Genomic and morphological heterogeneity in TNBC

Jorge S Reis-Filho, MD PhD FRCPath

Department of Pathology

Affiliate Member, HOPP and cBio

Memorial Sloan Kettering
Cancer Center™

Conflicts of Interest

- I have no financial relationships to disclose
- I will not discuss off label use and/ or investigational use in my presentation

Summary

- Definition
- Histological diversity
- Molecular heterogeneity
  - Gene expression profiling
  - Mutational profiling
- Intra-tumour genetic heterogeneity

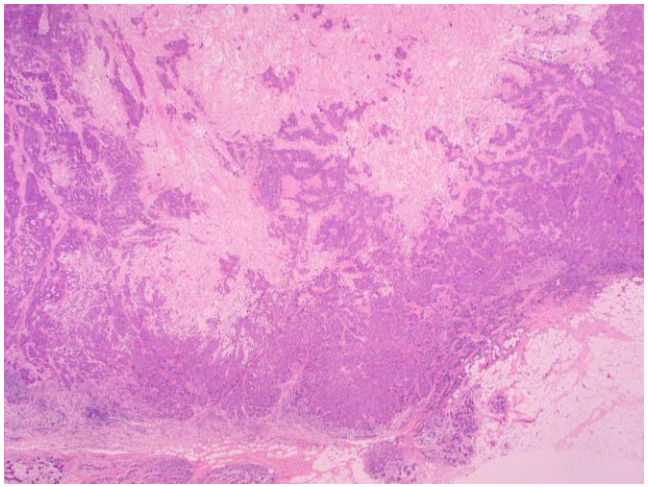
Definition – TNBC

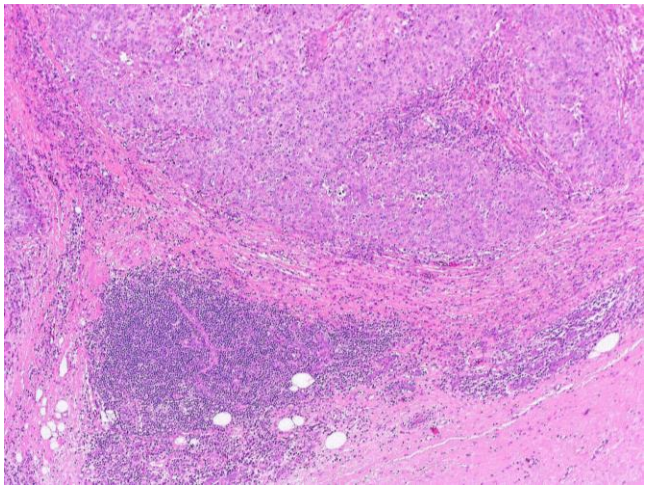
- ER negative (<1%)
- PR negative (<1%)
- HER2 negative (ASCO/ CAP negative)

Histological diversity

TNBC - Histopathological features

- Grade III
- Lymphocytic infiltrate
- Pushing borders
- High mitotic rate (>19/10HPF)
- Central necrosis
- Medullary features
- Metaplastic elements
  - Squamous cells
  - Spindle cells





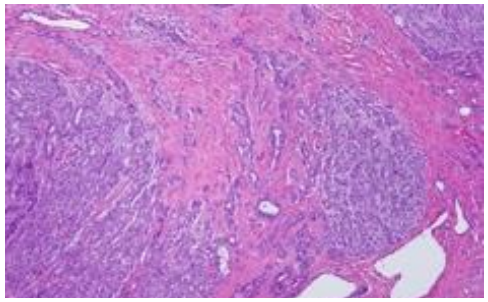
Fulford et al, Histopathology 2006; Livasy et al, Mod Pathol, 2006; Turner et al, Oncogene, 2007; Kreike et al. Breast Cancer Res, 2007

Triple-Negative Breast Cancer

Low grade tumours

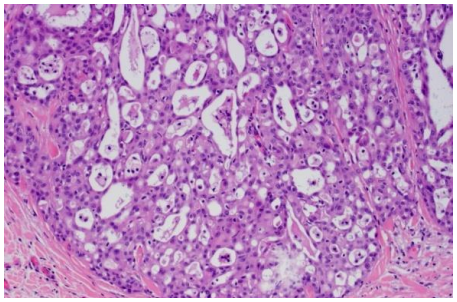
High grade tumours

Polymorphous low-grade adenocarcinoma



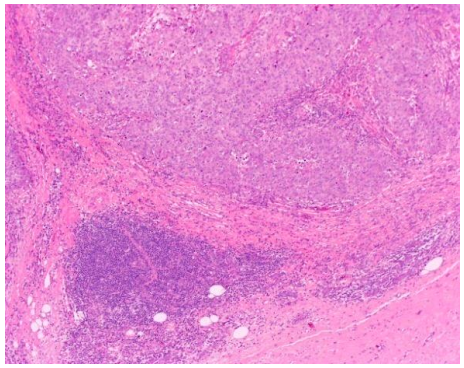
PRKD1 E710D

Secretory carcinoma

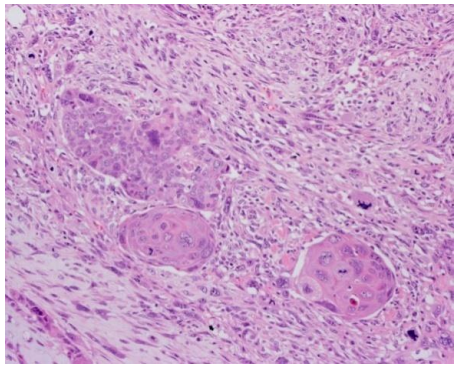


t(12;15) *ETV6-NTRK3*

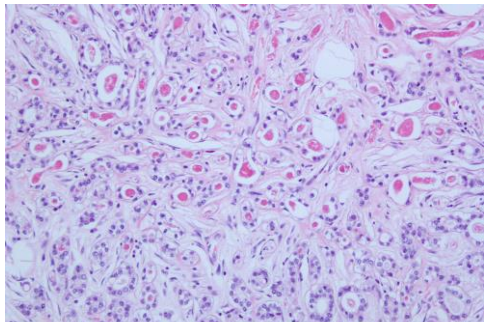
Carcinoma with medullary features



Metaplastic carcinoma

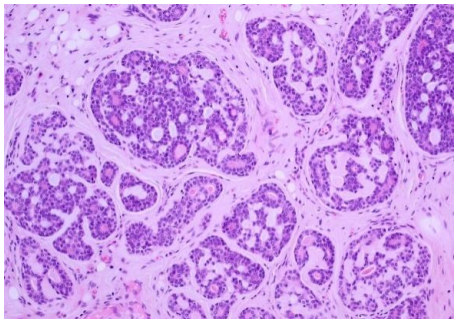


Acinic cell carcinoma



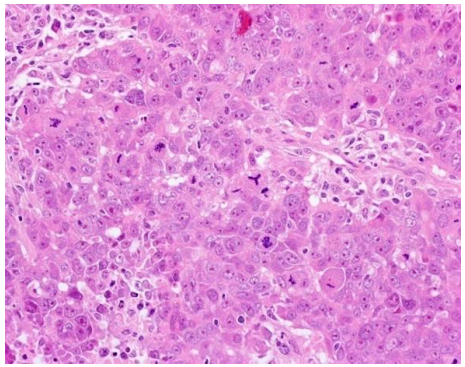
TP53 and *PIK3CA*

Adenoid cystic carcinoma

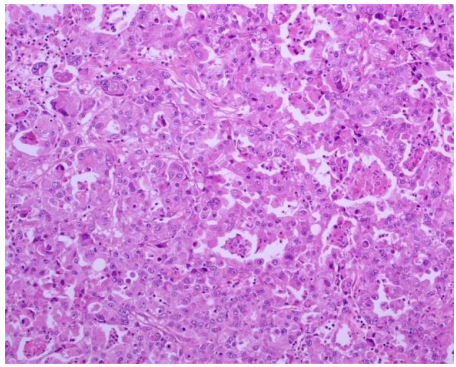


t(6;9) *MYB-NFIB*

High-Grade IDC-NST



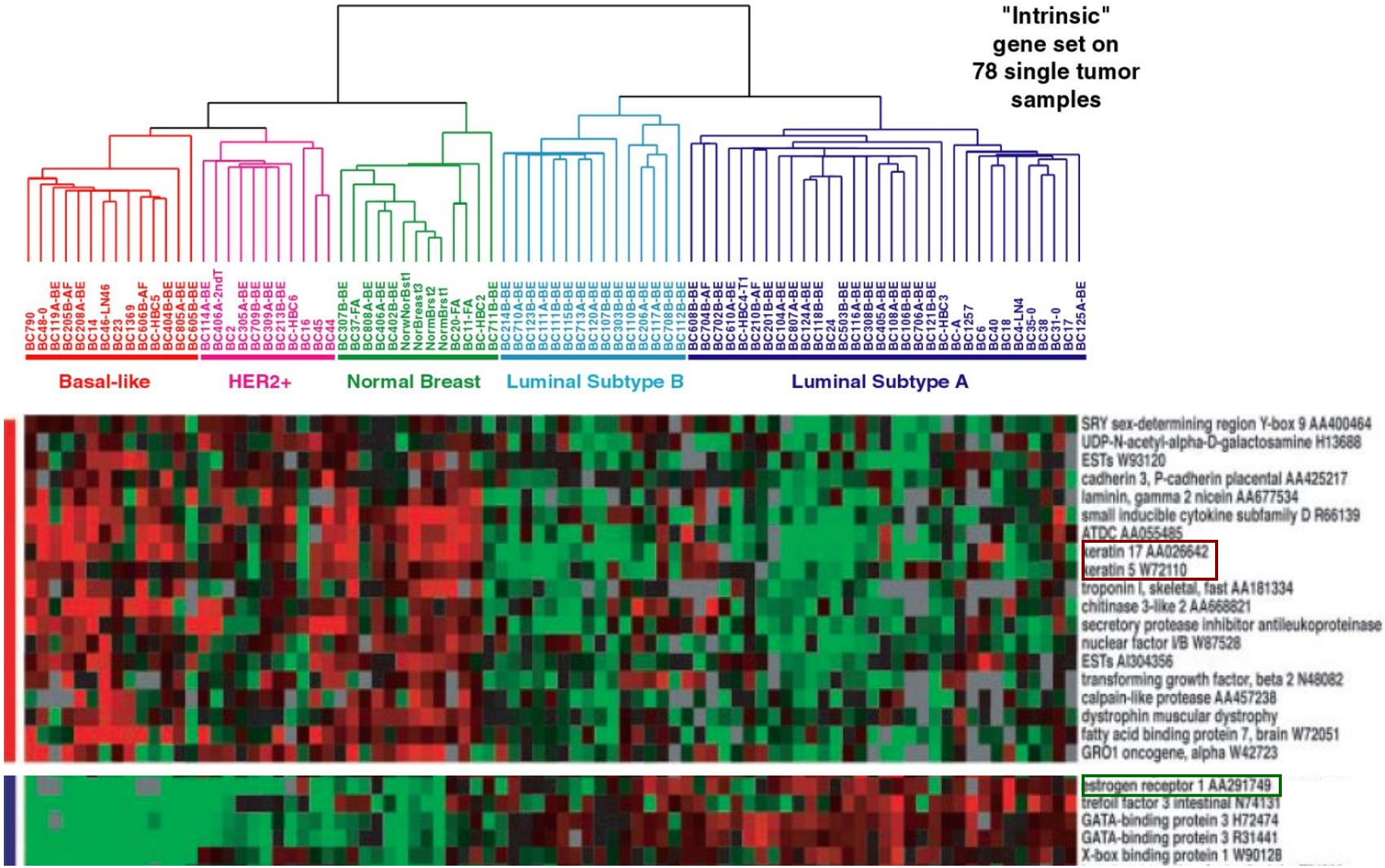
Apocrine Carcinoma



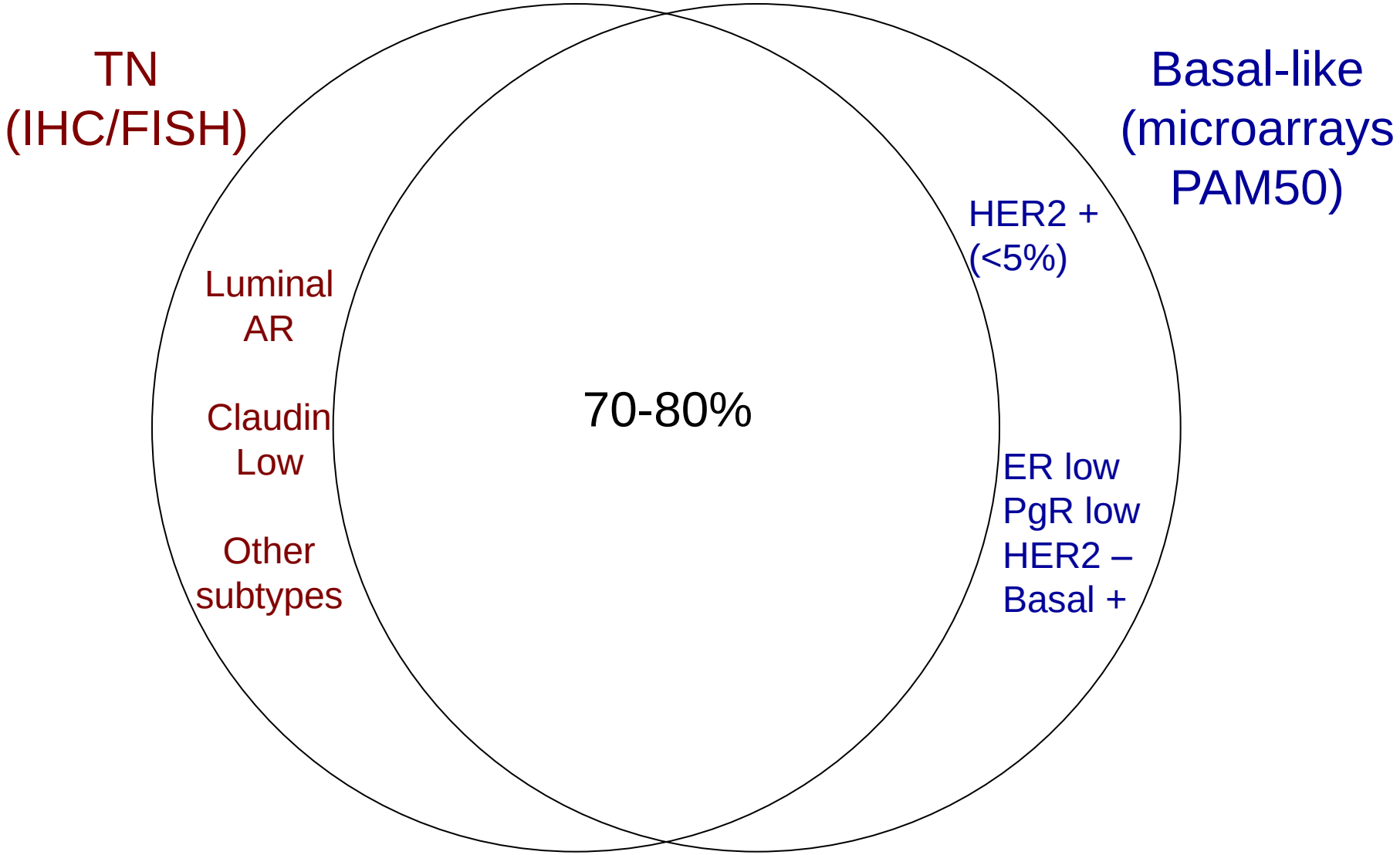
Weigelt et al., J Pathol 2008; Weigelt et al. Nat Rev Clin Oncol 2009 ; Wetterskog et al. J Pathol 2012; Weinreb et al. Nat Genet 2014; Guerini-Rocco et al. J Pathol, in press; Martelotto et al. J Pathol, in press.

Molecular subtypes of TNBCs

Basal-like breast cancers and TNBCs



TN is not a synonym for basal-like phenotype!



TNBC subtypes

BL1: Basal-like 1

BL2: Basal-like 2

IM: Immunomodulatory

M: Mesenchymal-like

MSL: Mesenchymal Stem-like

LAR: Luminal AR

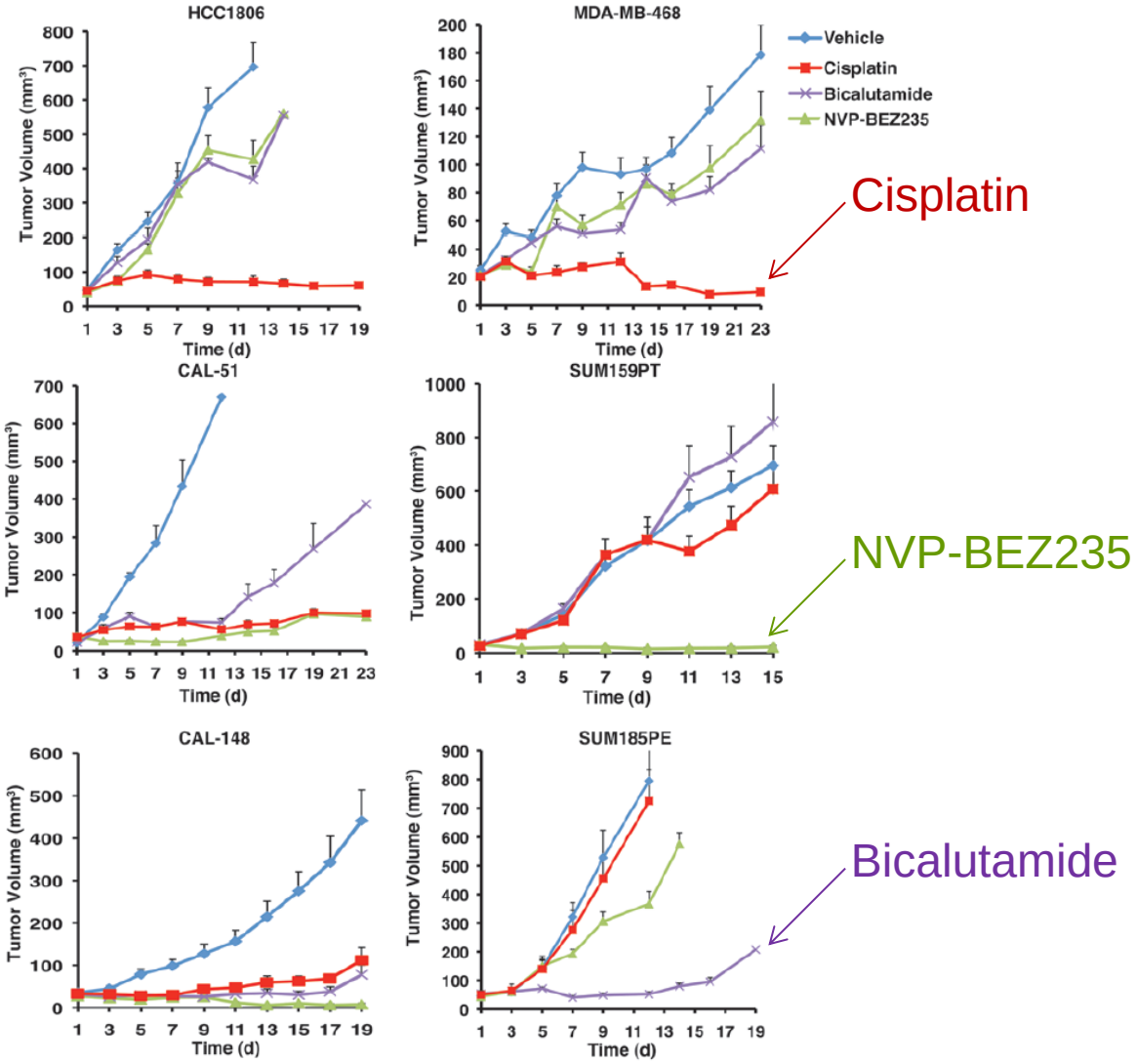
Lehmann et al, JCI 2011

Different types of TNBC respond to different therapies in preclinical models

Basal-like

Mesenchymal-like

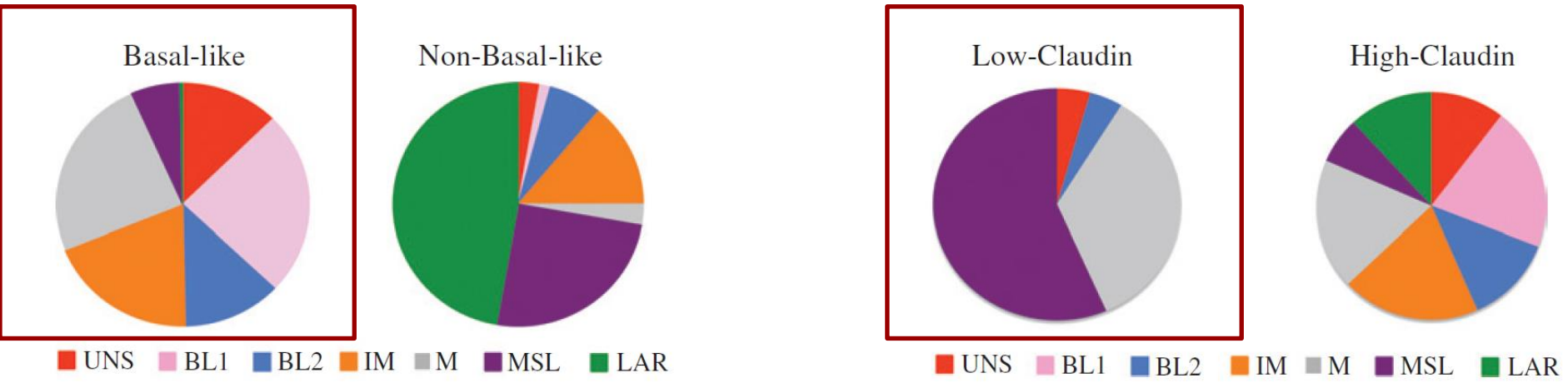
Luminal AR



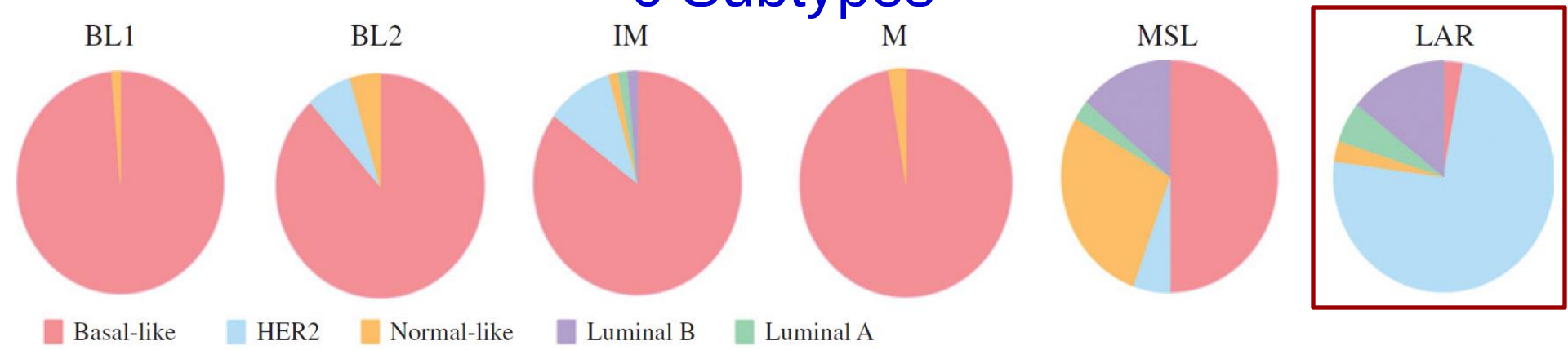
Lehmann et al, JCI 2011

PAM50 and 6 subtypes: 374 TNBCs

PAM50



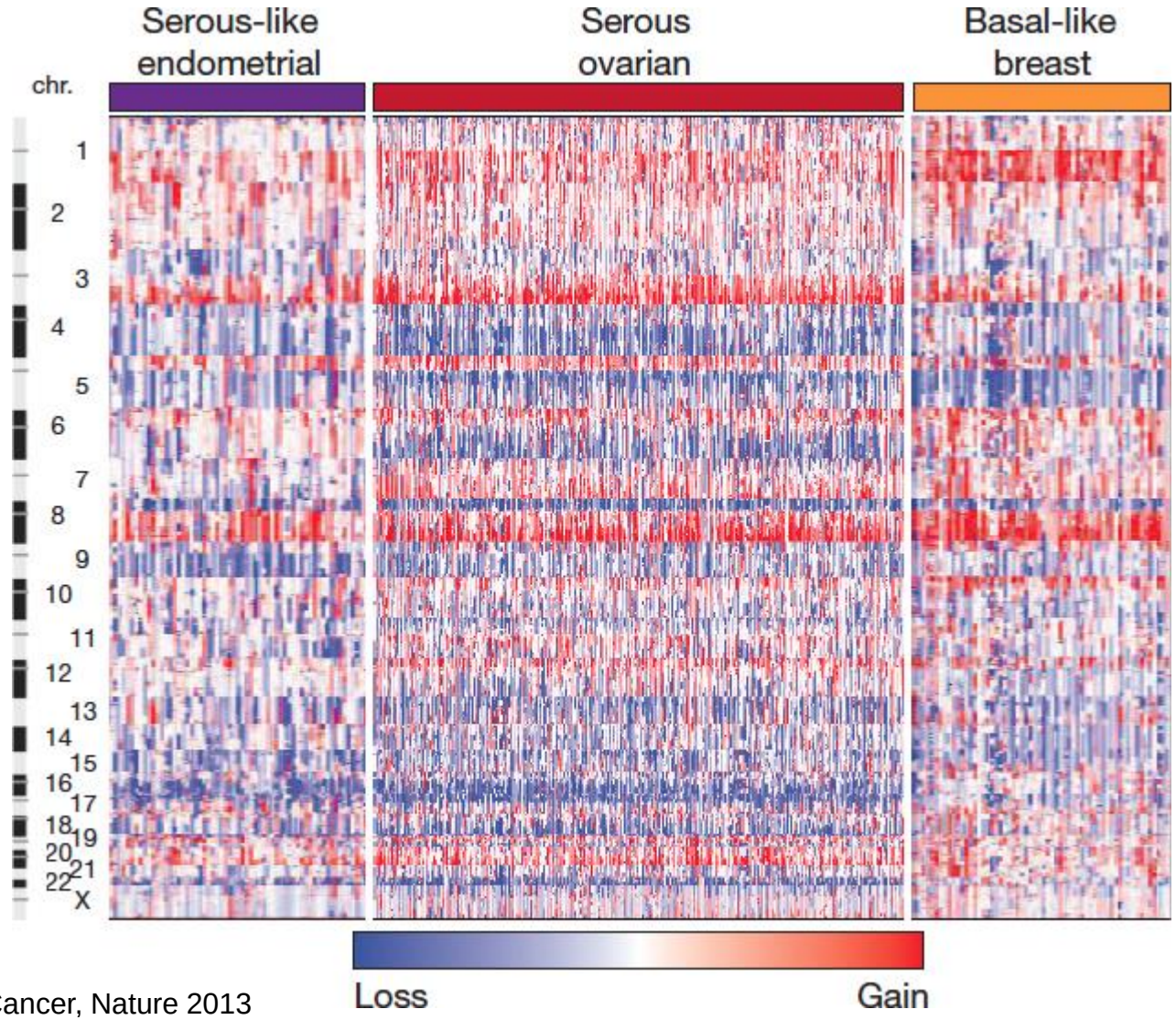
6 Subtypes



Lehmann & Pietenpol. J Pathol 2014

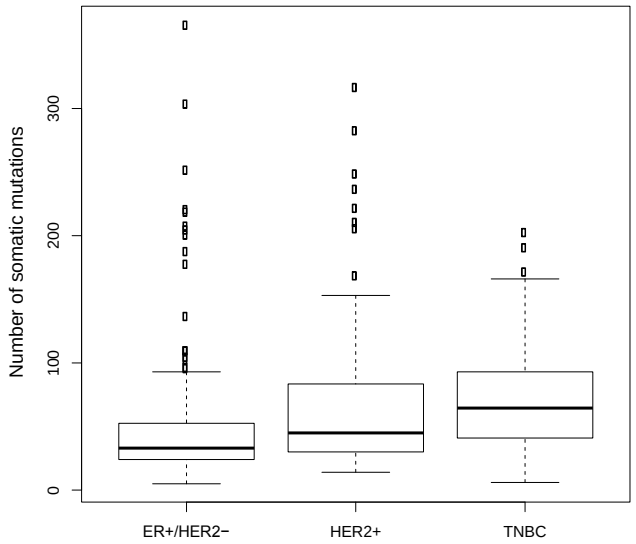
Mutational profiles

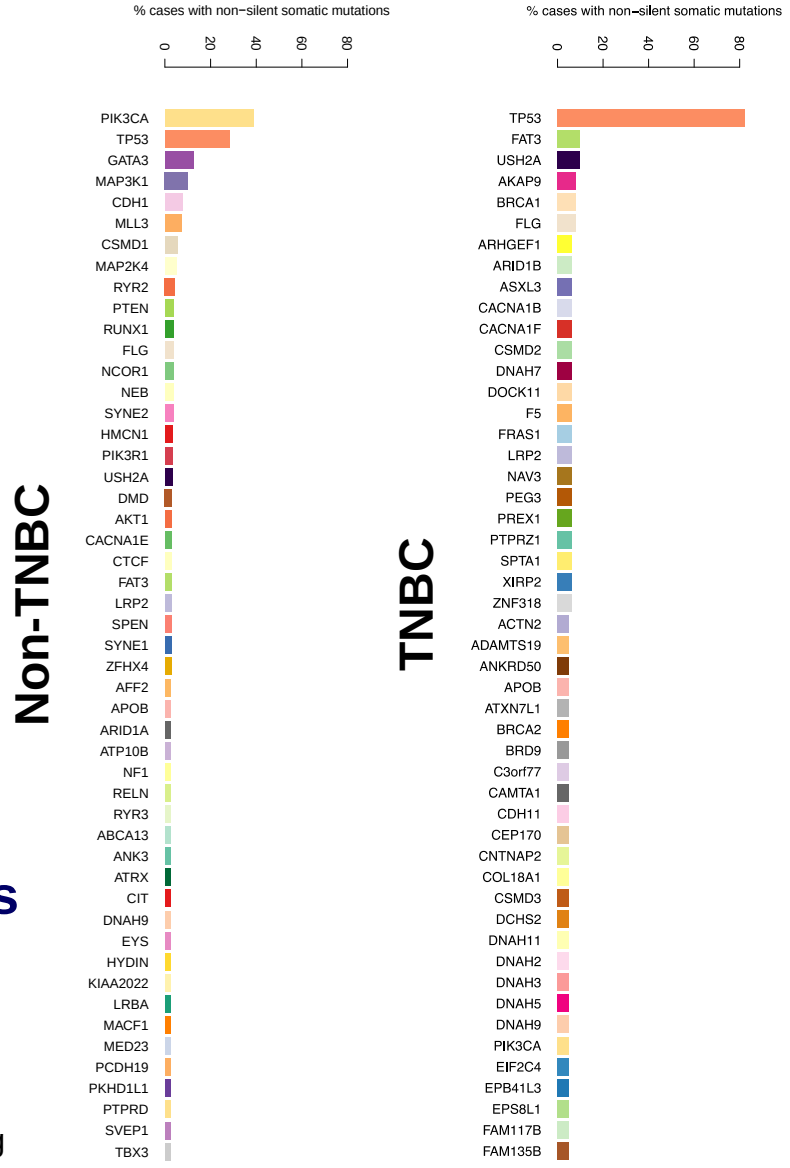
TNBCs display complex patterns of gene copy number alterations



TCGA Endometrial Cancer, Nature 2013

TNBCs have complex repertoires of somatic genetic alterations

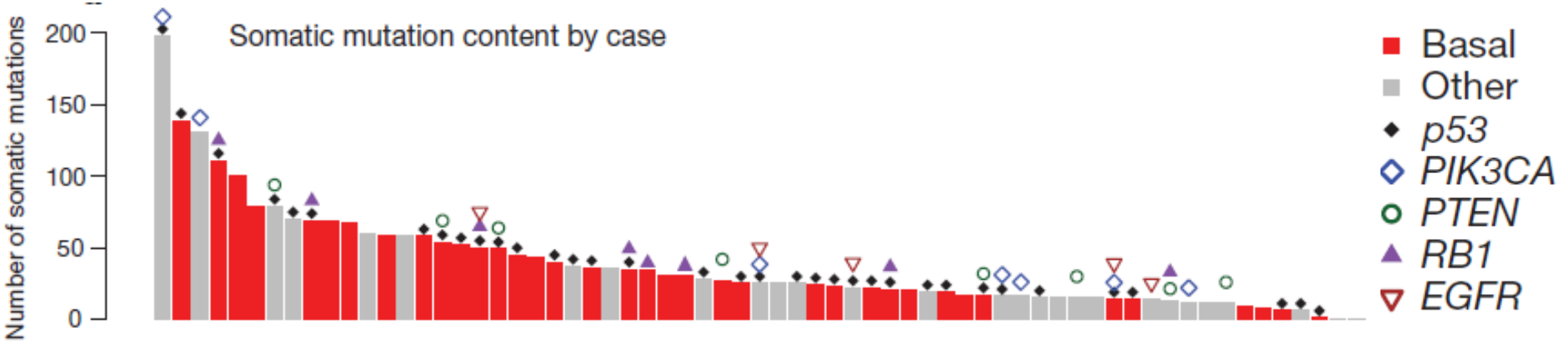




High number of somatic mutations
Few highly recurrently mutated genes

Shah et al. Nature 2012; Natrajan et al. J Pathol 2012, cbioportal.org

Triple-negative and basal-like cancers have complex mutational repertoire



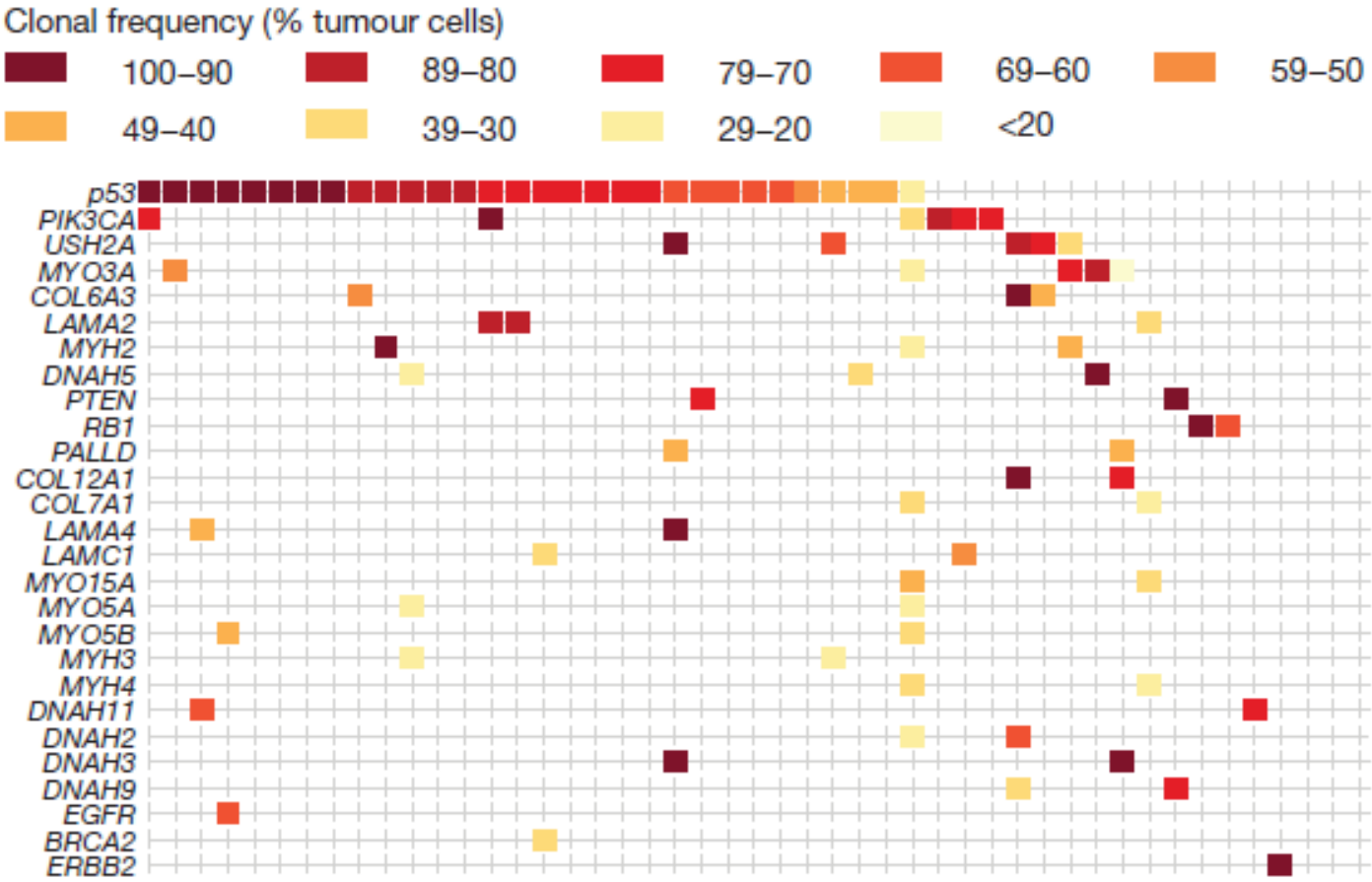
TNBC	PIK3CA H1047R/L	PIK3CA E545K
AR+ (n=25)	9	1
AR- (n=25)	1	0

Shah et al. Nature 2012

Lehmann et al. Breast Cancer Res 2014

Intra-tumour genetic heterogeneity

TNBCs often display intra-tumour genetic heterogeneity at diagnosis



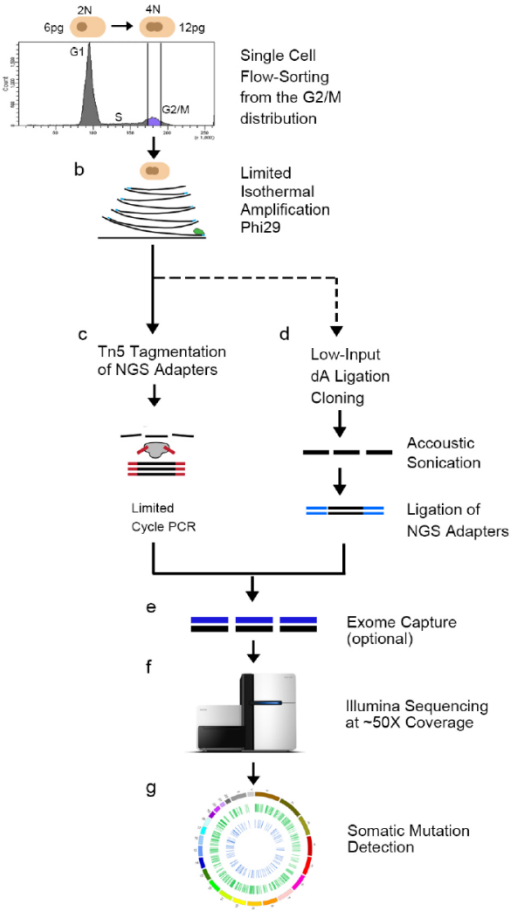
Shah et al. Nature 2012

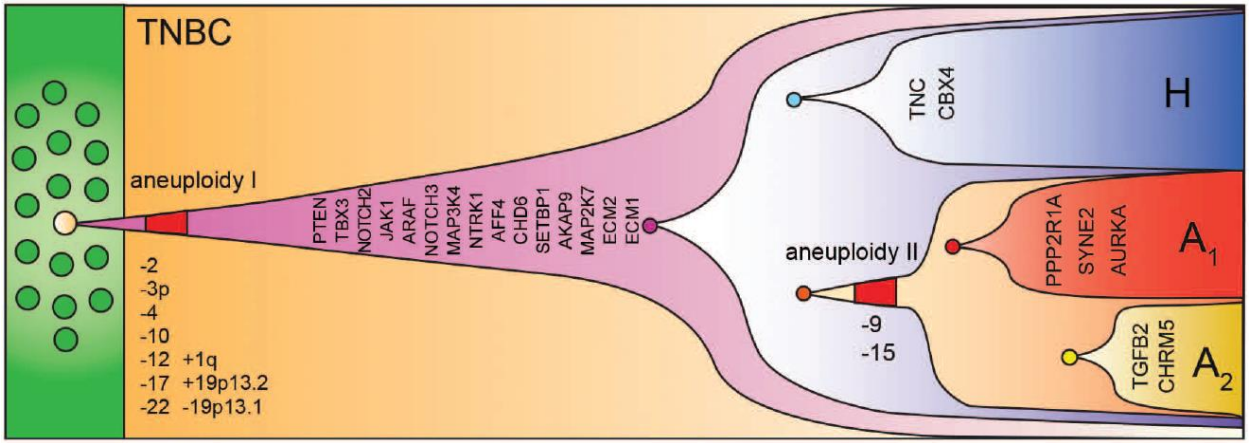
ARTICLE

doi:10.1038/nature13600

Clonal evolution in breast cancer revealed by single nucleus genome sequencing

Yong Wang[1], Jill Waters[1], Marco L. Leung[1,2], Anna Unruh[1], Whijae Roh[1], Xiuqing Shi[1], Ken Chen[3], Paul Scheet[2,4], Selina Vattathil[2,4], Han Liang[3], Asha Multani[1], Hong Zhang[5], Rui Zhao[6], Franziska Michor[6], Funda Meric-Bernstam[7] & Nicholas E. Navin[1,2,3]





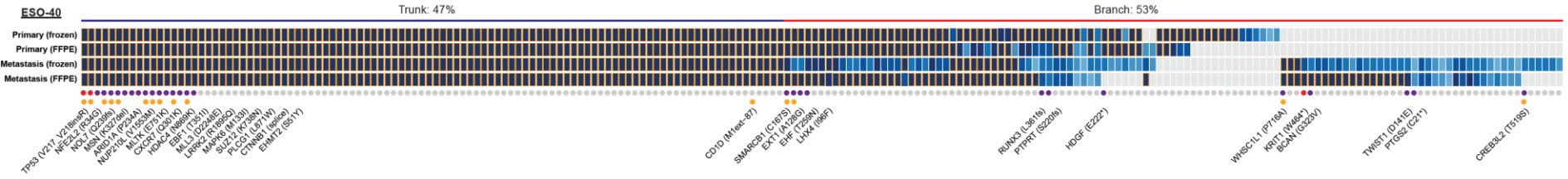
Conclusions

- TNBC is a heterogeneous disease
  - Histological subtypes with distinct outcomes
  - Molecular subtypes
  - Complex genomes
  - Few highly recurrently mutated genes
  - Display intra-tumour genetic heterogeneity at diagnosis
- TNBC is merely an operational term
  - Collection of heterogeneous diseases

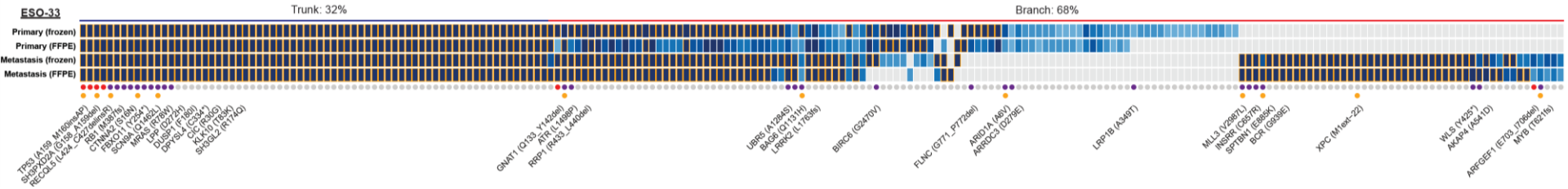
TNBC: primary and metastases from patients with *de novo* stage IV breast cancer

Whole exome sequencing 250x + SNP6 arrays + targeted capture validation (700x) of all mutations

Contra-lateral lymph node metastasis



Skin metastasis



Cancer cell fraction

- 0%
- >0%-1%
- >1%-5%
- >5%-20%
- >20%-40%
- >40%-60%
- >60%-80%
- >80%-100%
- Not assessed
- Clonal

- Pathogenic
- Likely pathogenic
- Indeterminate and likely non-pathogenic

Presence in Cancer Gene Census, Cancer5000-S and 127 Kandoth *et al.*

Ng CK, Bidard FC, Weigelt B, Norton L & Reis-Filho JS, unpublished

Not all TN are basal-like!
Not all basal-like are TN!

Bastien *et al. BMC Medical Genomics* 2012, **5**:44
http://www.biomedcentral.com/1755-8794/5/44

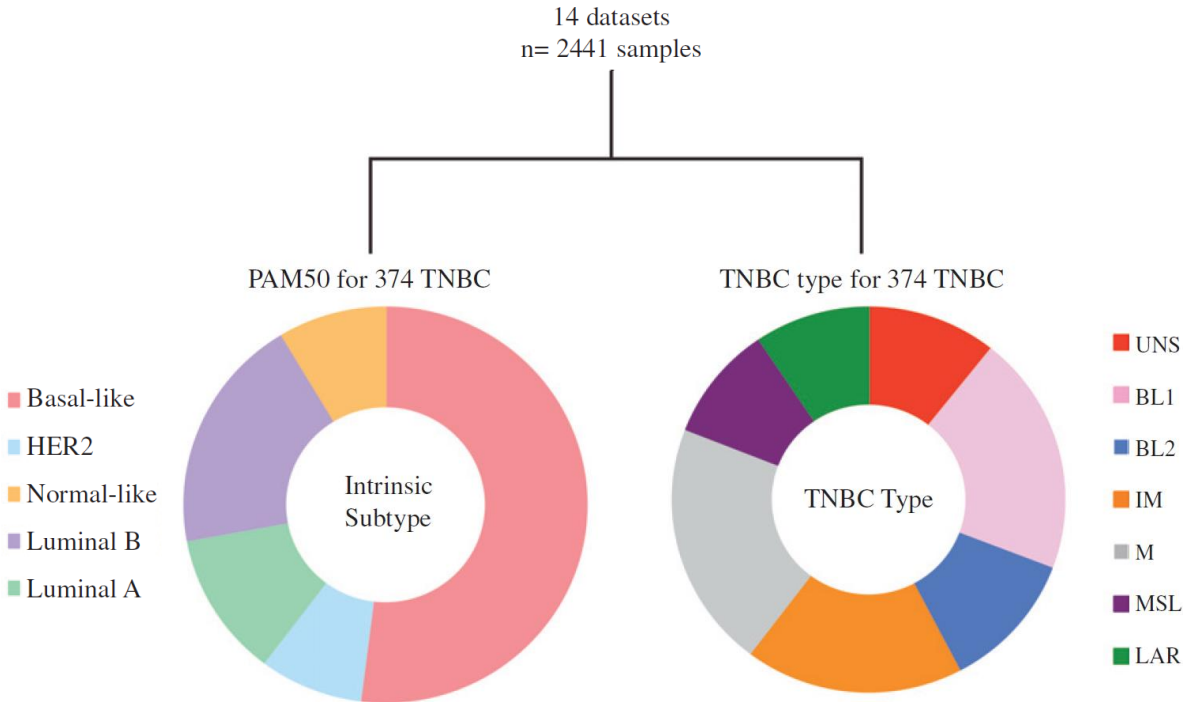
BMC Medical Genomics

RESEARCH ARTICLE Open Access

PAM50 Breast Cancer Subtyping by RT-qPCR and Concordance with Standard Clinical Molecular Markers

		PAM50 test (2012 version)				
		Basal	HER2	Luminal A	Luminal B	
IHC	TN	57	30	4	10	**43%**
	Non-TN	13	144	273	251	
		19%				

Comparison of classifications: PAM50 vs 6 subtypes of TNBC



Lehmann & Pietenpol. J Pathol 2014