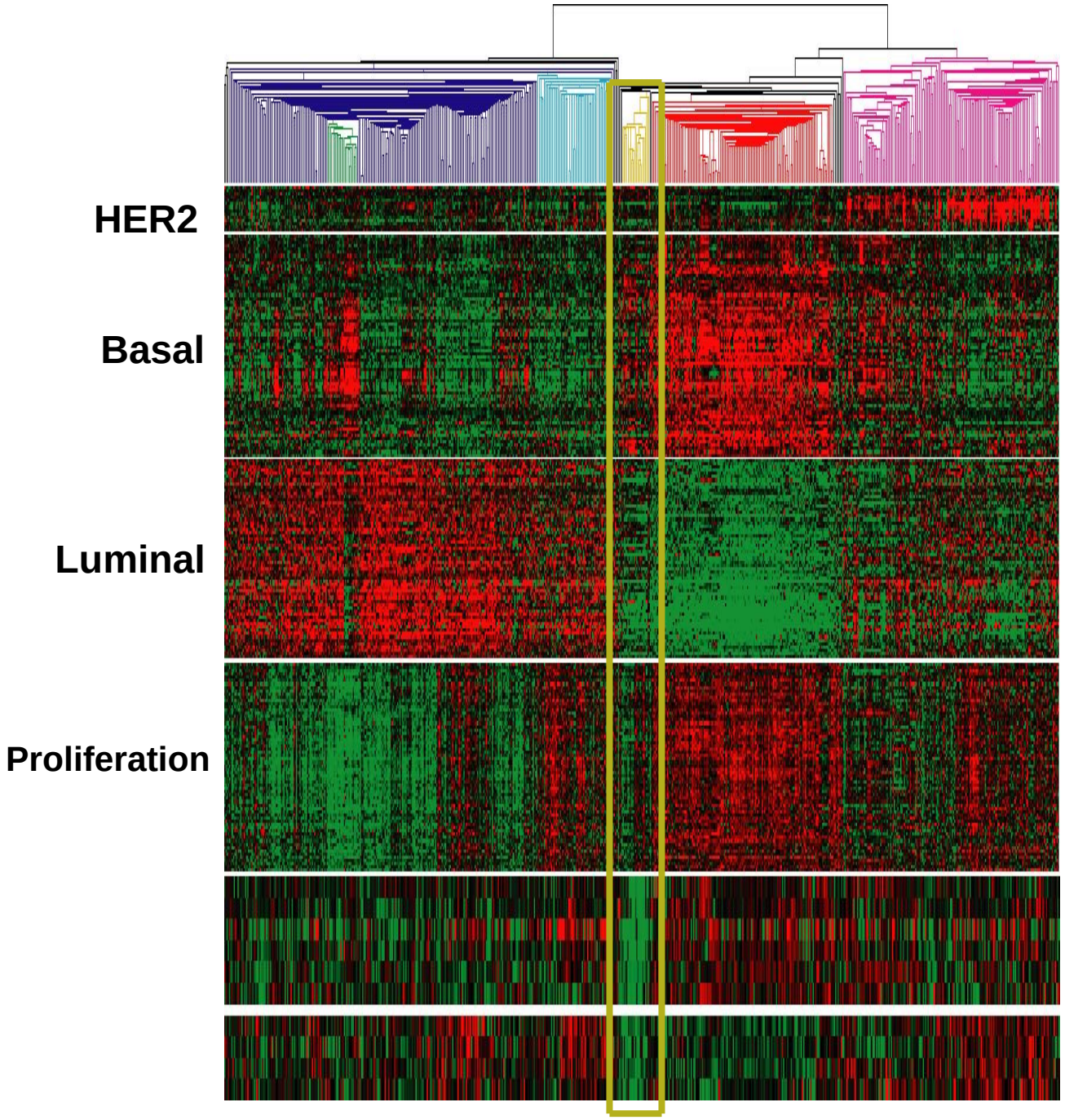
Population Differences in Breast Cancer: Survey in Indigenous African Women Reveal Overrepresentation of Triple Negative Breast Cancer. Huo et al., JCO 2009 (PMID:19704069)

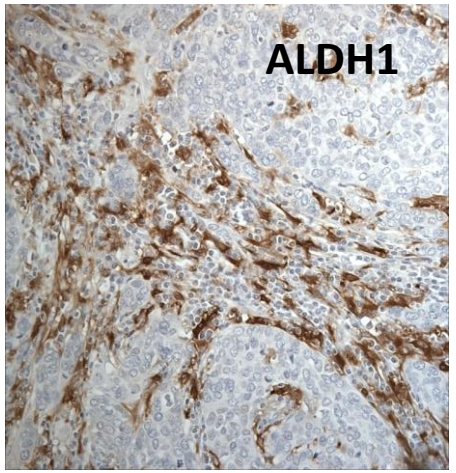
Funmi Olopade

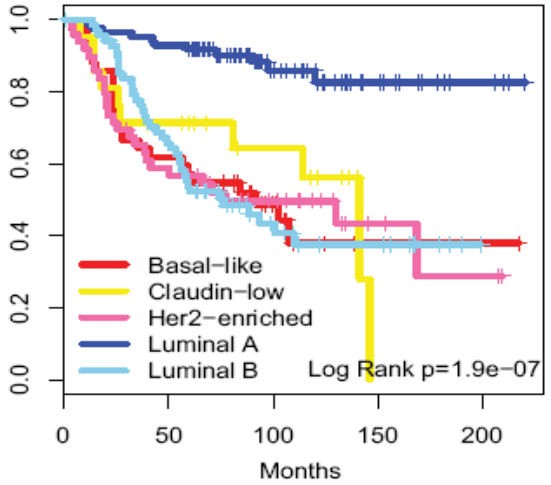


Claudin-low Subtype

1. ~5% of tumors
2. typically Triple Negative
3. low expression of cell-cell junction proteins
4. lymphocyte infiltrates
5. stem cell + EMT features

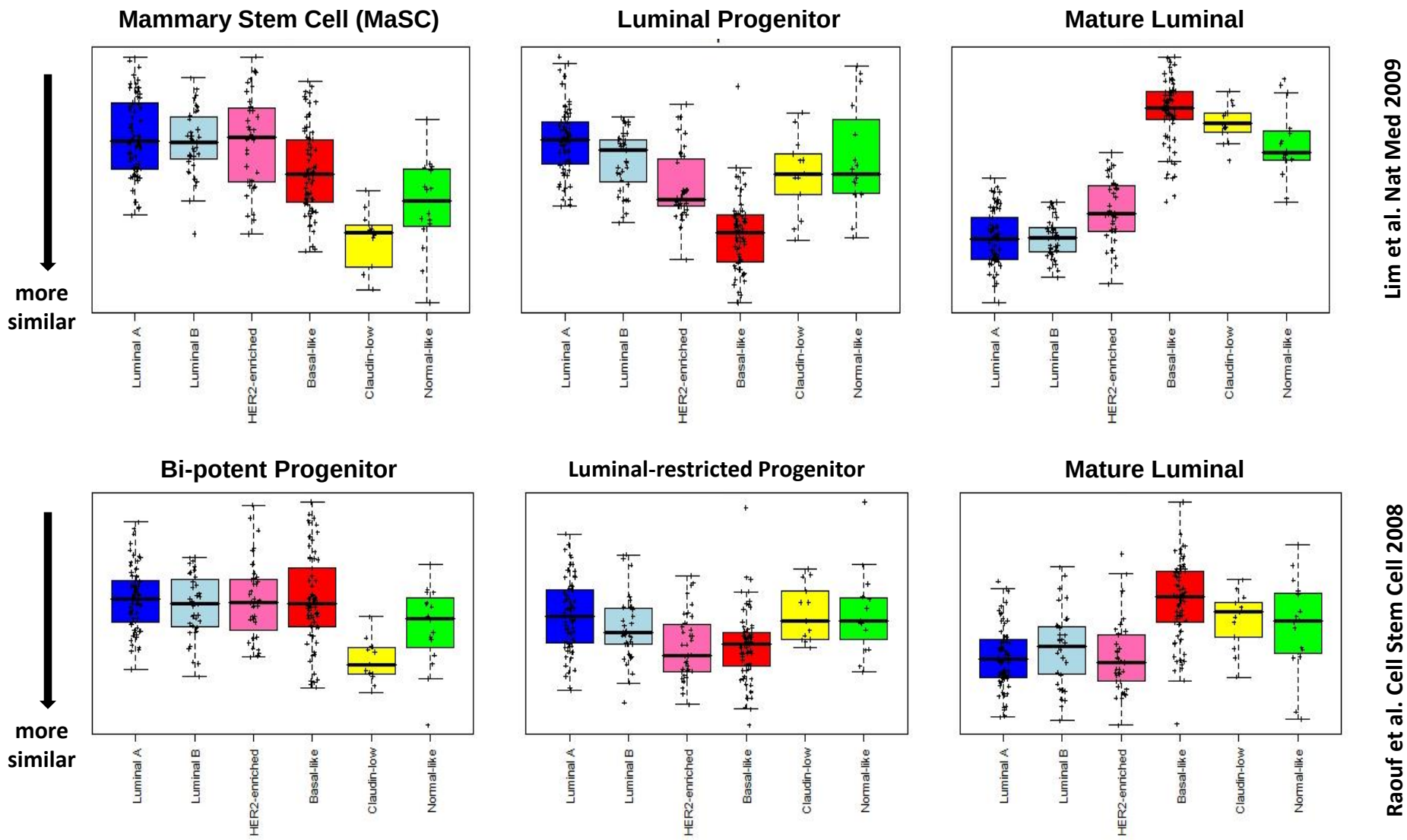


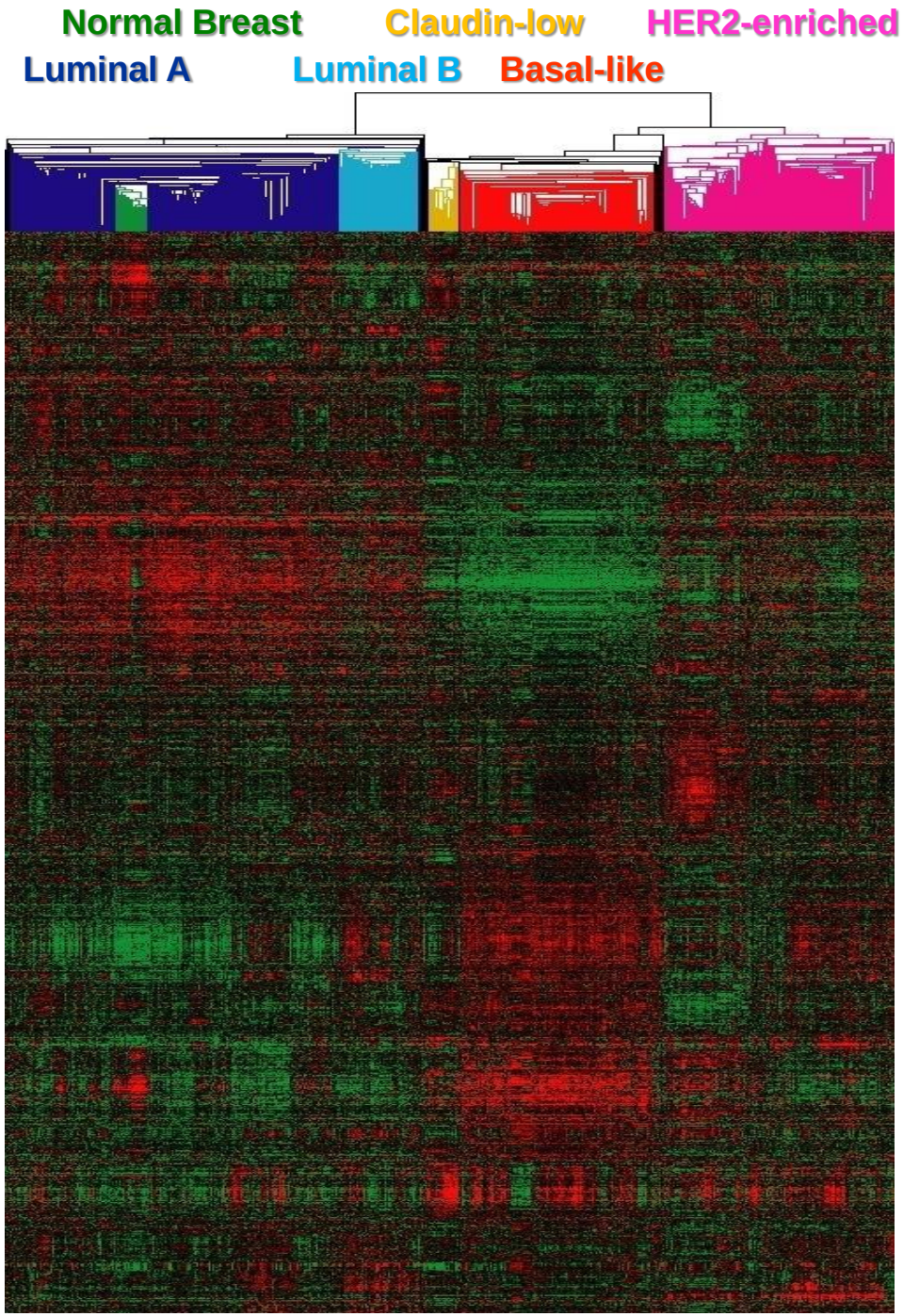




232 Human Breast Tumors analyzed for FAC sorted epithelial cell signatures

centroid predictor with smaller Euclidian distances indicating the greatest enrichment





Intrinsic Subtype Conclusions

1. Intrinsic subtyping has identified 5-6 robust subtypes with distinct patterns of gene expression and genomic alterations.

2. The ROR Score can be used to guide therapy decisions

3. The HER2-Enriched subtype is a biomarker for trastuzumab + chemotherapy sensitivity, and possibly for dual HER2-targeting

4. The Basal-like subtype may arise from a separate cell type in the breast with a distinct set of genomic features, risk features, and epidemiology.

University of North Carolina at Chapel Hill
Charles Perou and laboratory
Melissa Troester
Joel Parker and Lineberger Bioinformatics Group
Lisa Carey
Carey Anders
Corbin Jones and the High Throughput Sequencing Facility

Aleix Prat, Hospital Clínic de Barcelona, Universitat de Barcelona
Maggie C. U. Cheang, Institute of Cancer Research, London

The Cancer Genome Atlas Network
Alliance Clinical Trials Network

Funding:
NCI
Komen Career Catalyst Grant