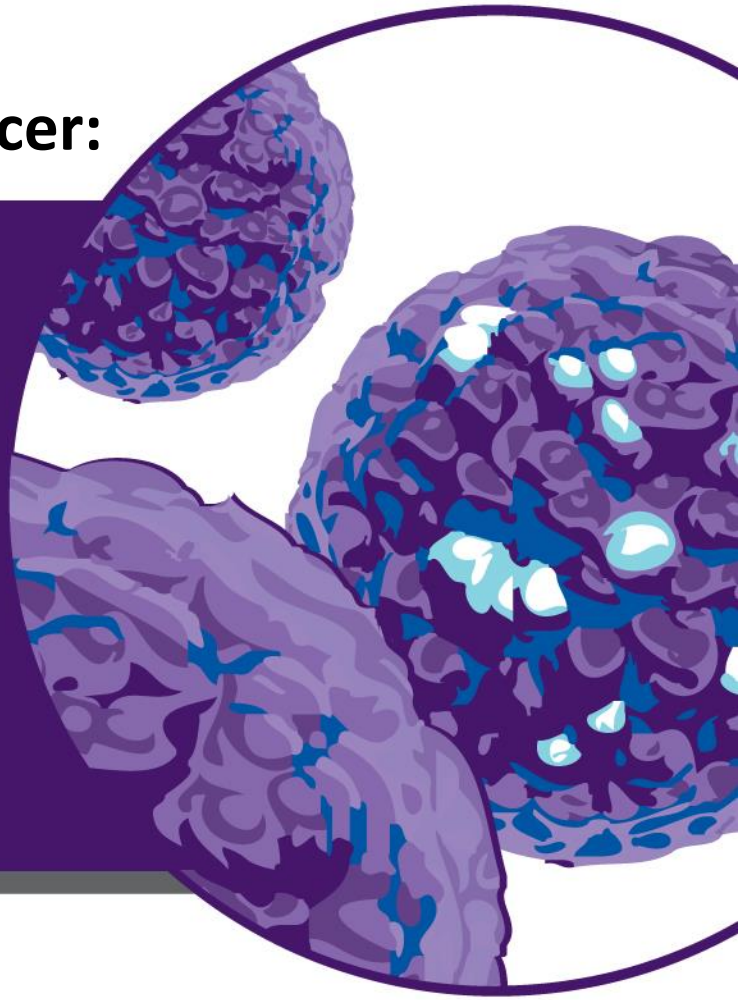
A Molecular Portrait of Asian Breast Cancer:

Multi-Omics and Immune Profiling of a Prospective Breast Cancer Cohort Enriched in Young, Premenopausal Patients

Zhengyan ‘George’ Kan

Pfizer Oncology Research, San Diego, CA



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Disclosure

- I am an employee of Pfizer Inc.
- I own Pfizer stocks.

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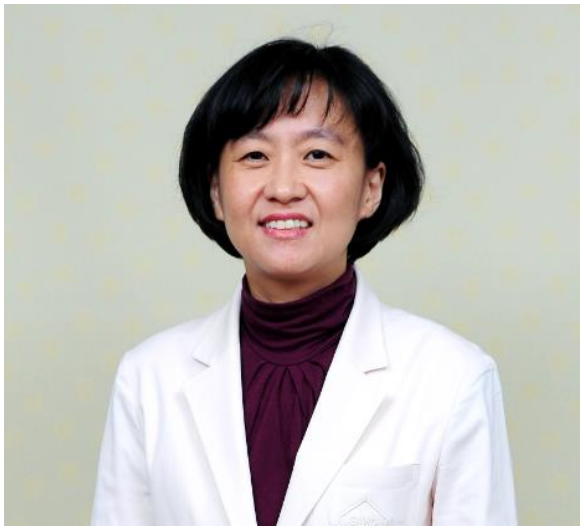
Collaboration between SMC and Pfizer



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Outline

- Background on Asian young, pre-menopausal breast cancer (YBC)
- Genomic landscape of Asian YBC and OBC
- Comparing molecular characteristics between YBC and OBC
- Immune-oncology (IO) profiling using expression signature and histopathological analyses

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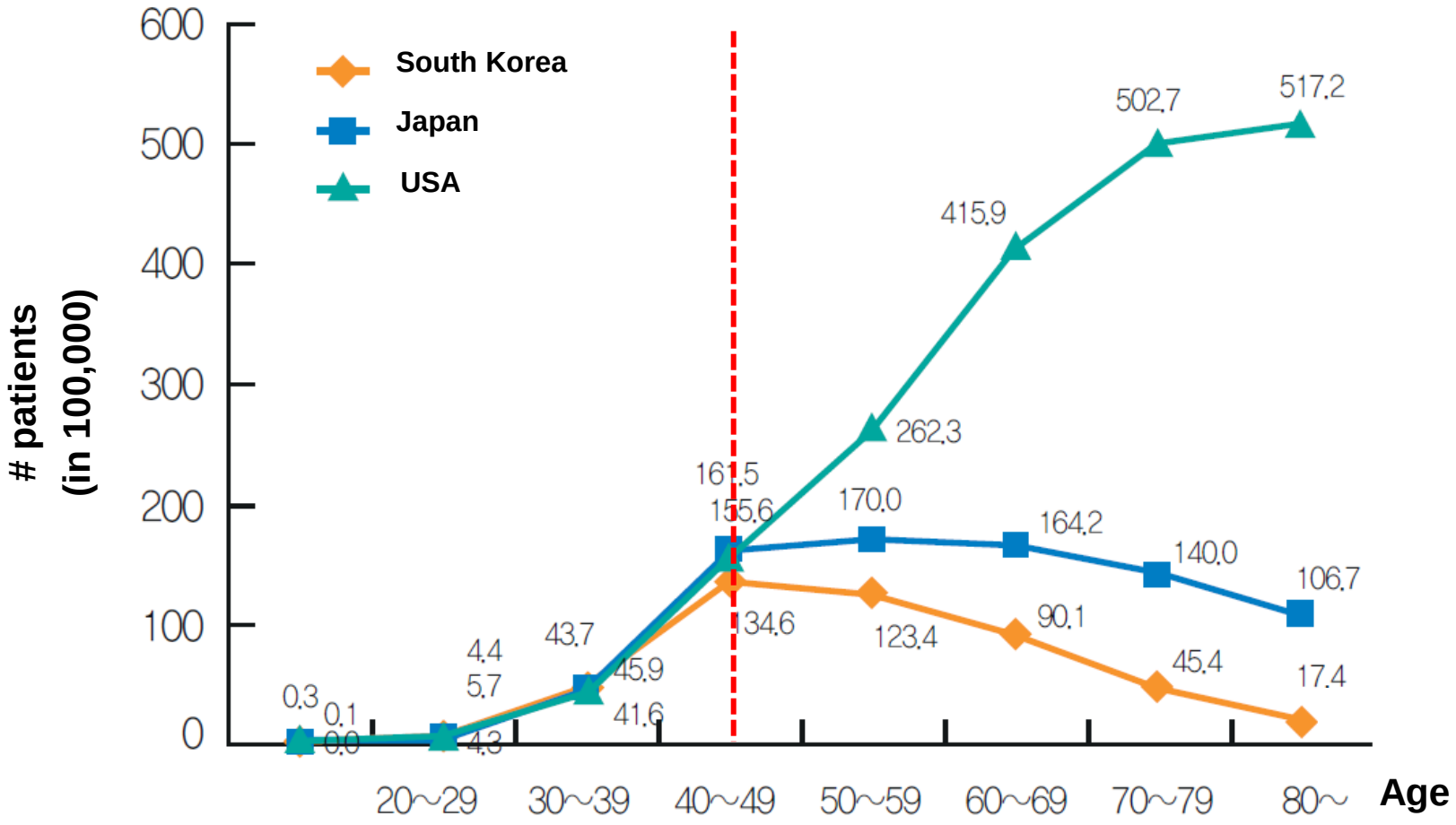
The Proportion of YBC is Significantly Higher in East Asia than in the West



South Korea: KBCS registry (2008)
Japan: Cancer statistics in Japan (2007)
USA: SEER data (2004-2008)

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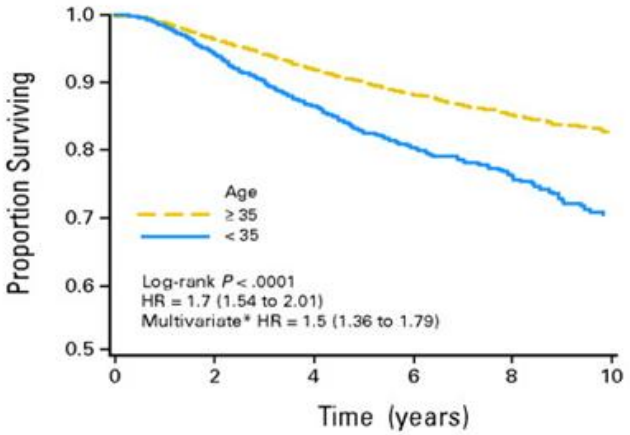
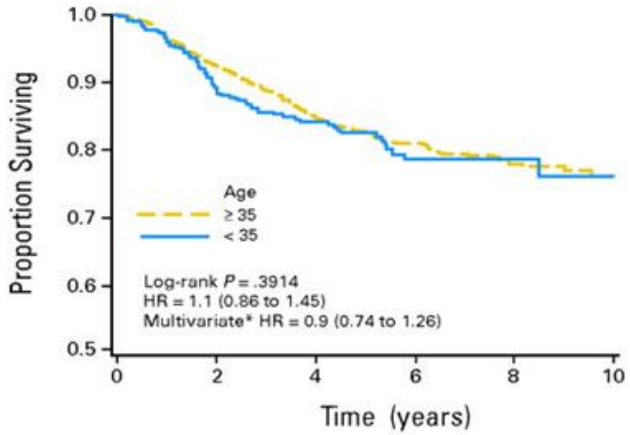
Poor Outcome of HR+ Breast Cancer at Very Young Age is due to Tamoxifen Resistance

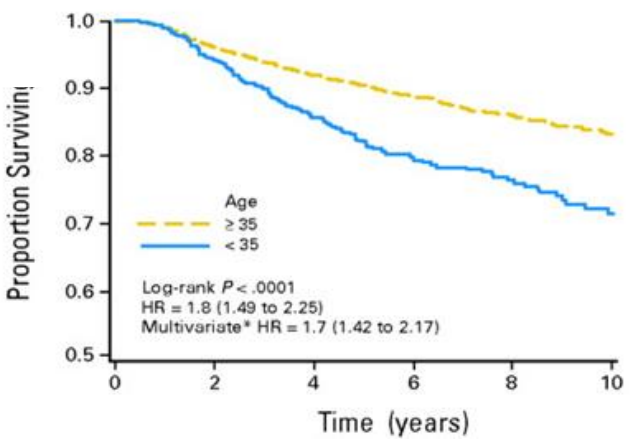
All pts



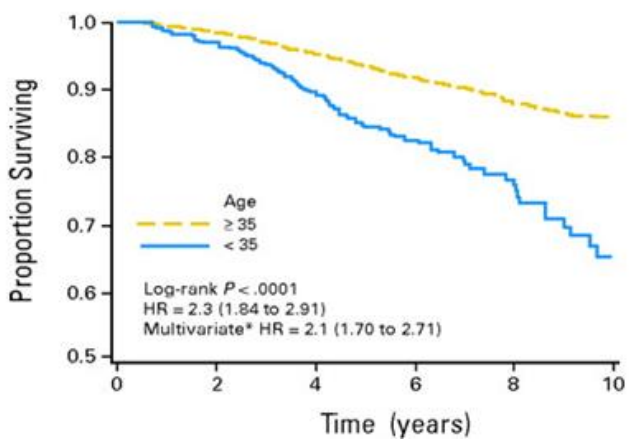
HR(-)



HR unknown



HR(+)



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Report from the Korean Breast Cancer Society. **J Clin Oncol. 2007** Jun 10;25(17):2360-8.

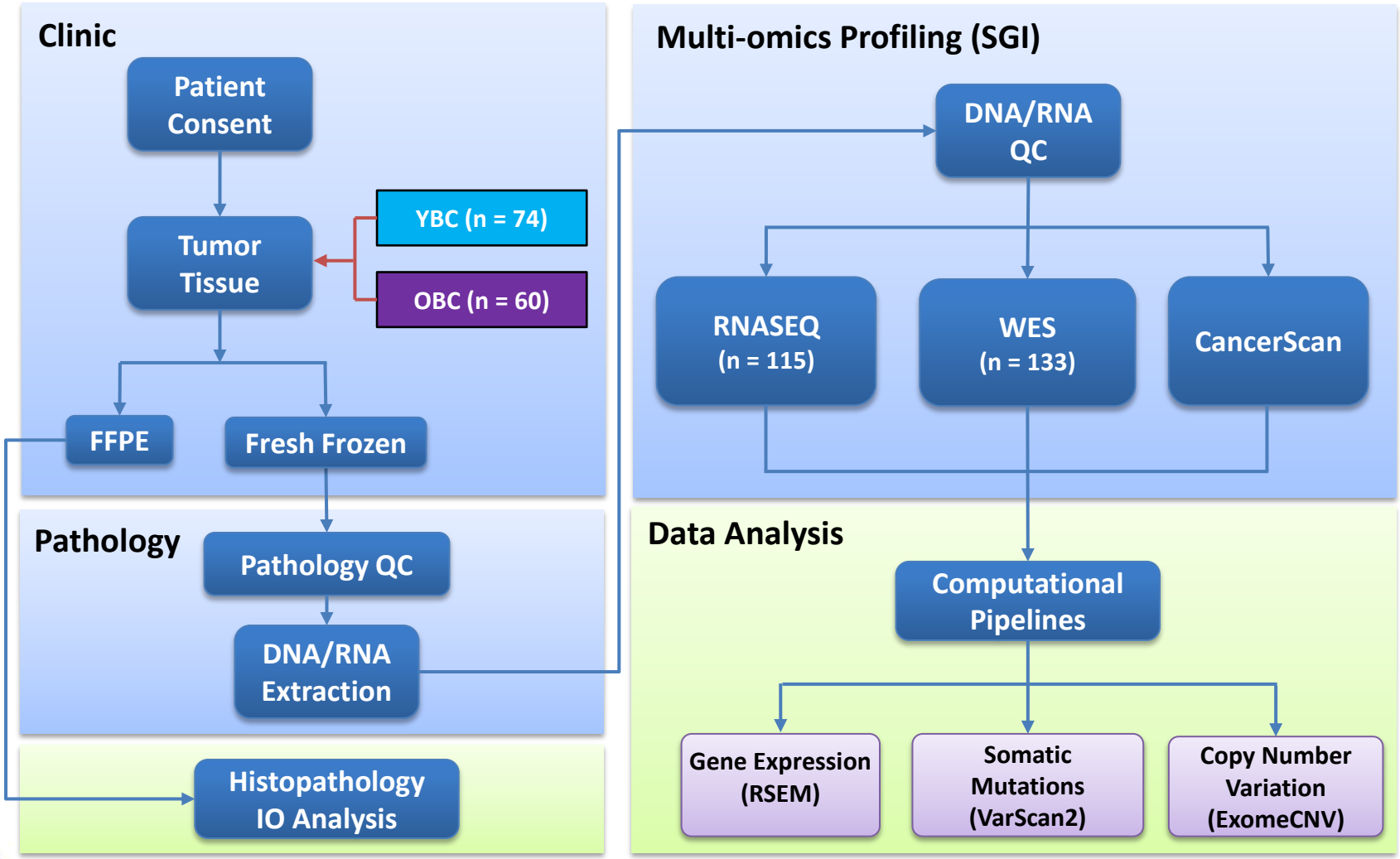
Introduction

- The proportion of YBC (age ≤ 40) among BC in East Asia is estimated to be 16-32%, significantly higher than the 7% reported in Western countries.

- Breast cancers (BC) in younger, premenopausal patients (YBC) tend to be more aggressive with worse prognosis, higher chance of relapse and poorer response to endocrine therapies compared to breast cancers in older patients (OBC).

- Genomic and molecular characterizations have deepened our understanding of breast cancer biology, however, the molecular bases of Asian YBC remains poorly characterized.

Study Work Flow



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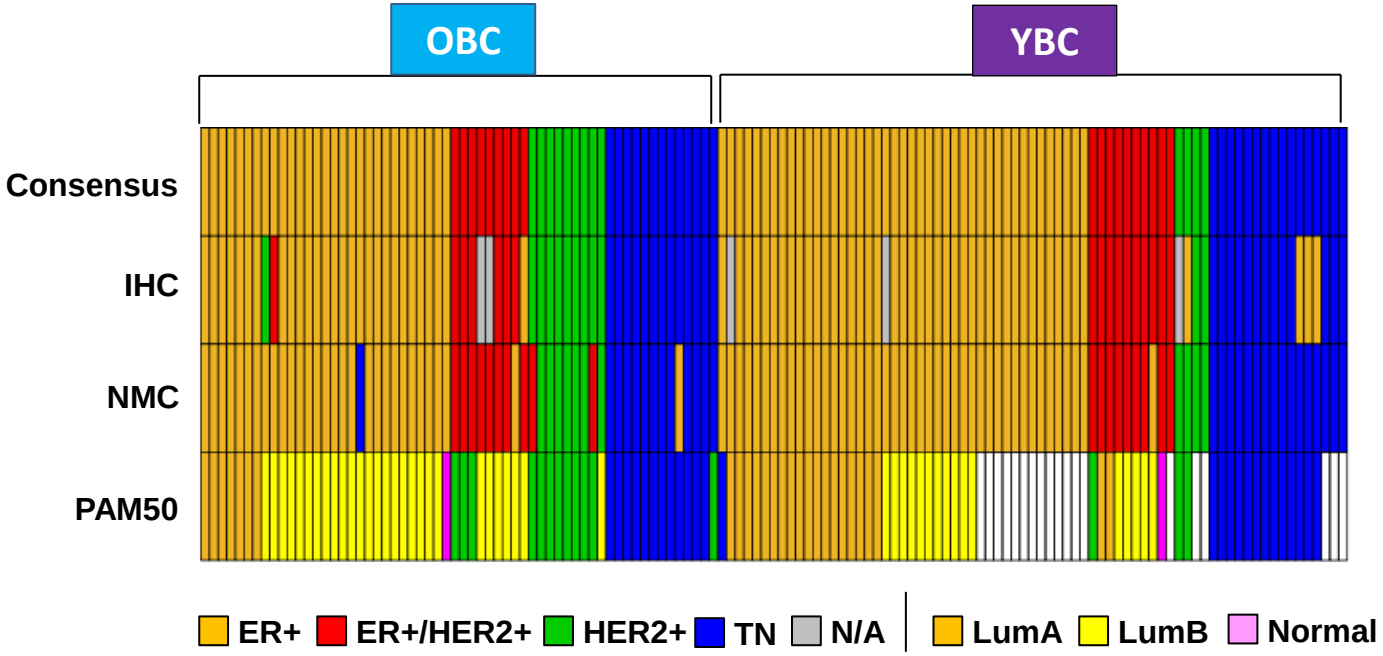
Molecular Subtype Classification

- We identified molecular subtypes using three methods: ER and HER2 immunohistochemistry analyses (IHC); gene expression classifier called PAM50; naïve Bayesian classifier (NMC) based on *ESR1*, *PGR* gene expression and *ERBB2* copy number data.
- A consensus classification was derived based on all three classifications, which are 92% concordant.



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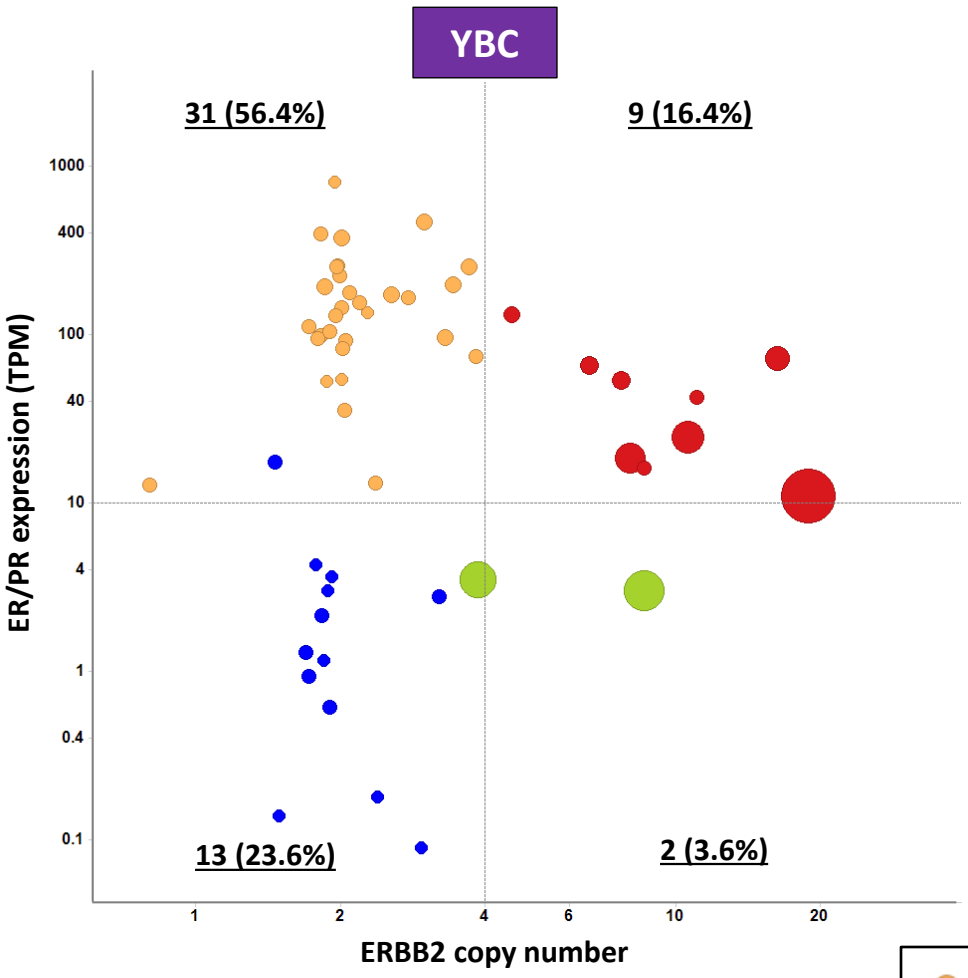
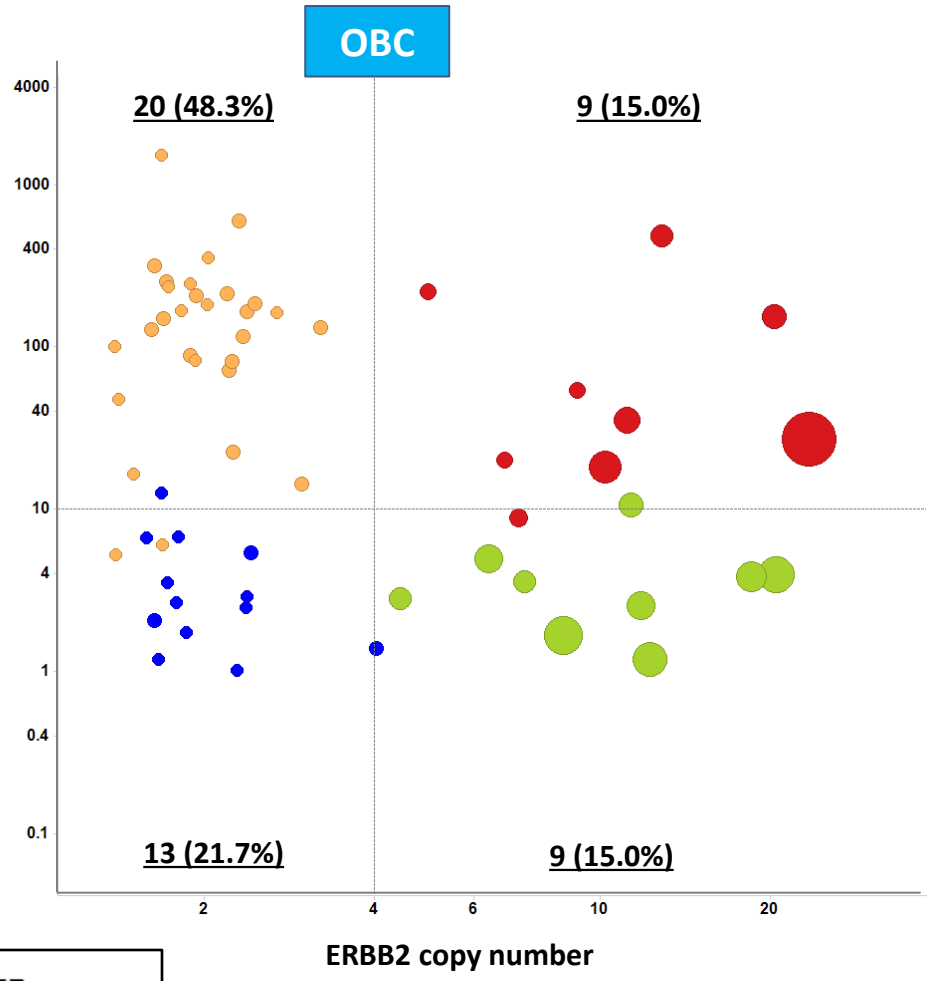
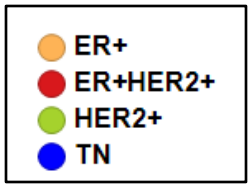
Molecular Subtype Comparison







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Significantly Mutated Genes

Gene	# Mut. samples	Mut. Freq. (n = 133)	Mut. Rate (Mb)	p-value	q-value	Mut. Freq. (TCGA)	Rank (TCGA)	Gene Description
TP53	63	47.37%	153.34549	0	0	36.9%	1	tumor protein p53
GATA3	18	13.53%	55.74866	8.88E-16	8.38E-12	10.7%	3	GATA binding protein 3
PIK3CA	39	29.32%	40.9562	3.77E-15	2.37E-11	35.5%	2	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
CBFB	6	4.51%	30.50222	4.19E-08	0.000198	1.6%	13	core-binding factor, beta subunit
PTEN	4	3.01%	9.93236	1.39E-06	0.00525	3.4%	9	phosphatase and tensin homolog
NF1	7	5.26%	2.88505	6.55E-05	0.195	2.8%	25	neurofibromin 1
ARID1A	6	4.51%	3.28988	7.23E-05	0.195	2.4%	N/A	AT rich interactive domain 1A (SWI-like)

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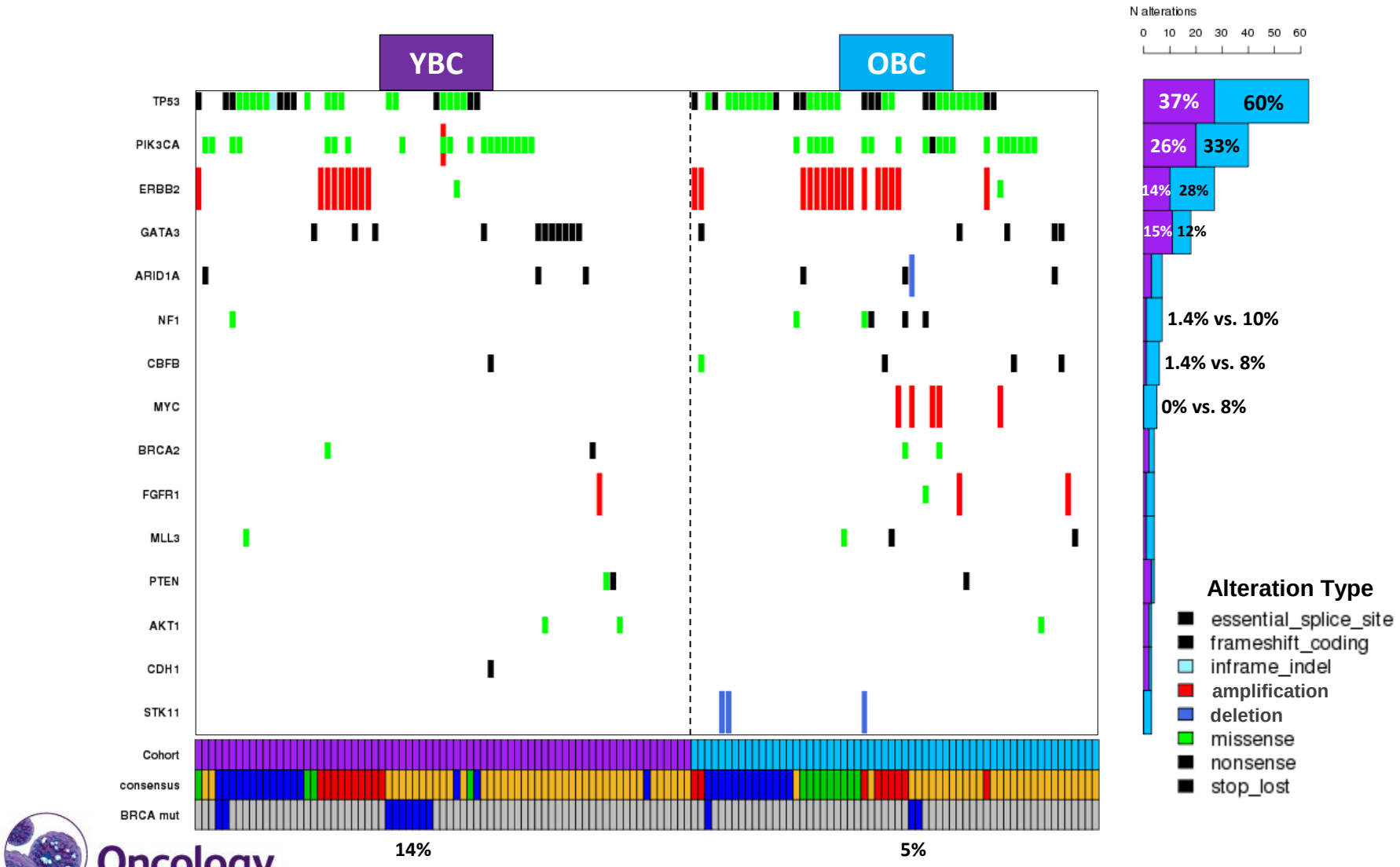
Landscape of Genomic Alterations



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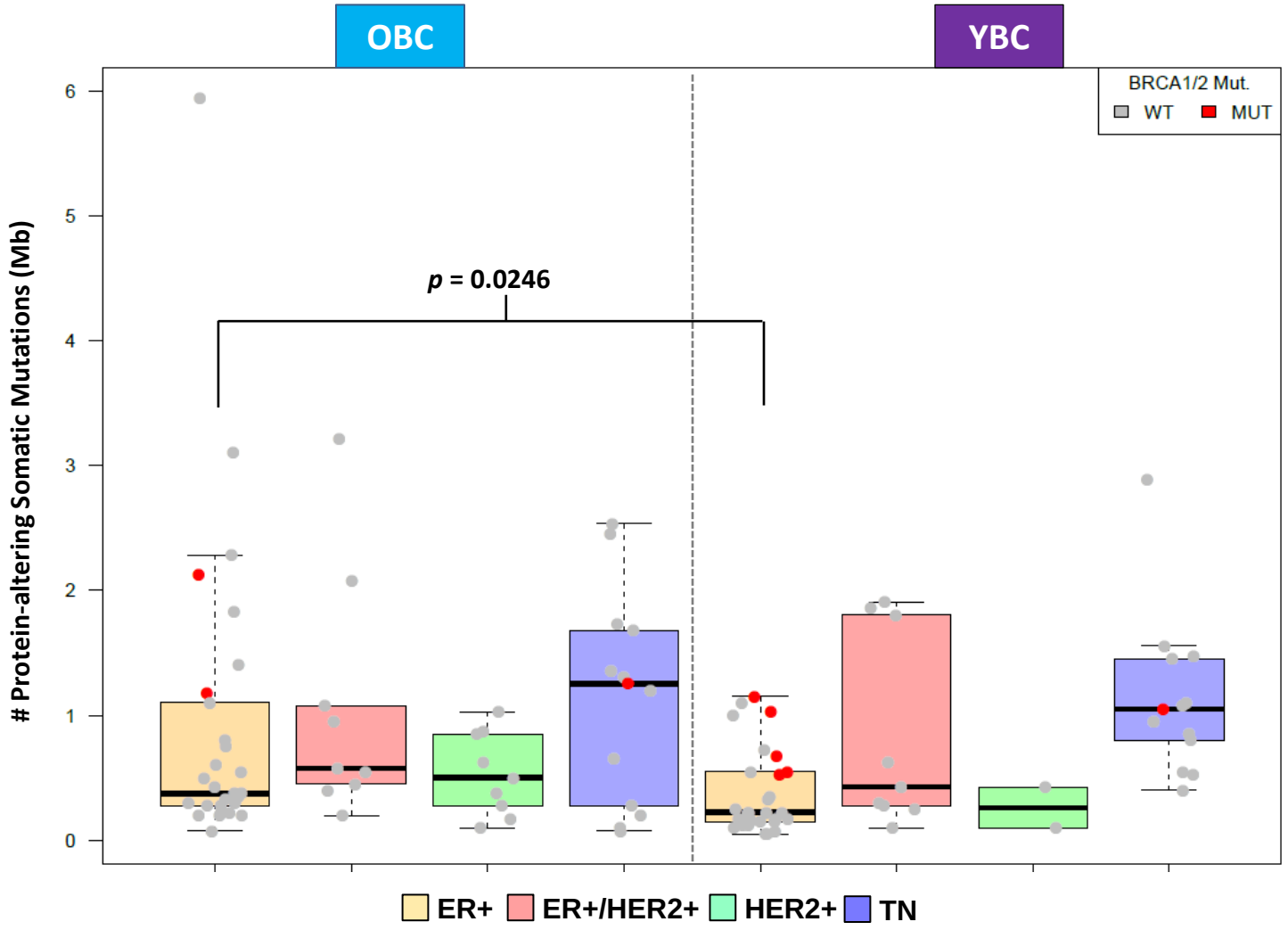
Mutations More Prevalent in OBC than in YBC



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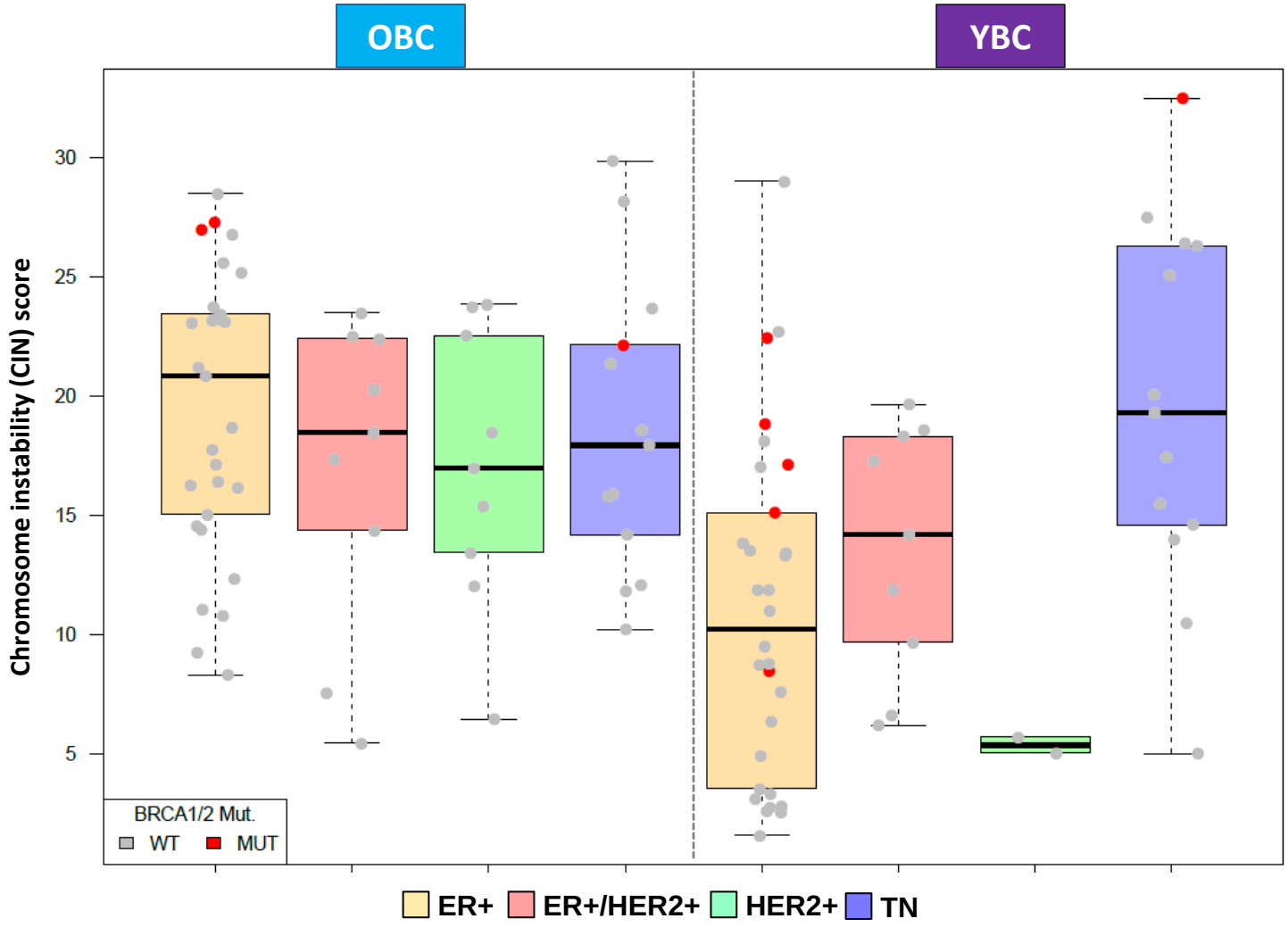
CNVs More Prevalent in OBC than in YBC



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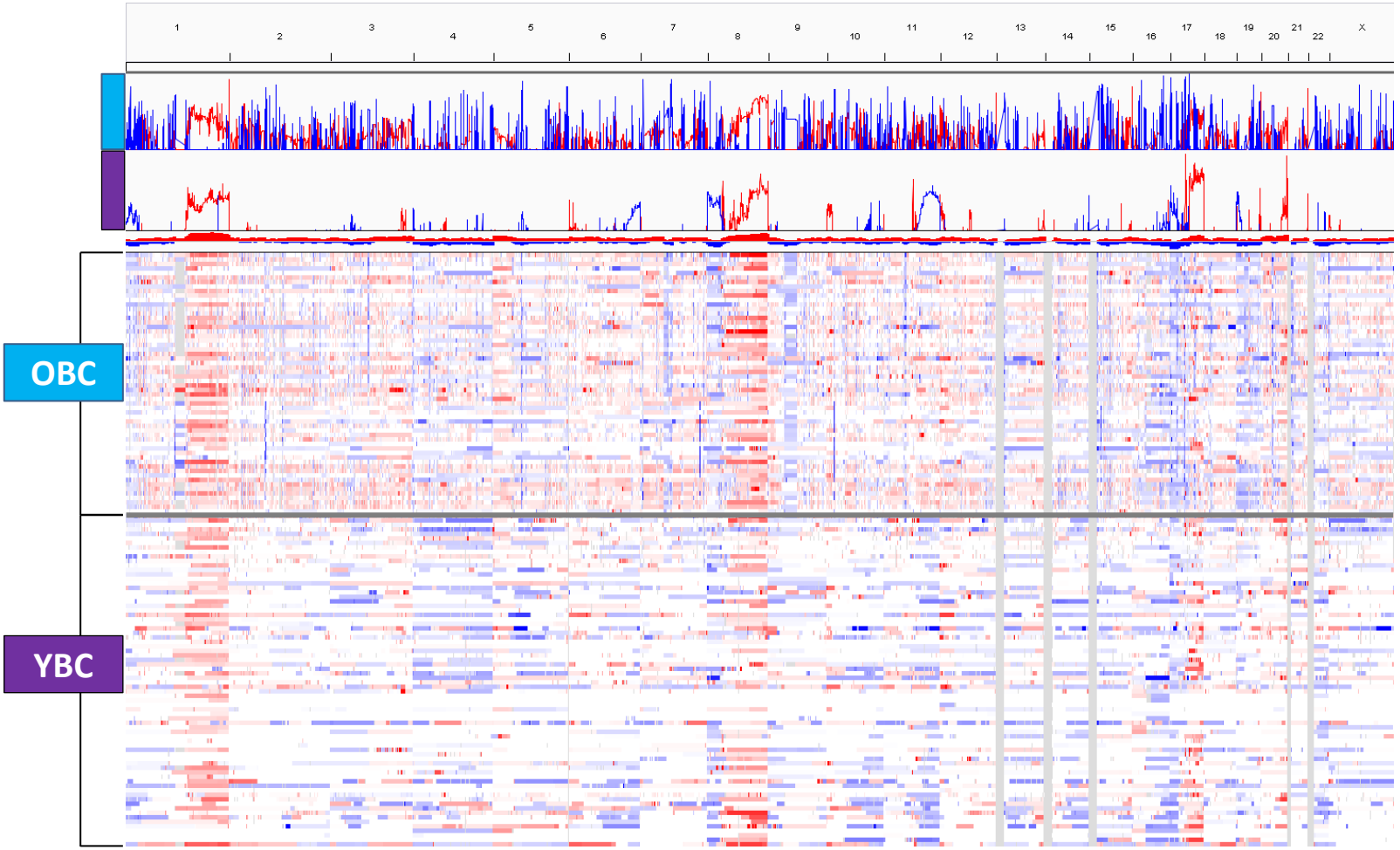
CNV More Prevalent in OBC than in YBC



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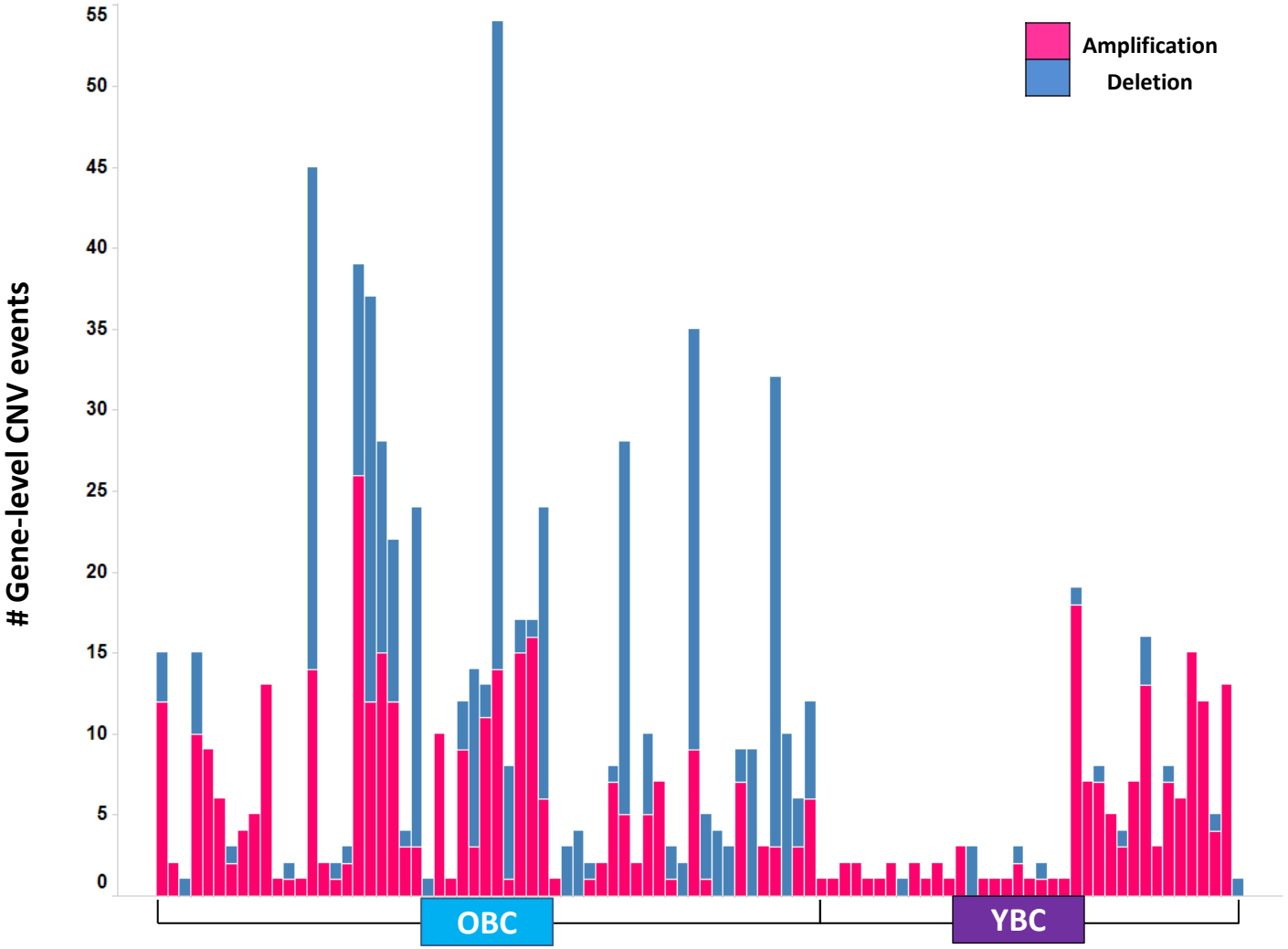
CNV More Prevalent in OBC than in YBC



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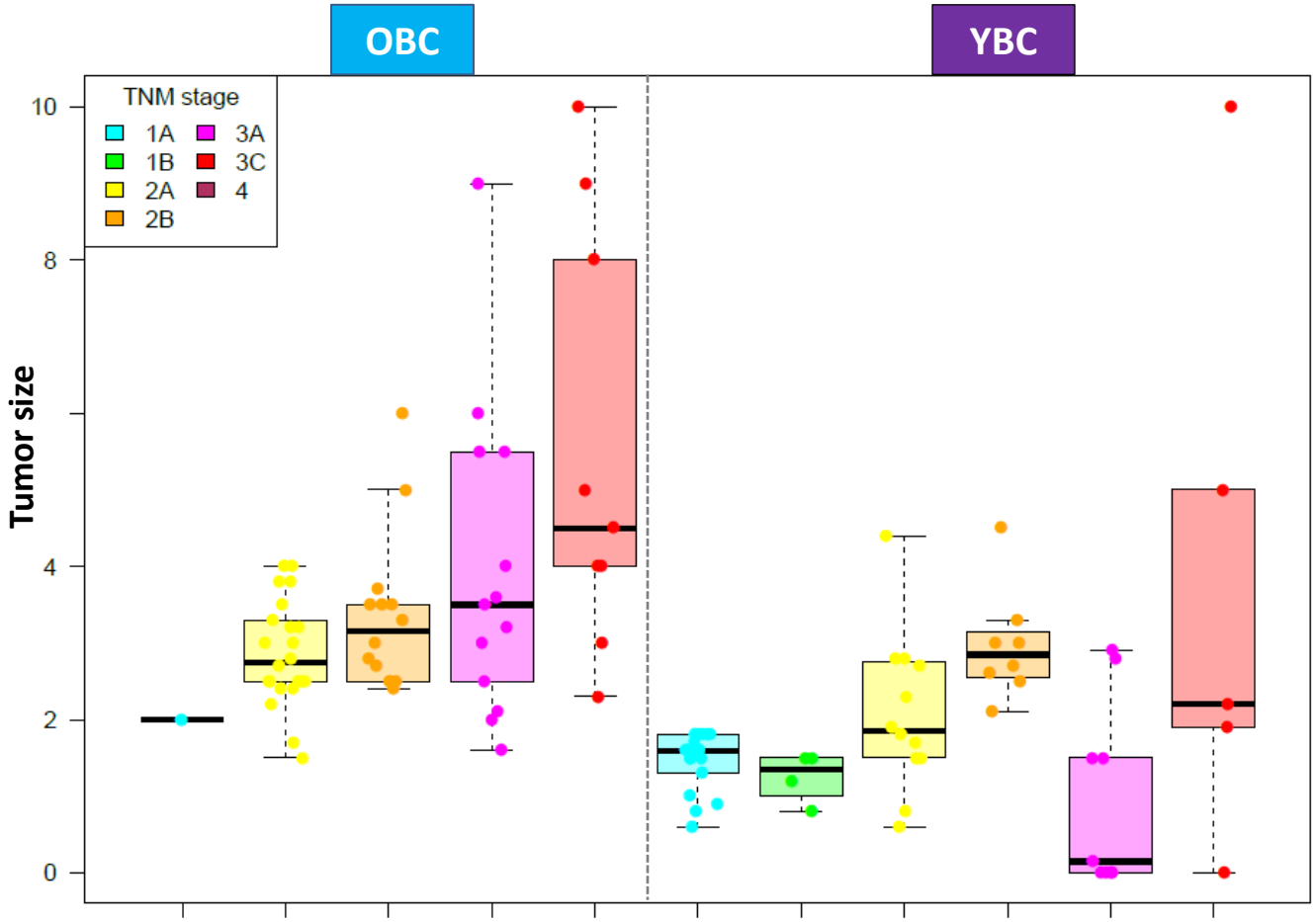
OBC Tumors More Proliferative than YBC



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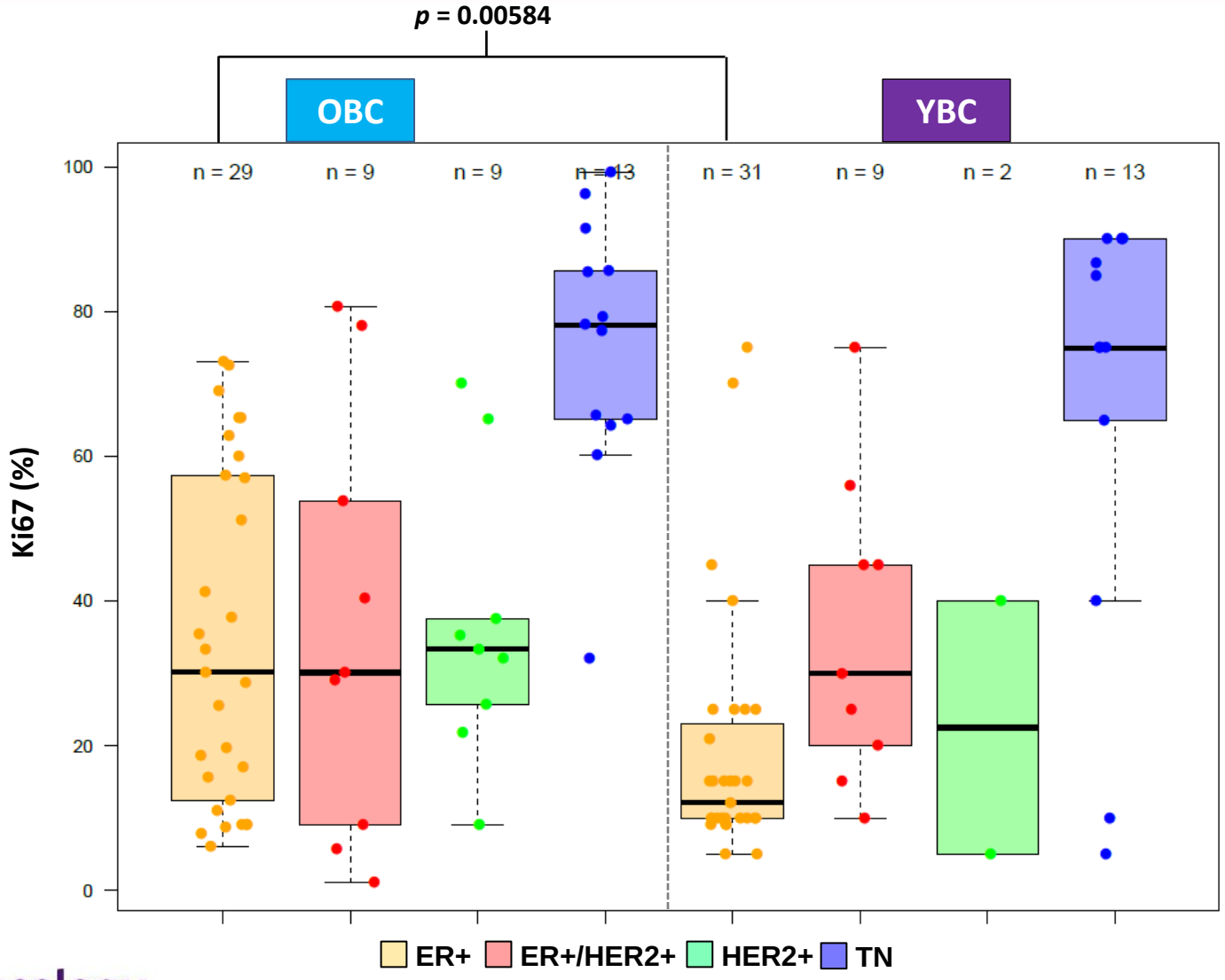
OBC Tumors More Proliferative than YBC



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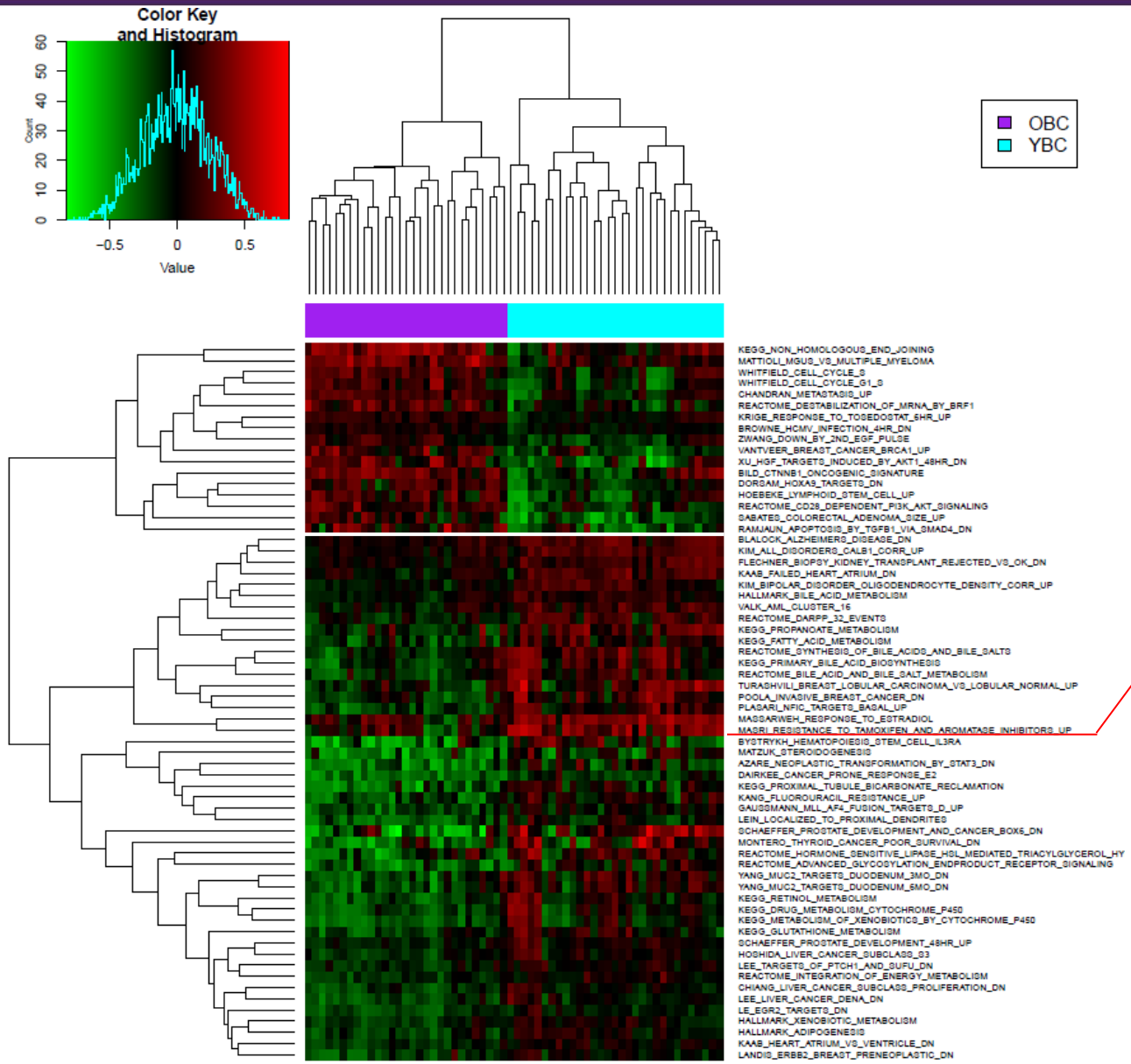
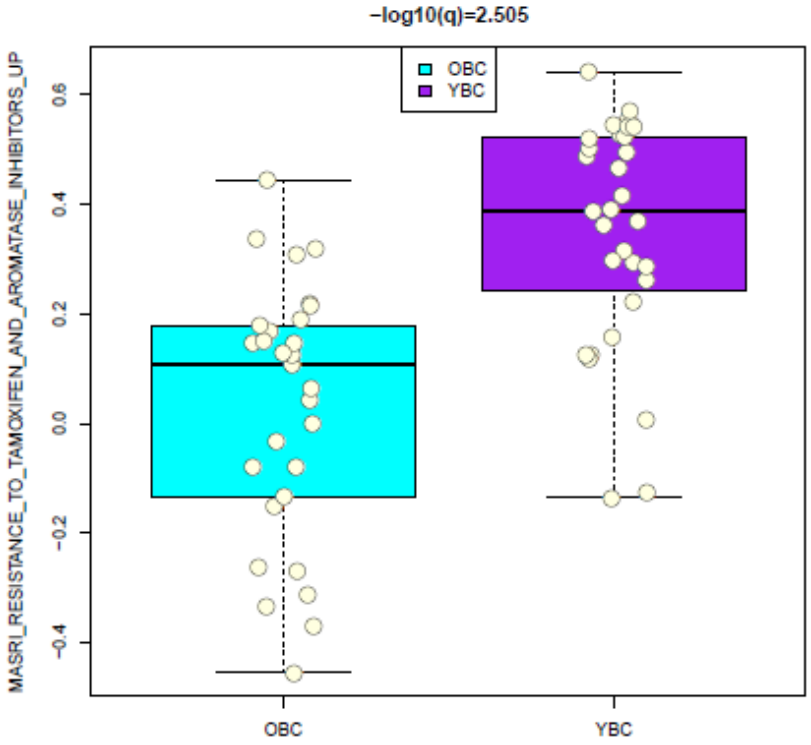
What Pathways are Differentially Expressed in HR+ YBC vs. OBC?



MASRI RESISTANCE TO TAMOXIFEN AND AROMATASE INHIBITORS UP

Endocrine Therapy Resistance Signatures Up-regulated in YBC



Research Article

Genome-Wide Analysis of Aromatase Inhibitor-Resistant, Tamoxifen-Resistant, and Long-Term Estrogen-Deprived Cells Reveals a Role for Estrogen Receptor

Selma Masri,[1] Sheryl Phung,[1] Xin Wang,[1] Xiwei Wu,[2] Yate-Ching Yuan,[2] Lawrence Wagman,[3] and Shiuan Chen[1]

[1]Department of Surgical Research, [2]Division of Information Sciences, and [3]Department of General Oncologic Surgery, Beckman Research Institute of the City of Hope, Duarte, California

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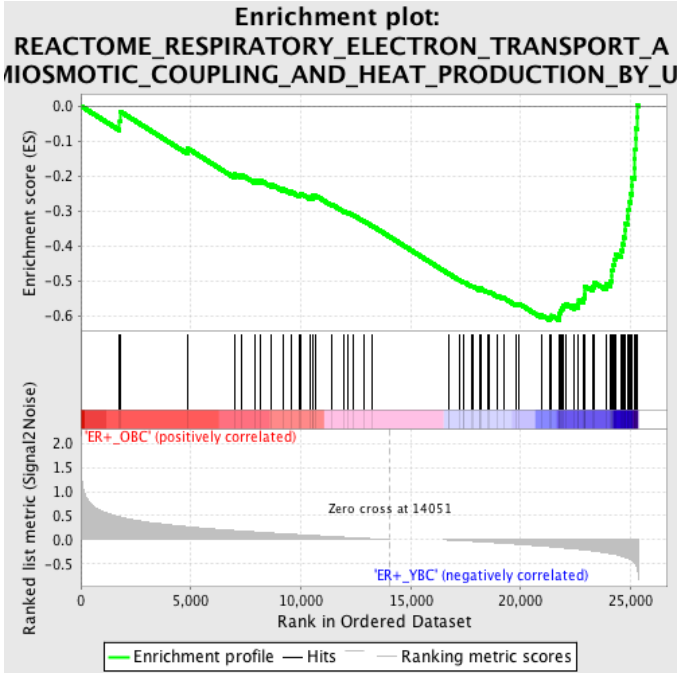
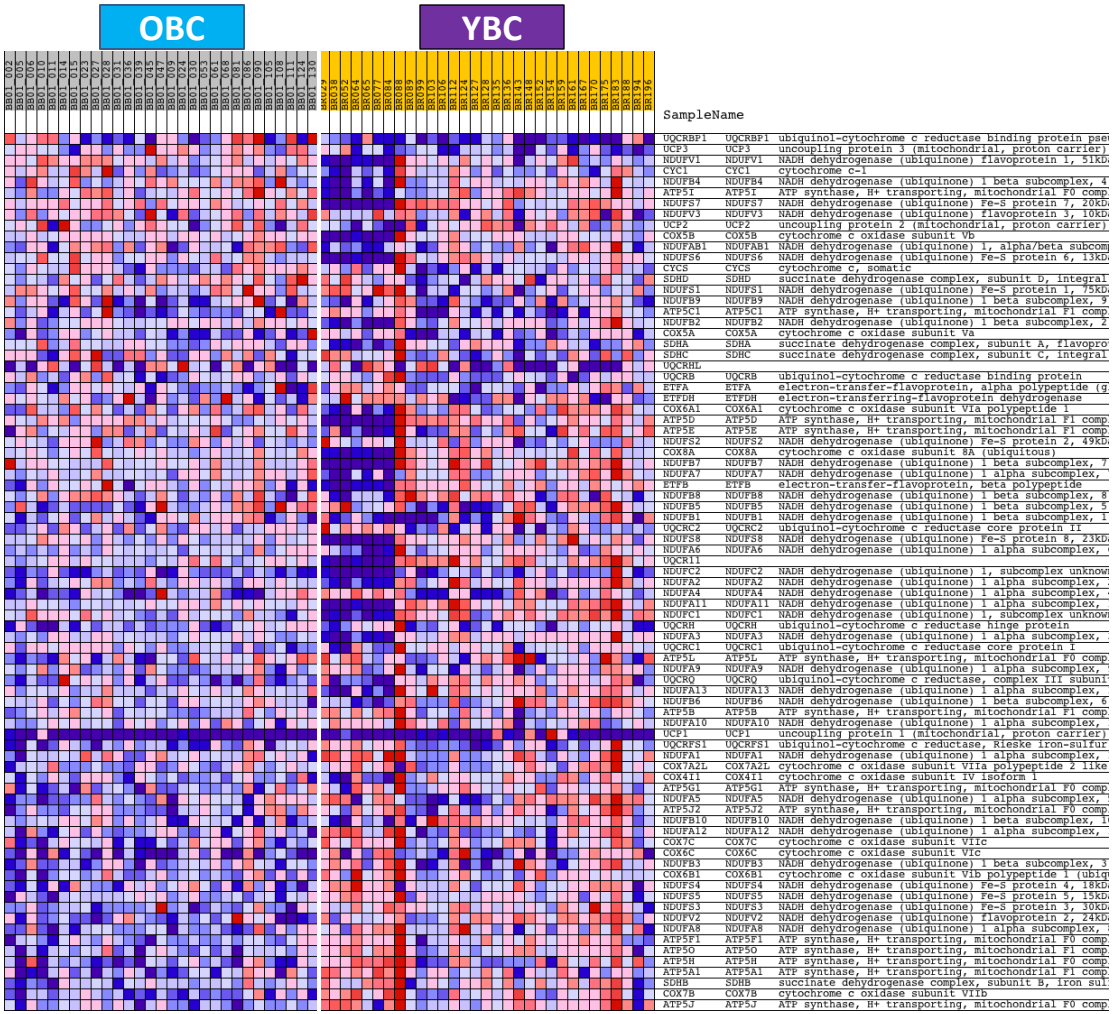
Oxidative Phosphorylation Pathways Up-regulated in HR+ YBC vs. OBC





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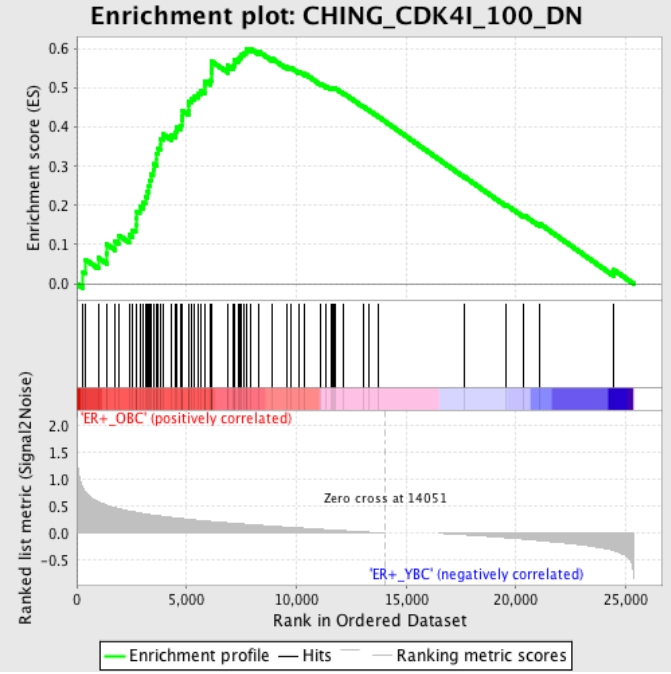
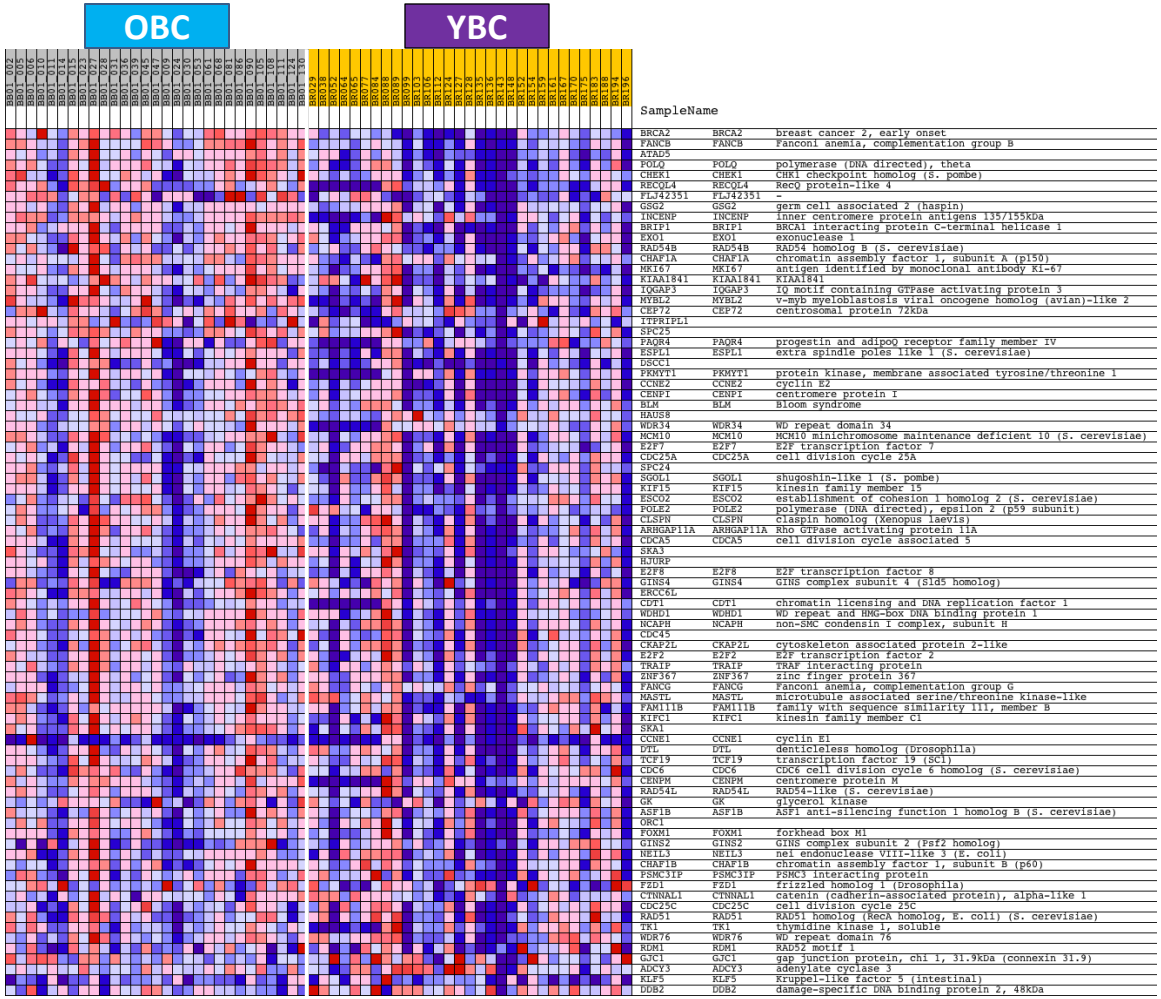
Cell Cycle and Proliferation Pathways Up-regulated in HR+ OBC vs. YBC





BRCA2	BRCA2	breast cancer 2, early onset
FANCB	FANCB	Fanconi anemia, complementation group B
ATAD5		
POLQ	POLQ	polymerase (DNA directed), theta
CHEK1	CHEK1	CHK1 checkpoint homolog (S. pombe)
RECQL4	RECQL4	RecQ protein-like 4
FLJ42351	FLJ42351	-
GSG2	GSG2	germ cell associated 2 (haspin)
INCENP	INCENP	inner centromere protein antigens 135/155kDa
BRIP1	BRIP1	BRCA1 interacting protein C-terminal helicase 1
EXO1	EXO1	exonuclease 1
RAD54B	RAD54B	RAD54 homolog B (S. cerevisiae)
CHAF1A	CHAF1A	chromatin assembly factor 1, subunit A (p150)
MKI67	MKI67	antigen identified by monoclonal antibody Ki-67
KIAA1841	KIAA1841	KIAA1841
IQGAP3	IQGAP3	IQ motif containing GTPase activating protein 3
MYBL2	MYBL2	v-myb myeloblastosis viral oncogene homolog (avian)-like 2
CEP72	CEP72	centrosomal protein 72kDa
ITPRIPL1		
SPC25		
PAQR4	PAQR4	progestin and adipoQ receptor family member IV
ESPL1	ESPL1	extra spindle poles like 1 (S. cerevisiae)
DSCC1		
PKMYT1	PKMYT1	protein kinase, membrane associated tyrosine/threonine 1
CCNE2	CCNE2	cyclin E2
CENPI	CENPI	centromere protein I
BLM	BLM	Bloom syndrome
HAUS8		
WDR34	WDR34	WD repeat domain 34
MCM10	MCM10	MCM10 minichromosome maintenance deficient 10 (S. cerevisiae)
E2F7	E2F7	E2F transcription factor 7
CDC25A	CDC25A	cell division cycle 25A
SPC24		
SGOL1	SGOL1	shugoshin-like 1 (S. pombe)
KIF15	KIF15	kinesin family member 15
ESCO2	ESCO2	establishment of cohesion 1 homolog 2 (S. cerevisiae)
POLE2	POLE2	polymerase (DNA directed), epsilon 2 (p59 subunit)
CLSPN	CLSPN	claspin homolog (Xenopus laevis)
ARHGAP11A	ARHGAP11A	Rho GTPase activating protein 11A
CDCA5	CDCA5	cell division cycle associated 5
SKA3		
HJURP		
E2F8	E2F8	E2F transcription factor 8
GINS4	GINS4	GINS complex subunit 4 (Sld5 homolog)
ERCC6L		
CDT1	CDT1	chromatin licensing and DNA replication factor 1
WDHD1	WDHD1	WD repeat and HMG-box DNA binding protein 1
NCAPH	NCAPH	non-SMC condensin I complex, subunit H
CDC45		
CKAP2L	CKAP2L	cytoskeleton associated protein 2-like
E2F2	E2F2	E2F transcription factor 2
TRAIP	TRAIP	TRAF interacting protein
ZNF367	ZNF367	zinc finger protein 367
FANCG	FANCG	Fanconi anemia, complementation group G
MASTL	MASTL	microtubule associated serine/threonine kinase-like
FAM111B	FAM111B	family with sequence similarity 111, member B
KIFC1	KIFC1	kinesin family member C1
SKA1		
CCNE1	CCNE1	cyclin E1
DTL	DTL	denticleless homolog (Drosophila)
TCF19	TCF19	transcription factor 19 (SC1)
CDC6	CDC6	CDC6 cell division cycle 6 homolog (S. cerevisiae)
CENPM	CENPM	centromere protein M
RAD54L	RAD54L	RAD54-like (S. cerevisiae)
GK	GK	glycerol kinase
ASF1B	ASF1B	ASF1 anti-silencing function 1 homolog B (S. cerevisiae)
ORC1		
FOXM1	FOXM1	forkhead box M1
GINS2	GINS2	GINS complex subunit 2 (Psf2 homolog)
NEIL3	NEIL3	nei endonuclease VIII-like 3 (E. coli)
CHAF1B	CHAF1B	chromatin assembly factor 1, subunit B (p60)
FSMC3IP	FSMC3IP	FSMC3 interacting protein
FZD1	FZD1	frizzled homolog 1 (Drosophila)
CTNNAL1	CTNNAL1	catenin (cadherin-associated protein), alpha-like 1
CDC25C	CDC25C	cell division cycle 25C
RAD51	RAD51	RAD51 homolog (RecA homolog, E. coli) (S. cerevisiae)
TK1	TK1	thymidine kinase 1, soluble
WDR76	WDR76	WD repeat domain 76
RDM1	RDM1	RAD52 motif 1
GJC1	GJC1	gap junction protein, chi 1, 31.9kDa (connexin 31.9)
ADCY3	ADCY3	adenylate cyclase 3
KLF5	KLF5	Kruppel-like factor 5 (intestinal)
DDB2	DDB2	damage-specific DNA binding protein 2, 48kDa

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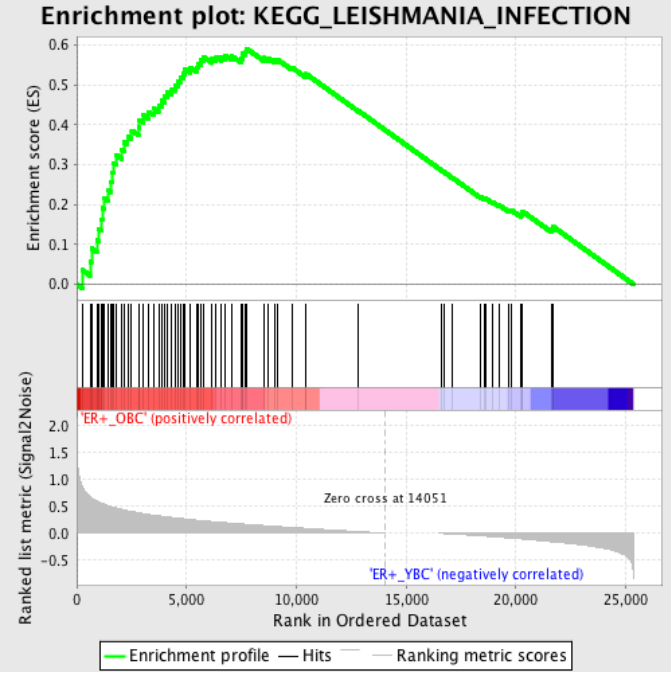
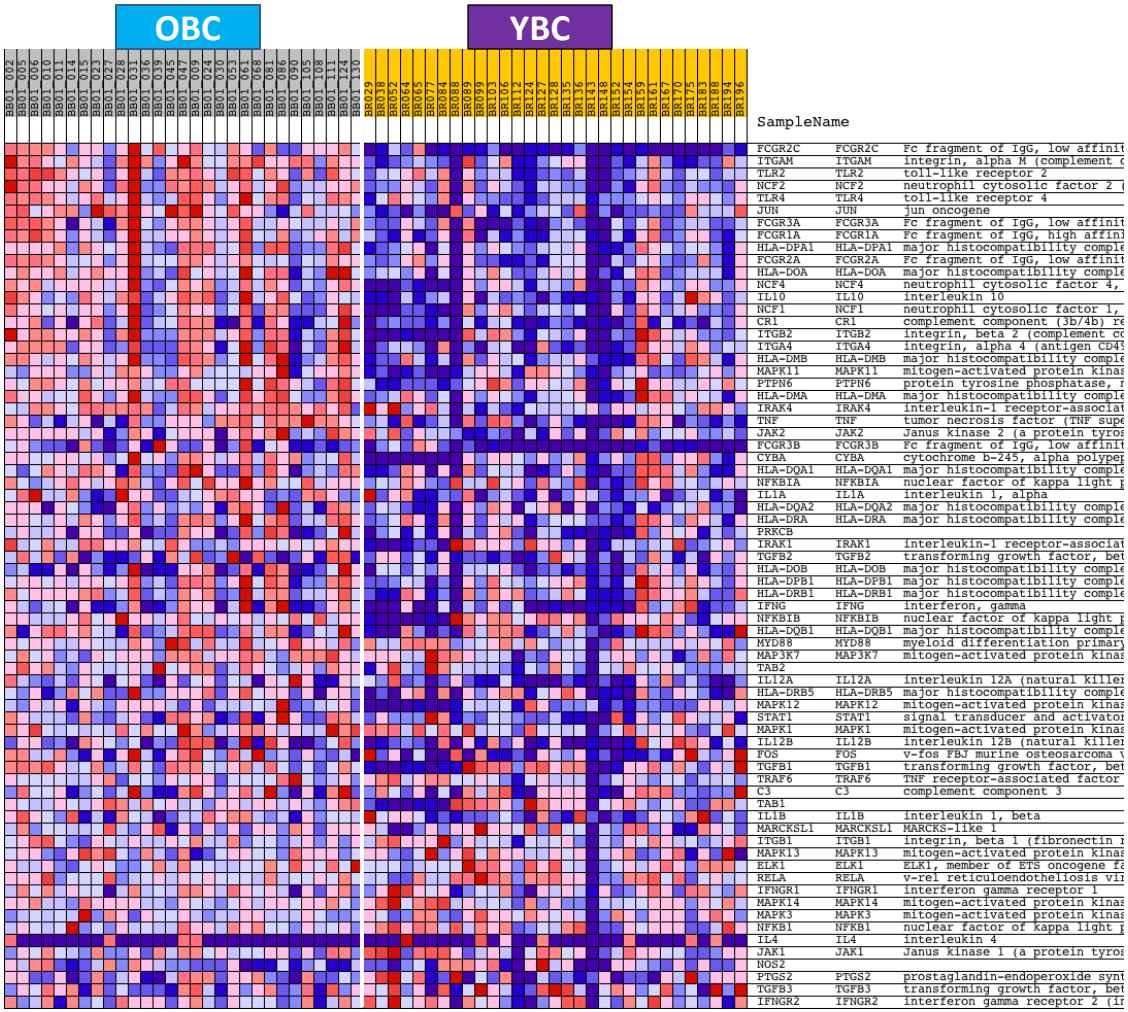
Immune and Inflammatory Pathways Up-regulated in HR+ OBC vs. YBC





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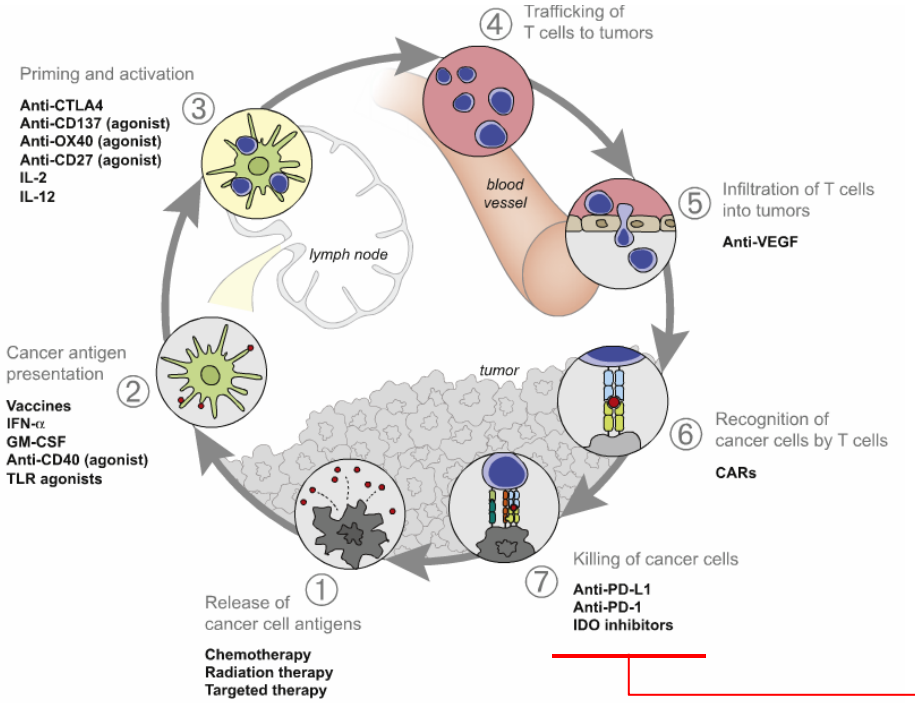
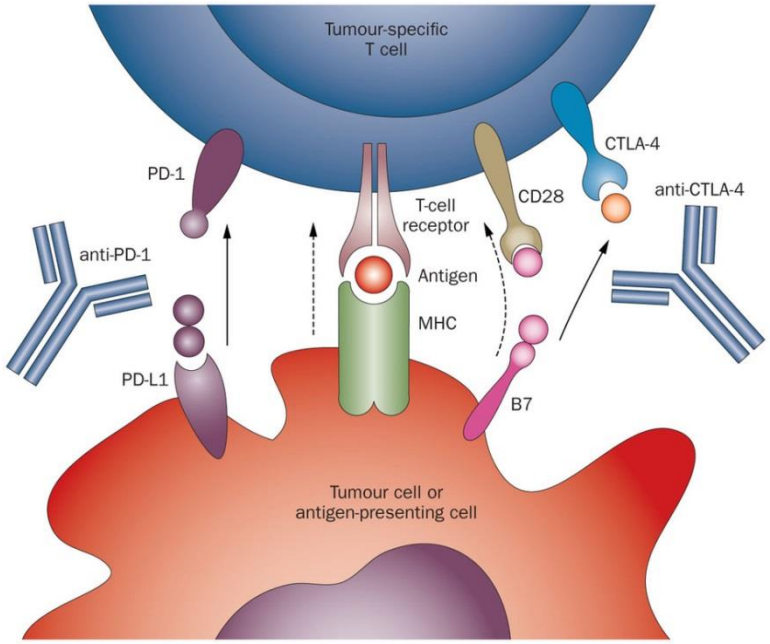
Immuno-oncology (IO) Therapies

- Tumor antigens may be recognized by immune surveillance and activates cell killing by tumor infiltrating cytotoxic T lymphocytes (CTL).
- T-cell responses are inhibited by immune checkpoint pathways mediated by CTLA4, PD1/PD-L1 etc.
- Immune checkpoint blockade by IO therapies amplifies anti-tumor immune responses - Nivolumab (αCTLA4), Pembrolizumab (αPD1), Avelumab (αPDL1).

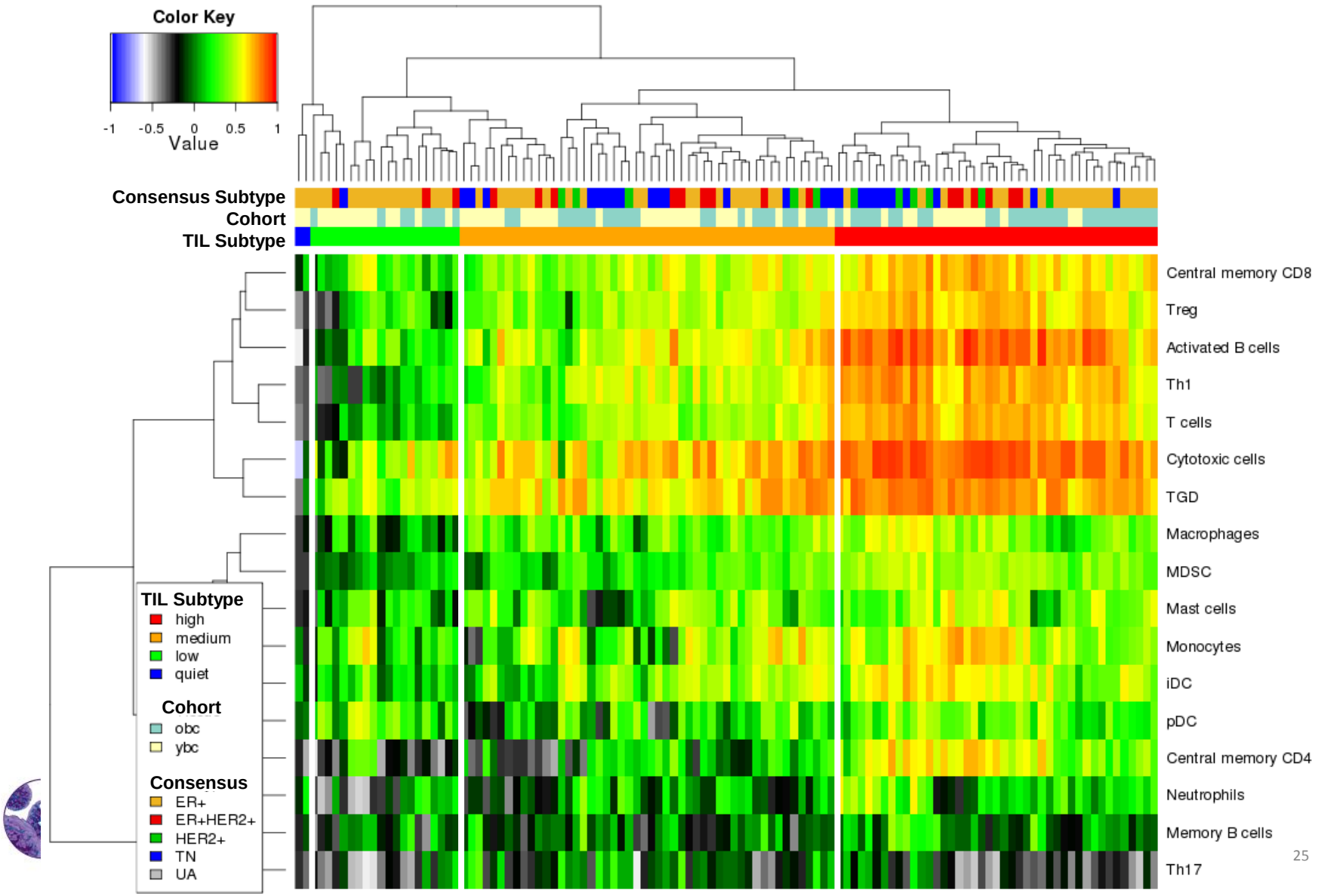




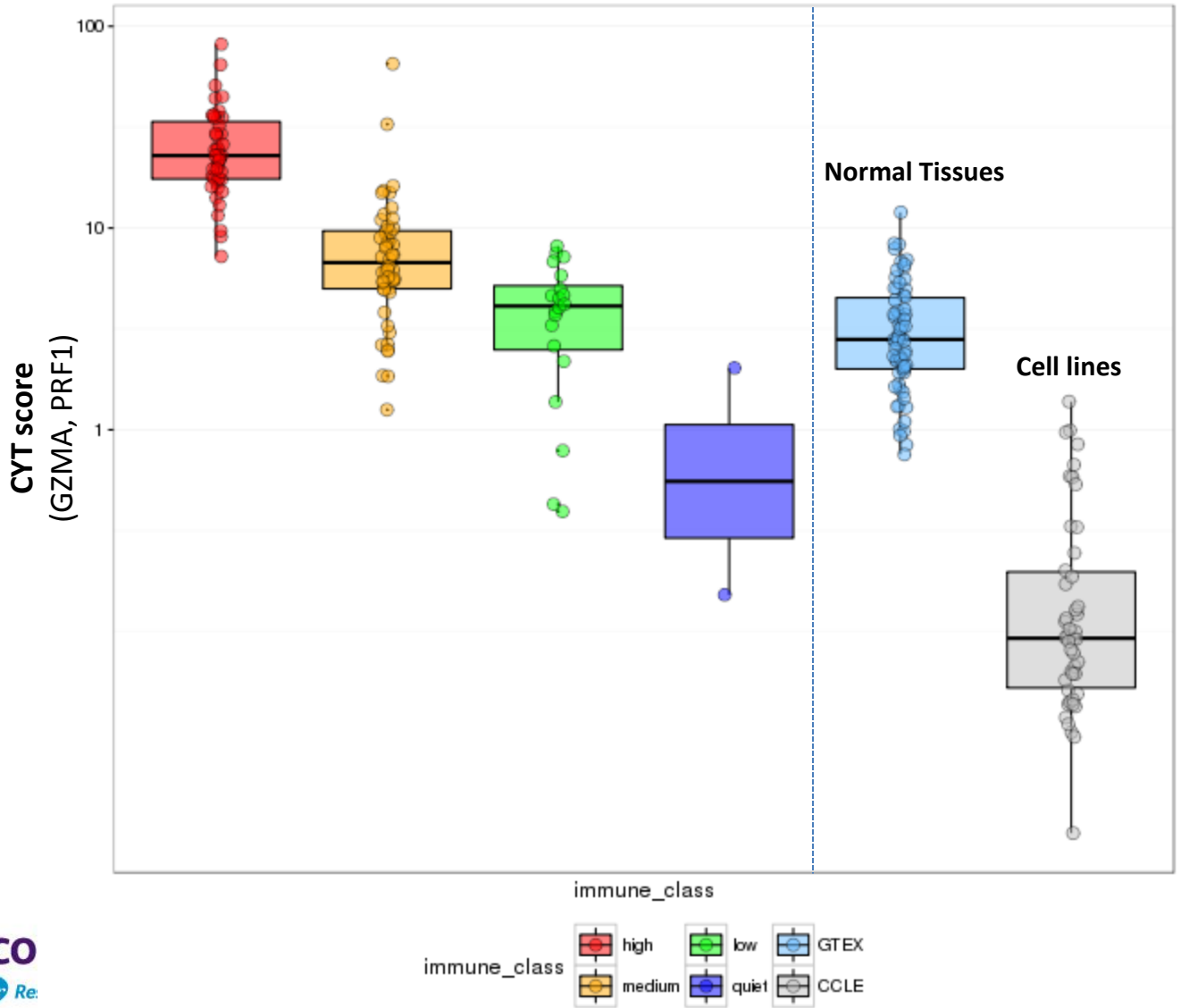
Chen & Mellman. **Oncology meets Immunology.** 2013. Immunity

Drake et al. **Breathing new life into immunotherapy.** 2014**.** Nature Reviews Clinical Oncology.

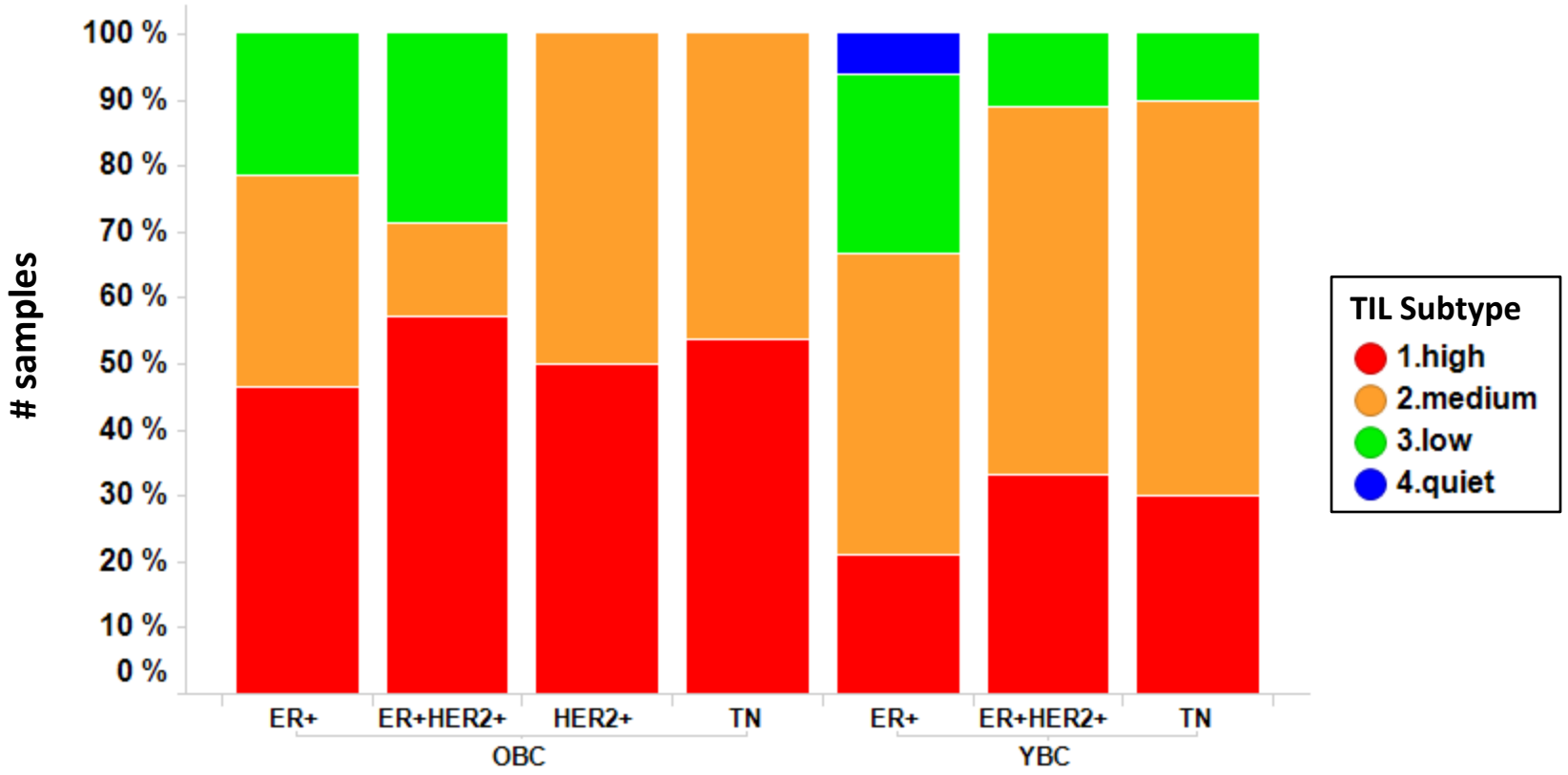
Classification of TIL Subtypes based on Immune Expression Signature



Cytolytic Activity Varies across TIL Subtypes, Normal Breast Tissues and Cell lines



OBC Seem More Immunogenic than YBC



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Histopathological IO analyses

- We performed H&E staining and immunohistochemistry (IHC) analyses of three TIL markers (*CD4*, *CD8* and *CD45*) on 111 tumors.

- TIL score was calculated as $\log_{10}T$, where T is the average TIL count from 5 separate regions of the H&E image.

- Digital imaging analysis was performed to quantify the relevant tissue area and the number of marker positive cells within those regions for each IHC slide.
  - Cell density is calculated as the number of marker positive cells in each mm^2 of analyzed tissue.

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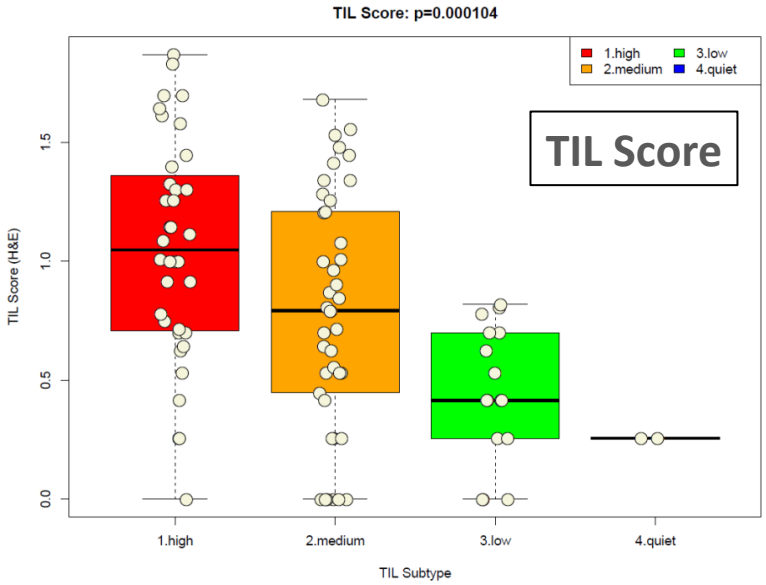
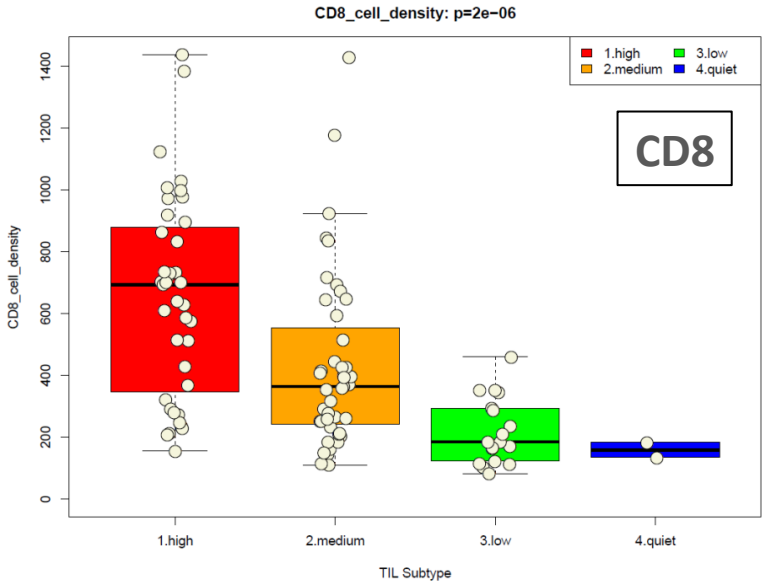
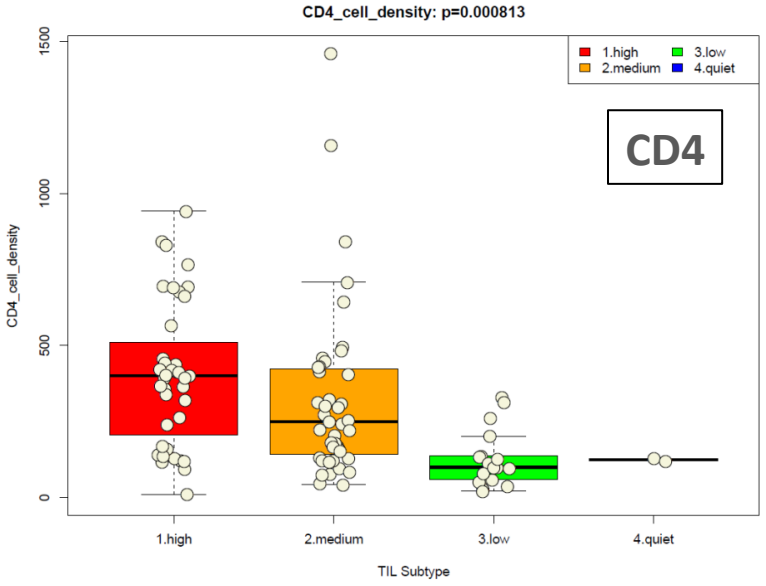
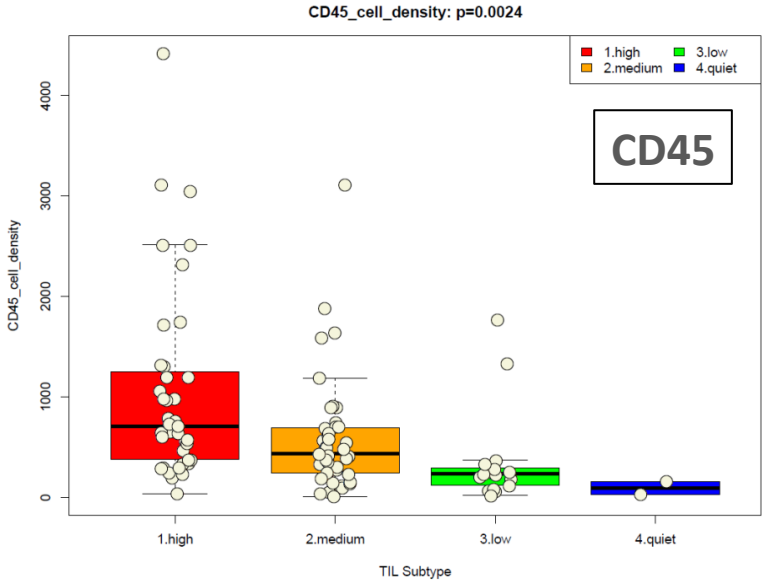
Histopathological and Expression IO Analyses are Highly Concordant

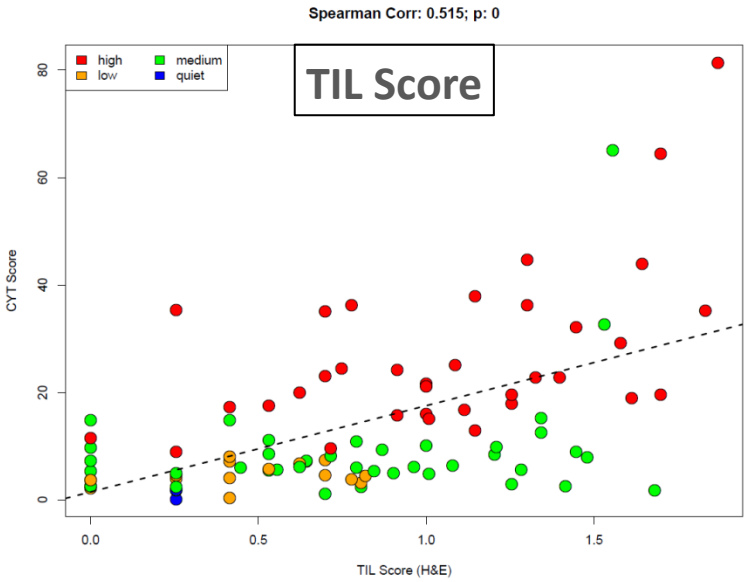


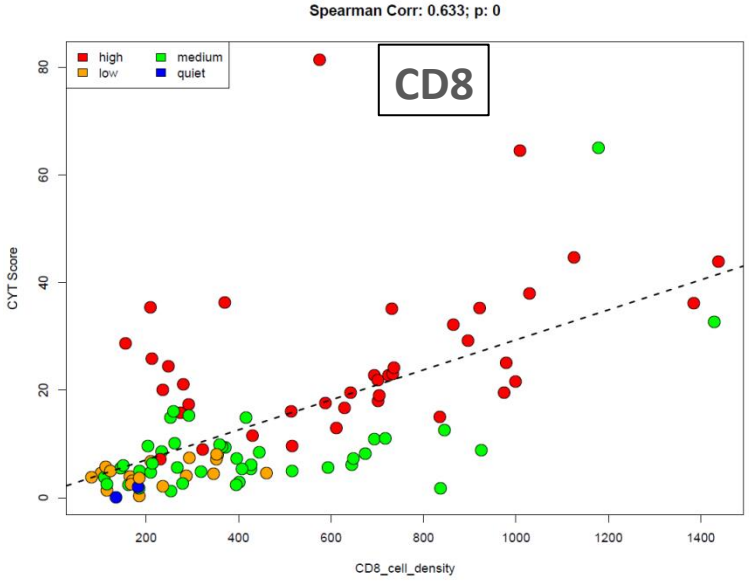


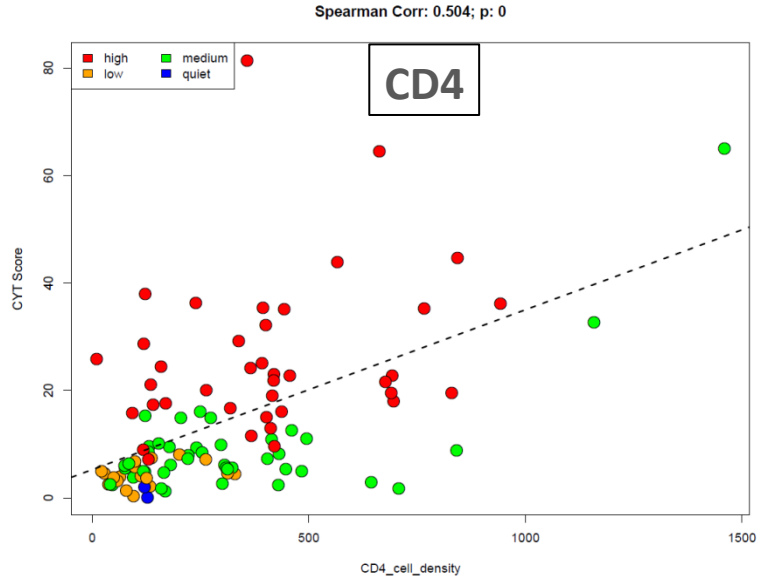


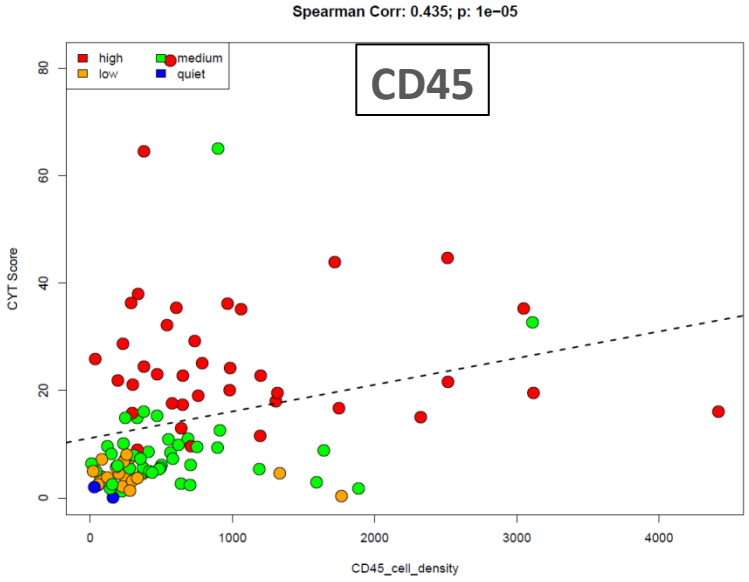


Histopathological and Expression IO Analyses are Highly Concordant









Summary

- We have performed the first large-scale multi-omics study of Asian breast cancer that would significantly contribute to the compendium of molecular data available for young, premenopausal breast cancer.
- The molecular landscape of Asian BC cohort is similar to Western BC studies in terms of major landmarks – ER over-expression, *ERBB2* amplification and mutations in *TP53*, *PIK3CA* and *GATA3*.
  - We have identified ARID1A as a significantly mutated gene in breast cancer.
- There are potentially significant molecular distinctions between Asian YBC vs. OBC.
  - *BRCA1/BRCA2* germline loss-of-function mutations are enriched in HR+ YBC.
  - YBC tumors appear to be less proliferative and smaller in size than OBC while OBC tumors harbor more mutations and copy number alterations than YBC.
  - Endocrine resistance signatures are up-regulated in HR+ YBC than in OBC, pointing to a molecular mechanism for tamoxifen resistance previously reported for Korean YBC.
  - Within the HR+ subtype, energy metabolism pathways such as oxidative phosphorylation appears to be up-regulated in YBC while cell cycle/proliferation and immune/inflammatory pathways appear to be up-regulated in OBC.
- Gene expression signature analyses have identified four subtypes of varying tumor-infiltrating lymphocyte (TIL) and cytolytic activities.
  - YBC seems to be less immunogenic than OBC with a lower mutation burden.
  - Expression-based and histopathological analyses of IO markers are strongly correlated.

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Clinical Characteristics of Western YBC

Box 3 | Clinical characteristics in women <40

- High risk of local recurrence
- Short median time from diagnosis to local recurrence
- High risk of mortality following local recurrence
- High risk of contralateral breast cancer
- High proportion oestrogen receptor-negative or progesterone receptor-negative disease
- High proportion of HER2-positive disease
- High proportion *TP53*-positive tumours

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Narod, Steven A. (2012) *Nature Reviews Clinical Oncology*

Compare Subtype Proportions in YBC vs. OBC

IHC/Clinical	OBC	OBC (%)	YBC	YBC (%)
ER+	28	46.7%	46*	62.2%
ER+HER2+	7	11.7%	10	17.9%
HER2+	10	16.7%	2	3.6%
TN	13	21.7%	13	23.2%
UA	2	3.3%	3	5.4%
	60		**74**	

***p* = 0.08**

***p* = 0.006**

PAM50	OBC	OBC (%)	YBC	YBC (%)
LumA	7	11.7%	21	38.2%
LumB	28	46.7%	16	29.1%
Her2	12	20.0%	3	5.5%
Basal	12	20.0%	14	25.5%
Normal	1	1.7%	1	1.8%
	60		**55**	

***p* = 0.0011**

***p* = 0.06**

Consensus	OBC	OBC (%)	YBC	YBC (%)
ER+	29	48.3%	44	59.5%
ER+HER2+	9	15.0%	10	17.9%
HER2+	9	15.0%	4	7.1%
TN	13	21.7%	16	28.6%
	60		**74**	

***P* = 0.225**

***P* = 0.08**

***P* = 0.58**

(RNASEQ n = 115)

Consensus	OBC	OBC (%)	YBC	YBC (%)
ER+	29	48.3%	31	56.4%
ER+HER2+	9	15.0%	9	16.4%
HER2+	9	15.0%	2	3.6%
TN	13	21.7%	13	23.6%
	60		**55**	

***P* = 0.456**

***P* = 0.056**

***P* = 0.83**

- Contrary to previous reports, Asian YBC is enriched in Luminal A and HER2+ subtypes.
- In addition, Asian YBC is not significantly enriched in TNBC.
- Asian YBC is dominated by HR+ diseases - 77% including both ER+ and ER+/HER2+.

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Genomic alterations enriched in YBC or OBC.

Type	Gene	YBC (n=73)	OBC (n=60)	p-value	q-value
Somatic Mutation	*TP53*	27 (37.0%)	36 (60.0%)	0.0093	0.1395
Somatic Mutation	*NF1*	1 (1.4%)	6 (10.0%)	0.0456	0.293143
Somatic Mutation	*CBFB*	1 (1.4%)	5 (8.3%)	0.0903	0.507938
Somatic Mutation	*PIK3CA*	19 (26.0%)	20 (33.3%)	0.4444	1
Somatic Mutation	*GATA3*	11 (15.1%)	7 (11.7%)	0.6191	1
Somatic Mutation	*PTEN*	3 (4.1%)	1 (1.7%)	0.6266	1
Somatic Mutation	*ARID1A*	3 (4.1%)	3 (5.0%)	1	1
Amplification	*MYC*	0	5 (8.3%)	0.017	0.136
Amplification	*ERBB2*	10 (13.7%)	17 (28.3%)	0.0507	0.2028
Somatic Mutation	*BRCA1*	1 (1.4%)	0	0.55	
Germline LOF	*BRCA1*	3 (4%)	0	0.16	
Germline LOF	*BRCA2*	6 (8%)	3 (5.0%)	0.3533	
Somatic/Germline	*BRCA1/2*	10 (13.7%)	3 (5.0%)	0.08	

TP53, *NF1* protein-altering somatic mutations and *MYC*, *ERBB2* amplifications are enriched in OBC. Loss-of-function (LOF) mutations affecting *BRCA1* or *BRCA2* are enriched in YBC.

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What Pathways are Differentially Expressed in HR+ YBC vs. OBC?

Subtype	Up-regulated	Database	Geneset	# Genes	NES	FDR q-val
HR+	YBC	Hallmark	OXIDATIVE_PHOSPHORYLATION	199	-2.81478	0
HR+	YBC	KEGG	PARKINSONS_DISEASE	113	-2.58741	0
HR+	YBC	REACTOME	RESPIRATORY_ELECTRON_TRANSPORT	65	-2.52911	0
HR+	YBC	Biocarta	PROTEASOME_PATHWAY	28	-2.48144	0
HR+	YBC	KEGG	OXIDATIVE_PHOSPHORYLATION	116	-2.47474	0
HR+	YBC	REACTOME	FORMATION_OF_ATP_BY_CHEMIOSMOTIC_COUPLING	13	-2.32748	0
HR+	YBC	Hallmark	ESTROGEN_RESPONSE_EARLY	200	-2.32048	0
HR+	YBC	REACTOME	TCA_CYCLE_AND_RESPIRATORY_ELECTRON_TRANSPORT	117	-2.21898	0.00328
HR+	YBC	KEGG	DRUG_METABOLISM_CYTOCHROME_P450	72	-2.21243	0.00285
HR+	YBC	Hallmark	ESTROGEN_RESPONSE_LATE	199	-2.13894	0
HR+	OBC	KEGG	LEISHMANIA_INFECTION	70	1.73803	0.03707
HR+	OBC	KEGG	PRIMARY_IMMUNODEFICIENCY	35	1.61149	0.09367
HR+	OBC	KEGG	INTESTINAL_IMMUNE_NETWORK_FOR_IGA_PRODUCTION	46	1.60056	0.08103
HR+	OBC	KEGG	ALLOGRAFT_REJECTION	35	1.58956	0.07455
HR+	OBC	KEGG	NOD_LIKE_RECEPTOR_SIGNALING_PATHWAY	61	1.56616	0.08697
HR+	OBC	KEGG	SYSTEMIC_LUPUS_ERYTHEMATOSUS	134	1.5536	0.09184
HR+	OBC	Hallmark	ALLOGRAFT_REJECTION	200	1.49757	0.06265
HR+	OBC	Hallmark	G2M_CHECKPOINT	200	1.46906	0.05
HR+	OBC	Hallmark	MYC_TARGETS_V2	58	1.4509	0.04217
HR+	OBC	Hallmark	E2F_TARGETS	199	1.41913	0.05067
HR+	OBC	Hallmark	MITOTIC_SPINDLE	199	1.41661	0.04119
HR+	OBC	Hallmark	INFLAMMATORY_RESPONSE	198	1.40403	0.04037

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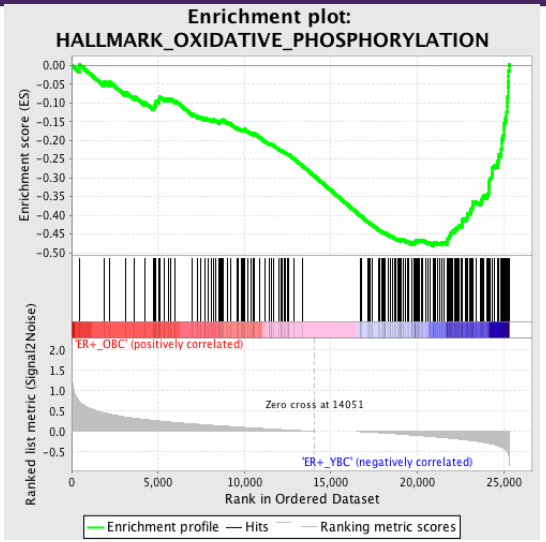
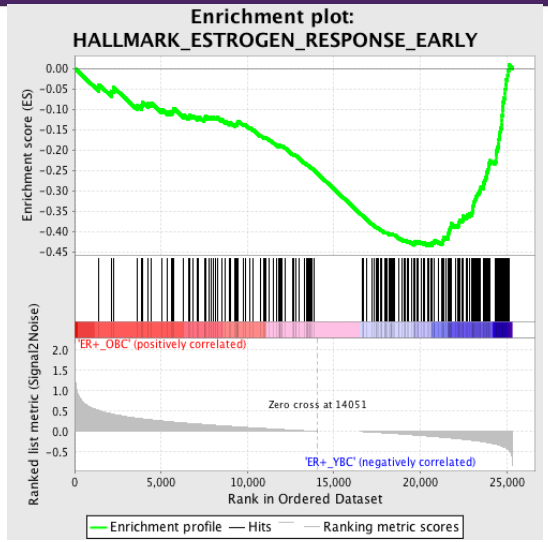
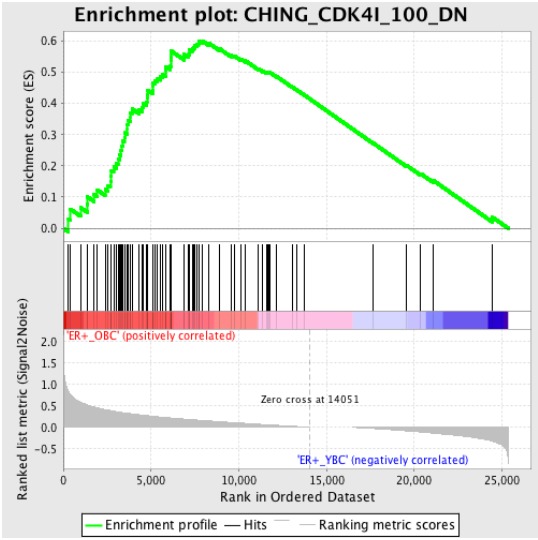
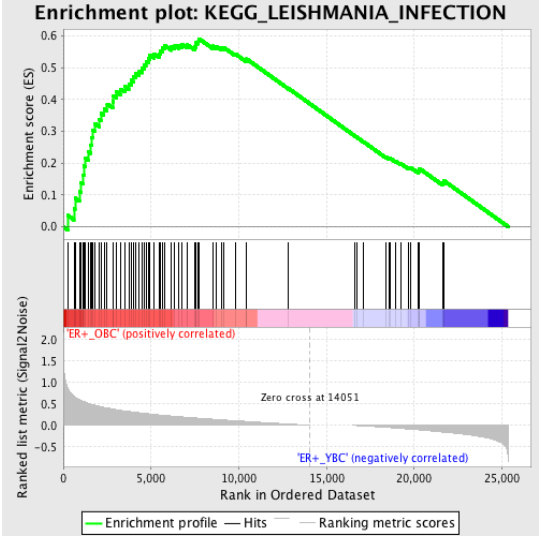
Energy metabolism
Estrogen response
Immune/inflammatory
Cell cycle/proliferation

GSEA Analyses Revealed Differentially Expressed Pathways in YBC vs. OBC









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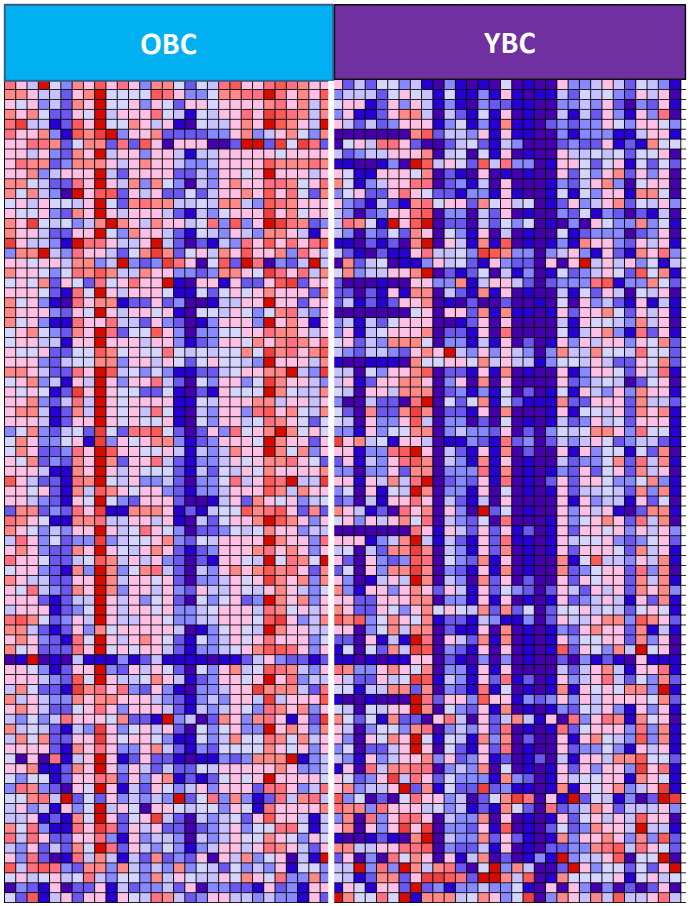
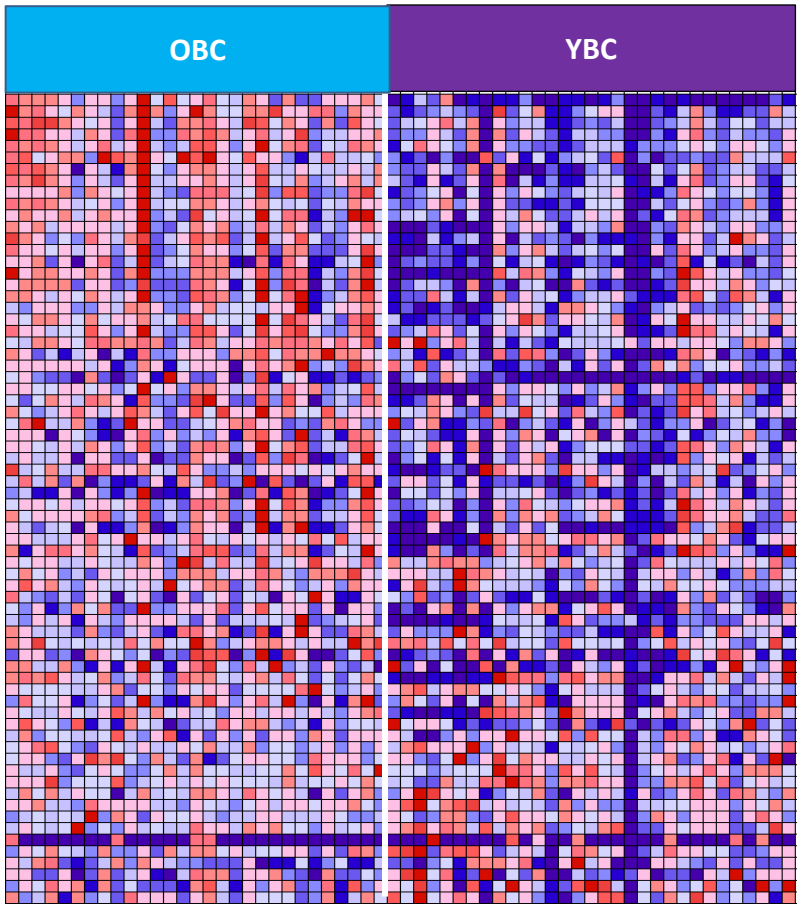
The enrichment plot ranks genes based on relative overexpression from OBC (left) to YBC (right) and marks the positions of the pathway genes by vertical lines.

GSEA Analyses Revealed Differentially Expressed Pathways in YBC vs. OBC



KEGG: LEISHMANIA_INFECTION



CDK4I_100_DN

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Expression patterns of all pathway genes in OBC and YBC samples are shown in the heatmap (F-G).

Classification of TIL Subtypes based on Immune Cell Expression Signature

- Tumor infiltrated lymphocytes (TIL) play important roles in tumor suppression and immuno-oncology (IO) therapies such as checkpoint inhibitors (αPD-L1).

- Using gene expression signatures representing distinct immune cell types [REF], we classified the cohort into four subtypes of varying TIL activities: high, medium, low and quiet.

- OBC tumors are significantly enriched (*p*-value: 0.01291) in the TIL-high subtype than YBC tumors, suggesting that OBC tumors are more immunogenic than YBC tumors.

- This is consistent with the observation that OBC exhibits higher burden of protein-altering somatic mutations than YBC samples (40 vs. 26, *p*-value: 0.034), presumably giving rise to more neoantigens.

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“Big” Questions

- What are the molecular drivers of Asian BC?
- What are the differences between YBC and OBC?
- Can we learn something new about Breast Cancer in general?

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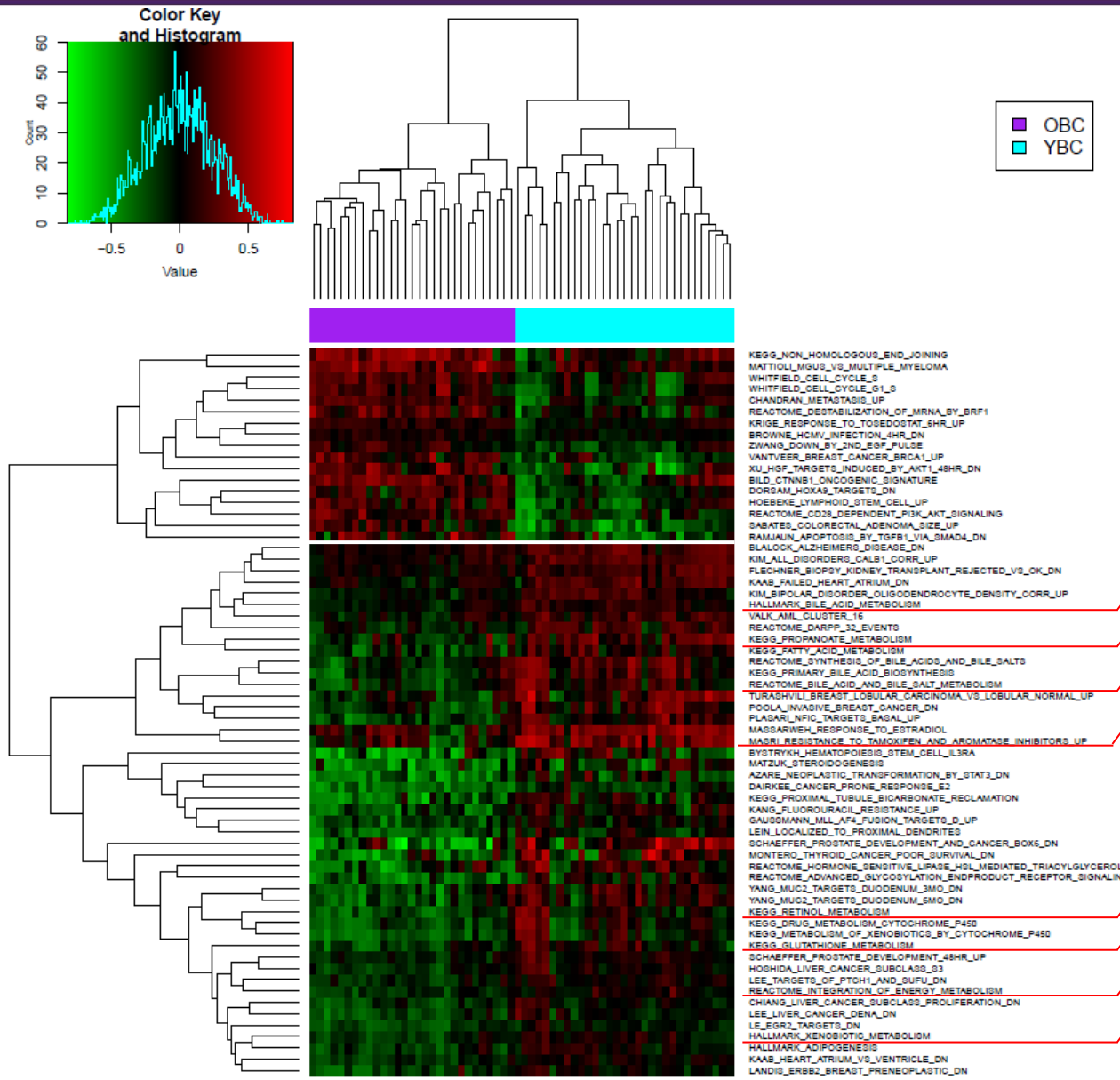
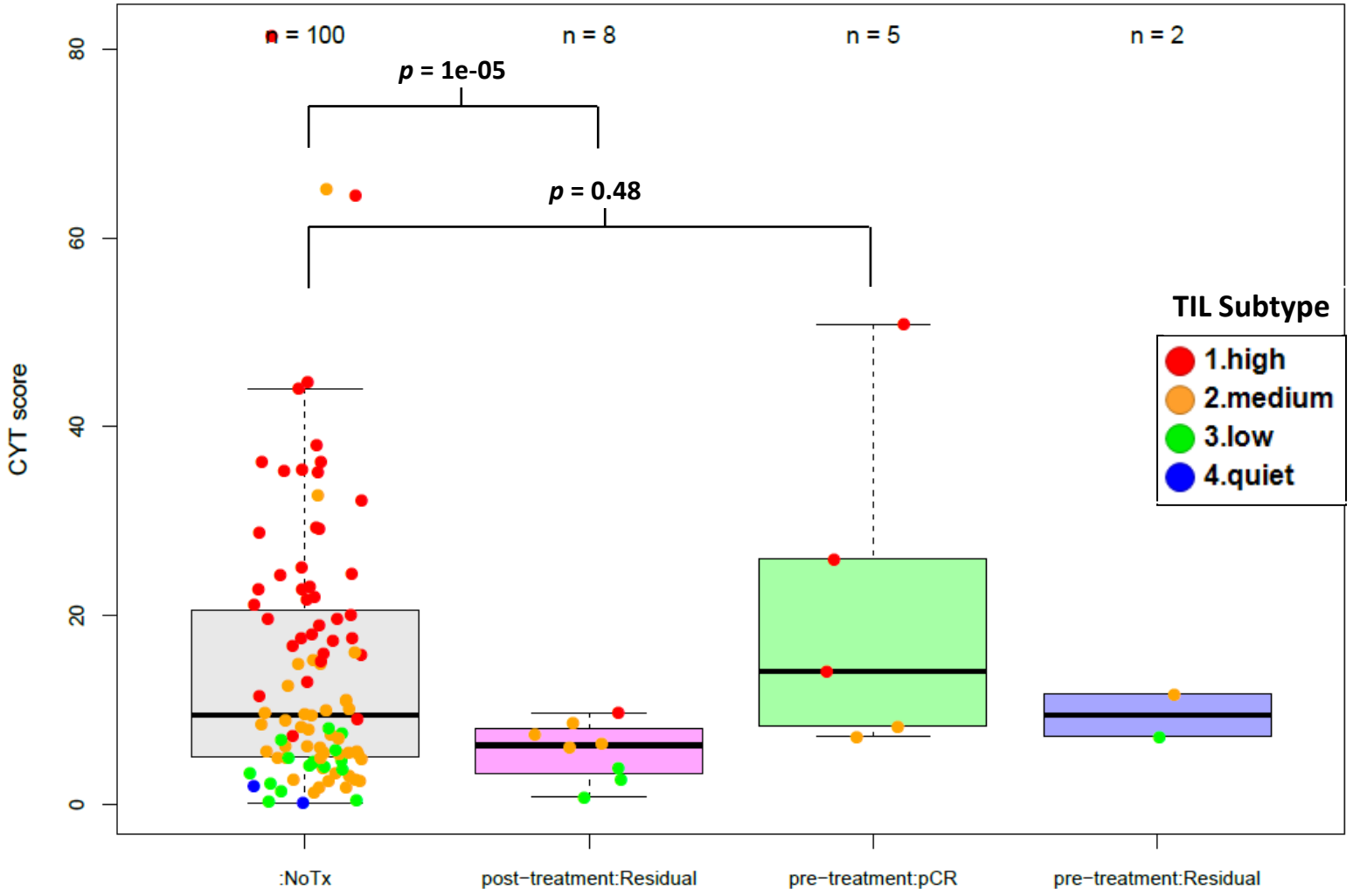
What Pathways are Differentially Expressed in HR+ YBC vs. OBC?



Cytolytic Activity Varies with Chemotherapy Treatment Statuses



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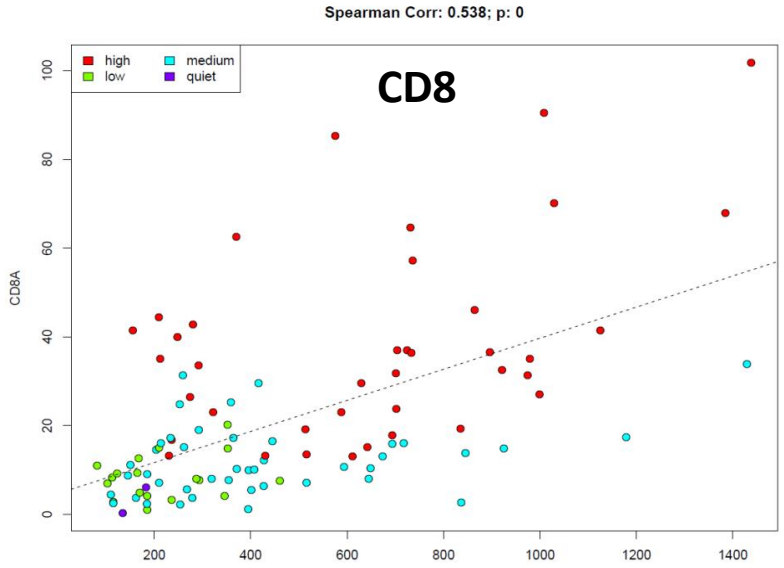
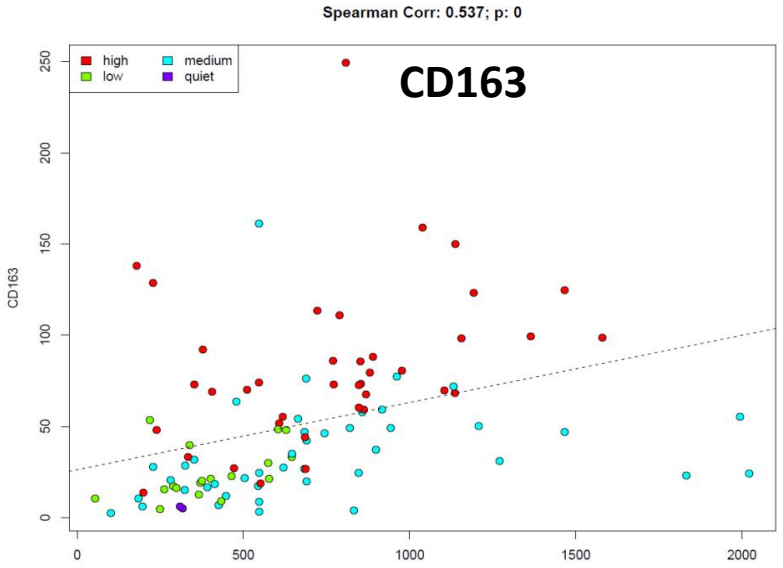
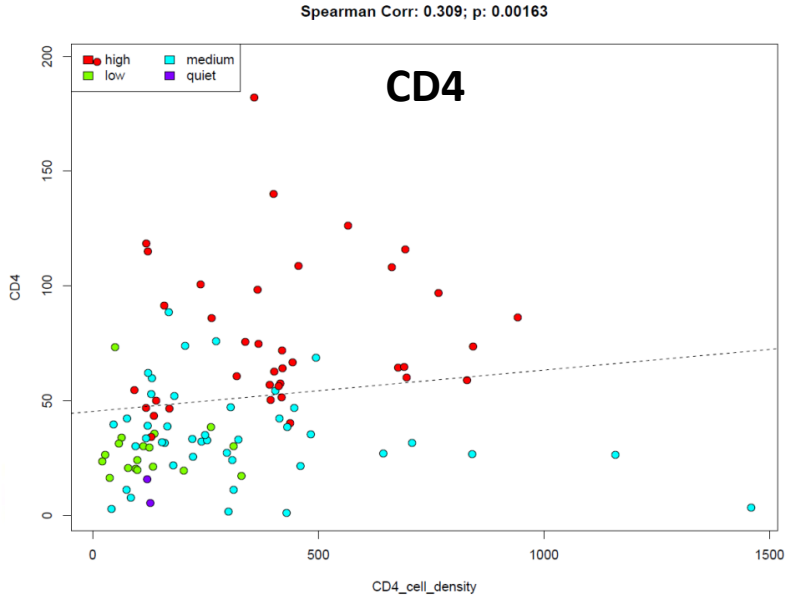
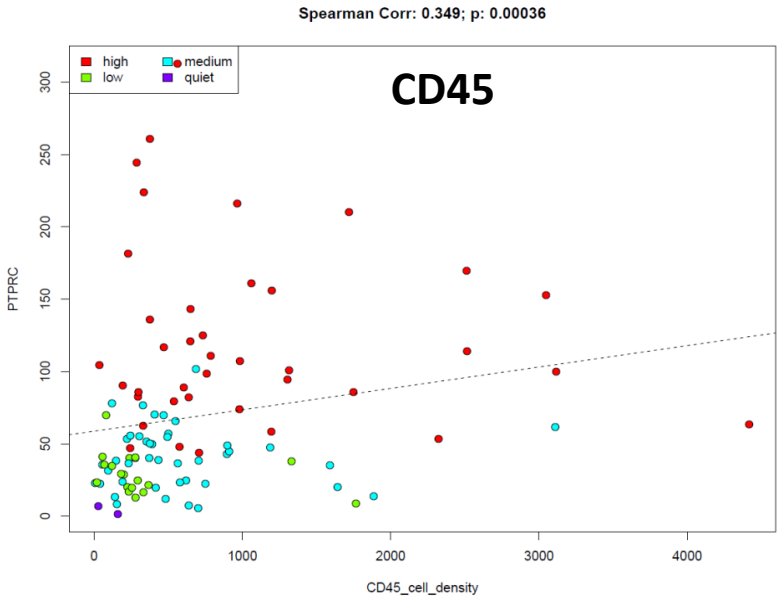
IHC Cell Density vs. Gene Expression

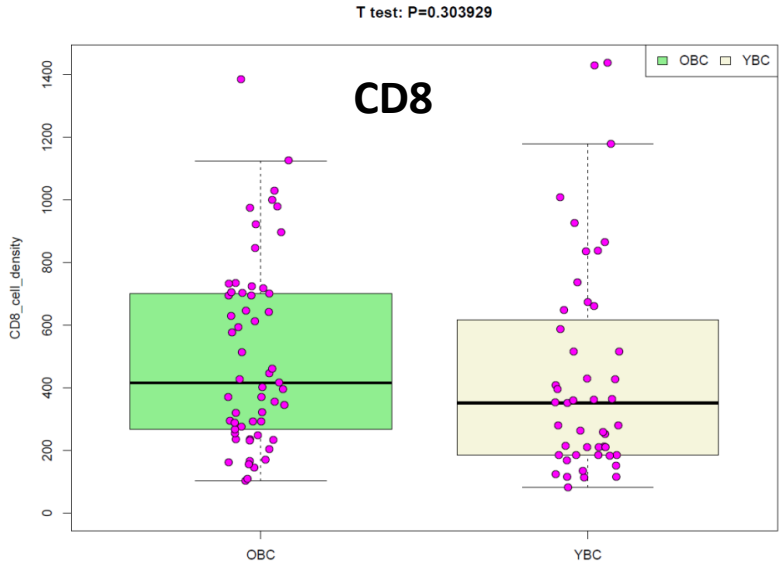


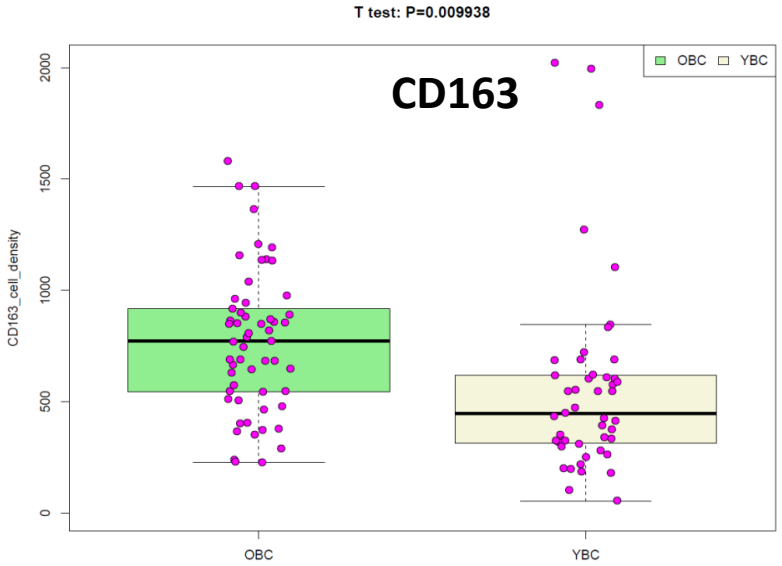


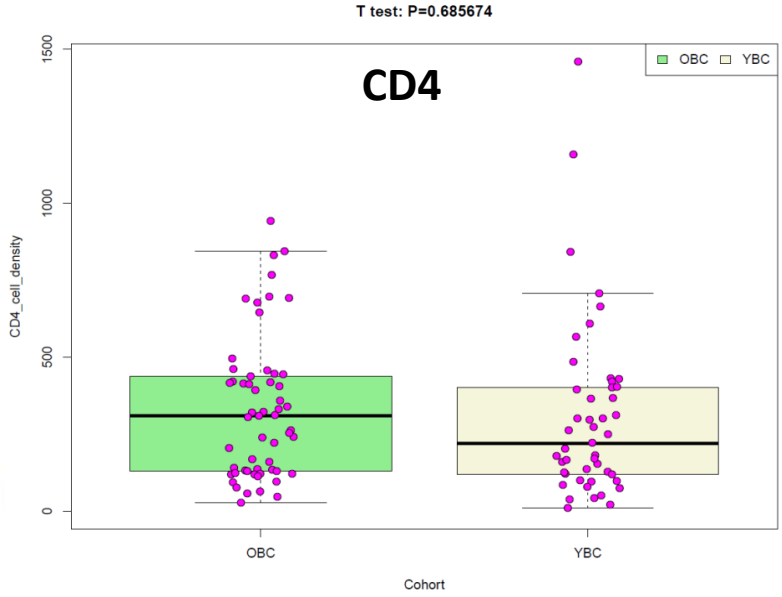


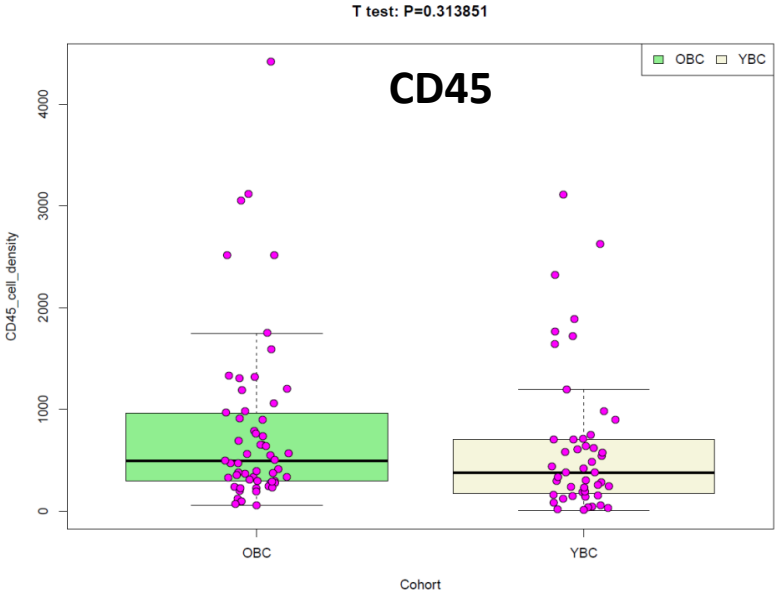


Comparing IHC Cell Densities in YBC vs. OBC

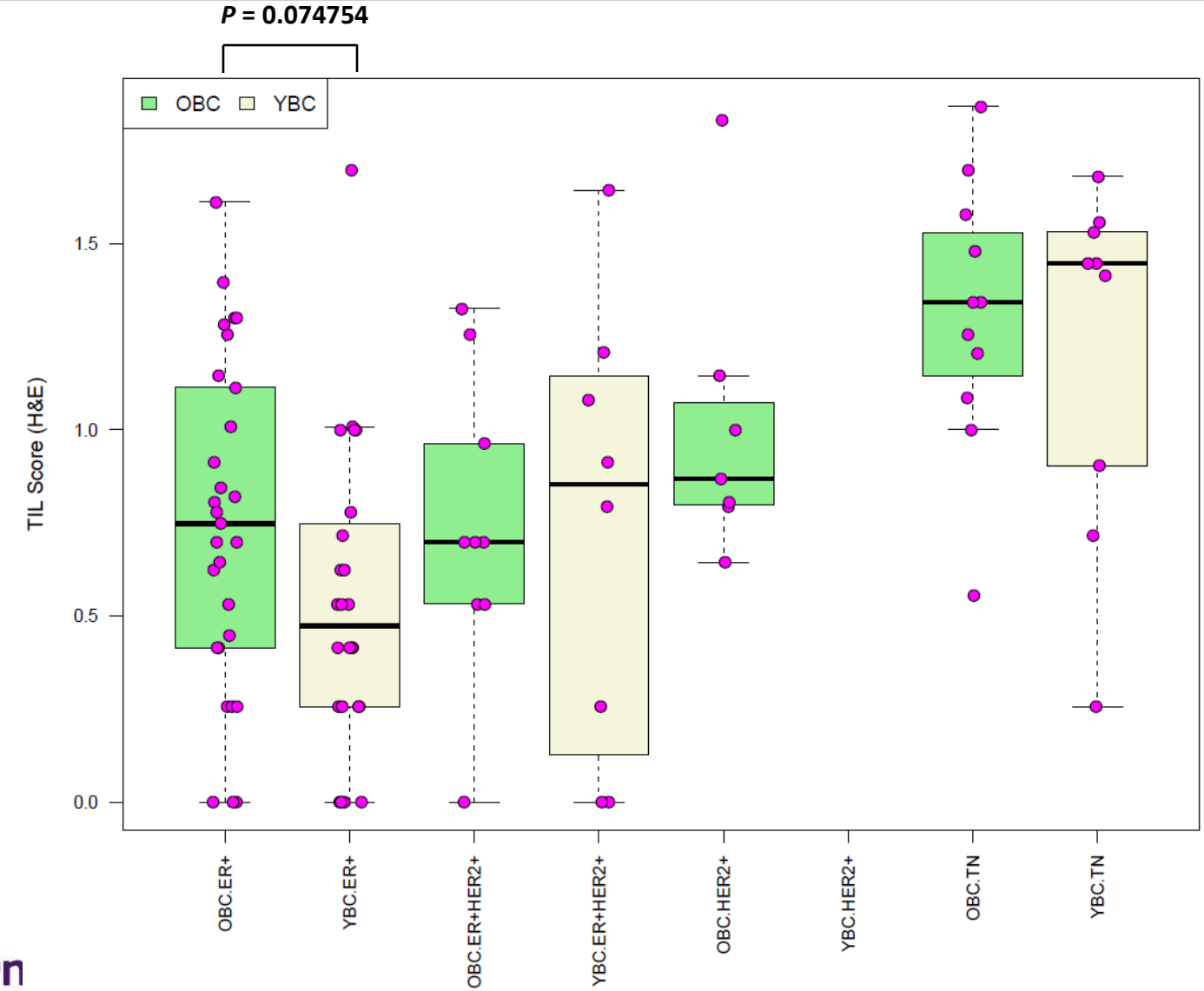








TIL Score Higher in HR+ OBC vs. YBC



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