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Computación y Estudios Clínicos

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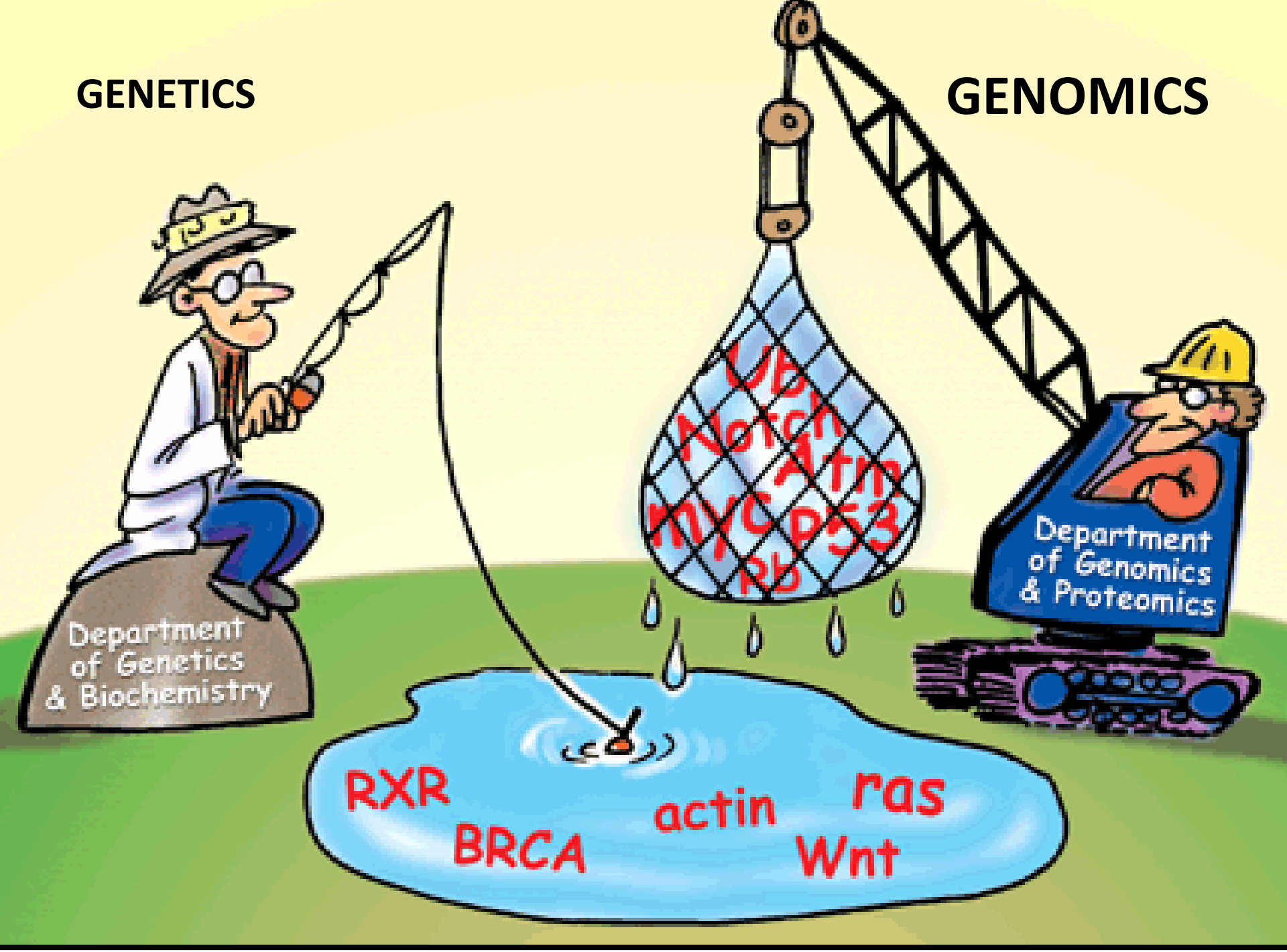
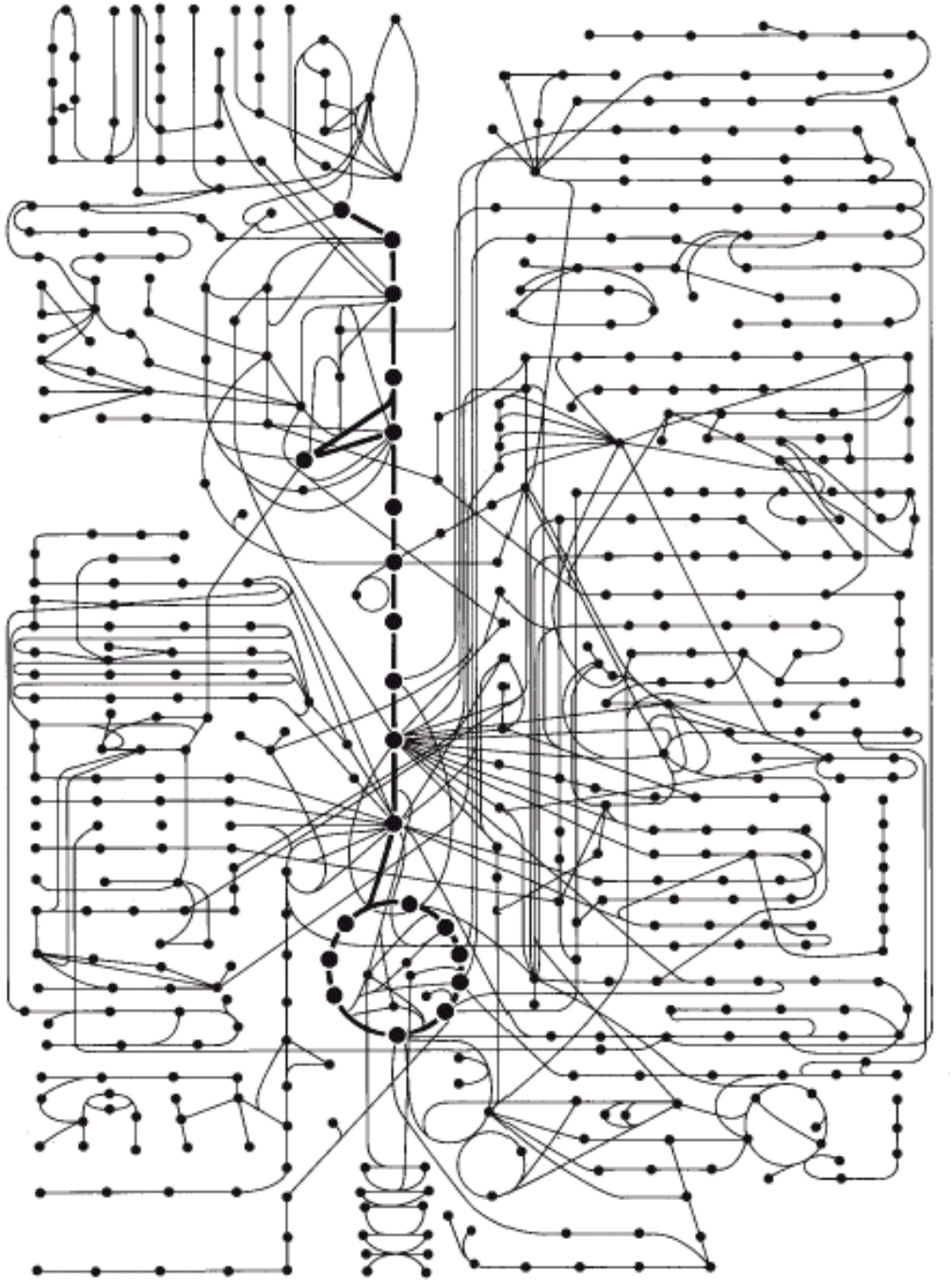
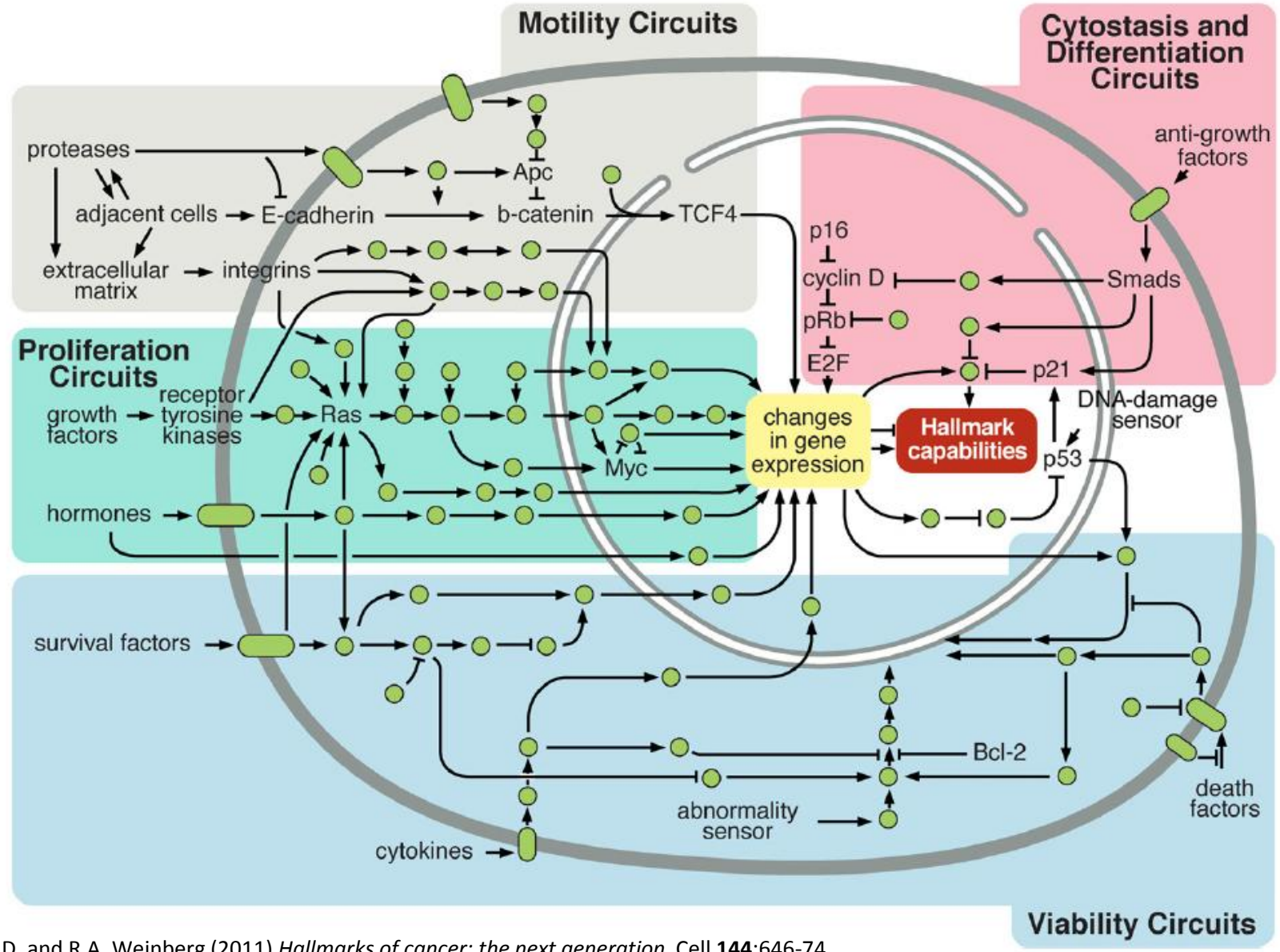
30 Octubre 2014


GENETICS
GENOMICS
Department of Genetics & Biochemistry
Department of Genomics & Proteomics
RXR
BRCA
actin
ras
Wnt

500 metabolic pathways and their interconnections in a typical NORMAL cell.



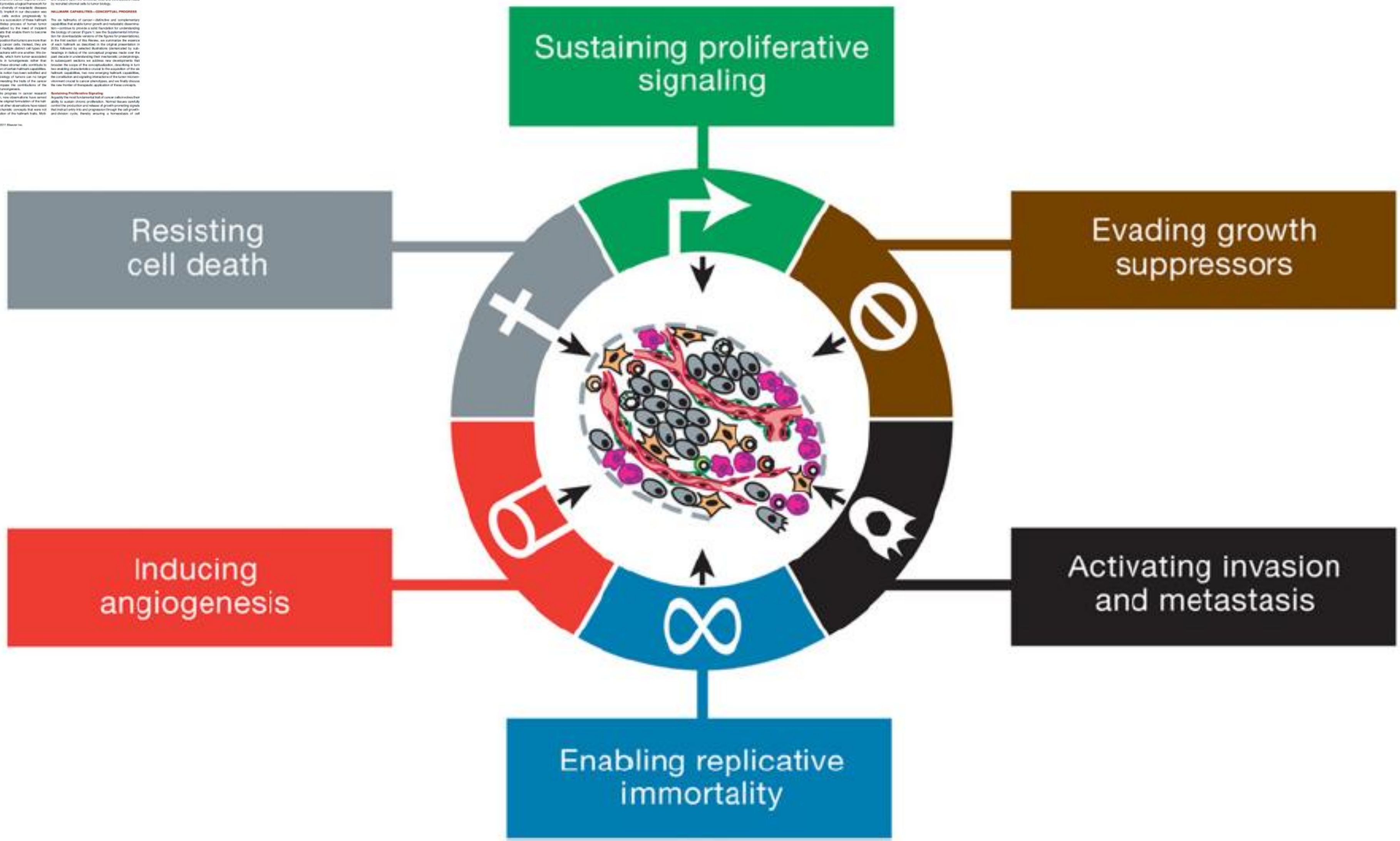
Programming of Hallmark Capabilities by Intracellular Circuitry



Hanahan, D. and R.A. Weinberg (2011) *Hallmarks of cancer: the next generation.* Cell **144**:646-74.


Hallmarks of Cancer: The Next Generation

Hallmarks of cancer: the next generation



Hanahan, D. and R.A. Weinberg (2011). Cell **144**:646-74.

THERAPEUTIC TARGETING

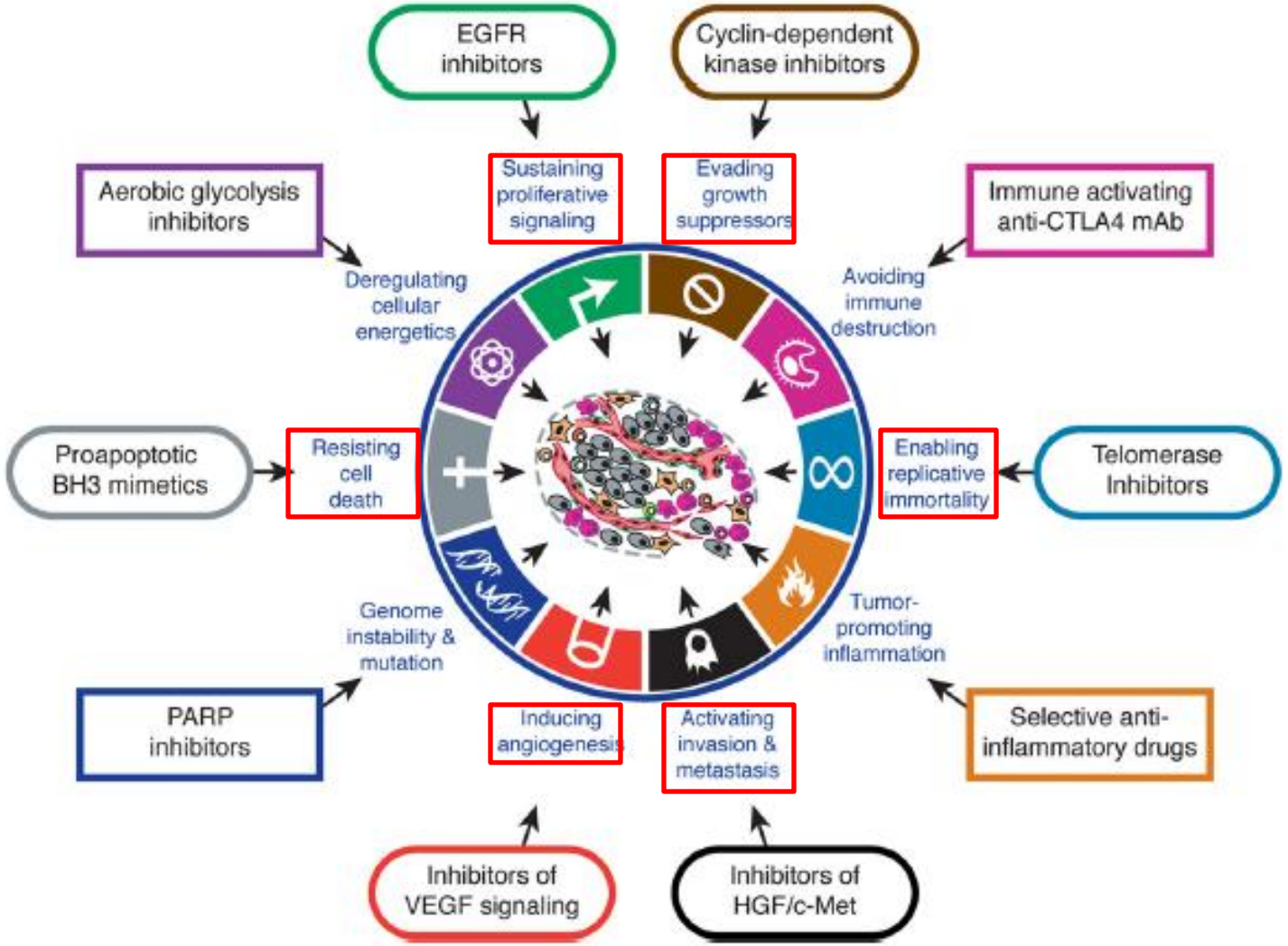


Figure 6. Therapeutic Targeting of the Hallmarks of Cancer

Drugs that interfere with each of the acquired capabilities necessary for tumor growth and progression have been developed and are in clinical trials or in some cases approved for clinical use in treating certain forms of human cancer. Additionally, the investigational drugs are being developed to target each of the enabling characteristics and emerging hallmarks depicted in Figure 3, which also hold promise as cancer therapeutics. The drugs listed are but illustrative examples; there is a deep pipeline of candidate drugs with different molecular targets and modes of action in development for most of these hallmarks.

Where cancer genomics should go next: a clinician's perspective

Discovery of a driver mutation with functional consequences in a particular disease:

- Inhibition of the protein that carries the mutation
- Proof of principle of efficiency as demonstrated by improved progression free and overall survival
- Patient stratification for treatment

Application of the inhibition based on oncogenomic studies to other diseases

Basic studies defining an alternative way of resistance in a different genetic/cell type context

New patient stratification in a new disease

Rafii et al., 2014

National Cancer Institute | National Human Genome Research Institute

The Cancer Genome Atlas

Understanding genomics to improve cancer care

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Four Subtypes of Stomach Cancer Identified

Researchers with the TCGA Research Network have found that stomach cancers, also called gastric cancers or gastric adenocarcinomas, fall into four distinct molecular subtypes.

Learn More

Stomach Cancer Subtypes IDed | Lung Cancer Research Published | Cancers Selected for Study | About TCGA

Leadership Update

Research Briefs

Launch Data Portal

The Cancer Genome Atlas (TCGA) Data Portal provides a platform for researchers to search, download, and analyze data sets generated by TCGA.

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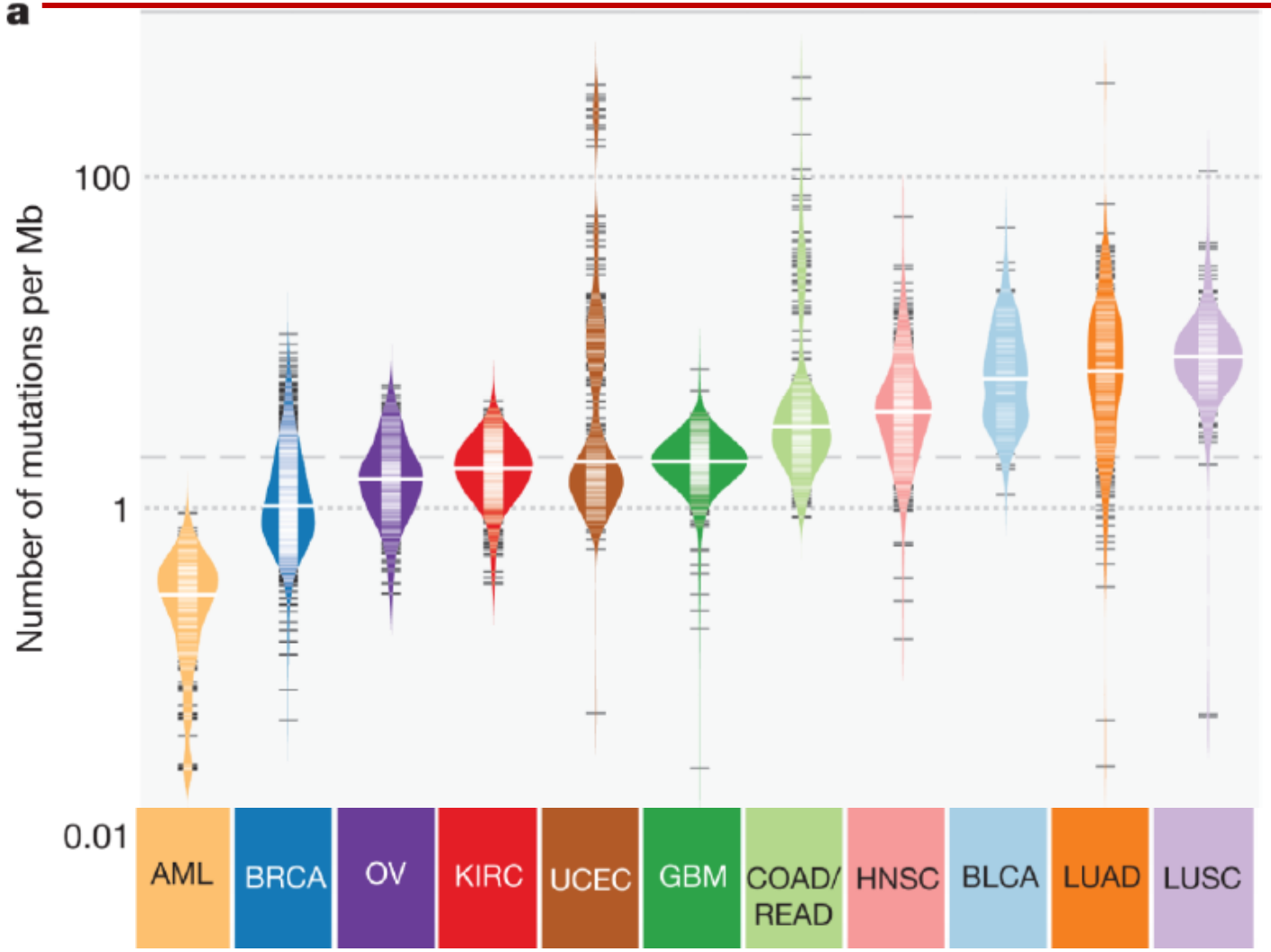
Cancer Type	Sample	Data
Central Nervous System		
Glioblastoma Multiforme	✓	✓
Lower Grade Glioma	✓	✓
Endocrine		
Adrenocortical Carcinoma	✓	✓
Papillary Thyroid Carcinoma	✓	✓
Paraganglioma & Pheochromocytoma	✓	✓
Gastrointestinal		
Cholangiocarcinoma	✓	
Colorectal Adenocarcinoma	✓	✓
Liver Hepatocellular Carcinoma	✓	✓
Pancreatic Ductal Adenocarcinoma	✓	✓
Stomach-Esophageal Cancer	✓	✓
Gynecologic		
Cervical Cancer	✓	✓
Ovarian Serous Cystadenocarcinoma	✓	✓
Uterine Carcinosarcoma	✓	✓
Uterine Corpus Endometrial Carcinoma	✓	✓
Head and Neck		
Head and Neck Squamous Cell Carcinoma	✓	✓
Uveal Melanoma	✓	
Hematologic		
Acute Myeloid Leukemia	✓	✓
Thymoma	✓	
Skin		
Cutaneous Melanoma	✓	✓
Soft Tissue		
Sarcoma	✓	✓
Thoracic		
Lung Adenocarcinoma	✓	✓
Lung Squamous Cell Carcinoma	✓	✓
Mesothelioma	✓	✓
Urologic		
Chromophobe Renal Cell Carcinoma	✓	✓
Clear Cell Kidney Carcinoma	✓	✓
Papillary Kidney Carcinoma	✓	✓
Prostate Adenocarcinoma	✓	✓
Testicular Germ Cell Cancer	✓	
Urothelial Bladder Carcinoma	✓	✓

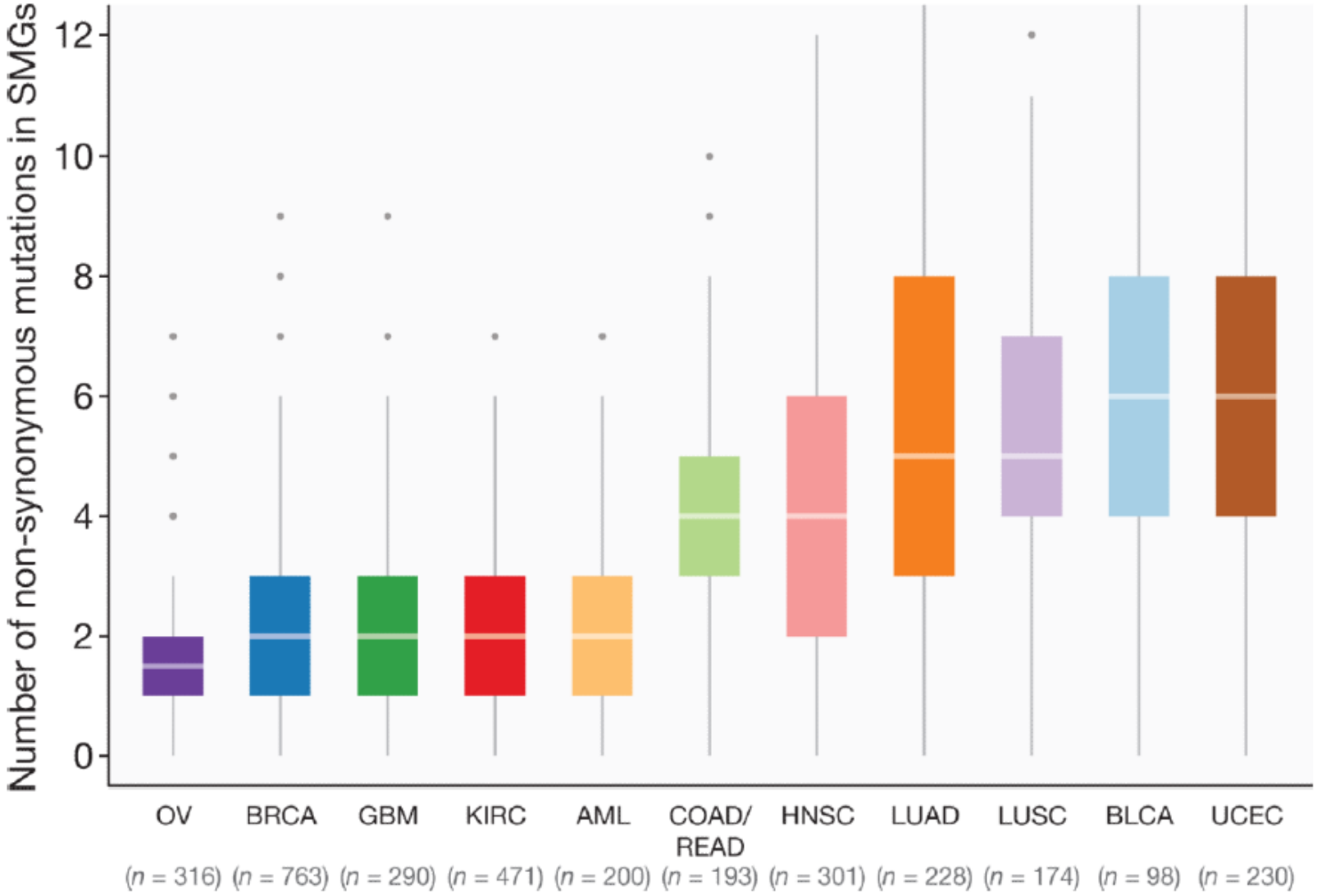
Mutation frequencies, spectra and contexts across 12 cancer types



- LAML, AML (Acute myeloid leukaemia)
- BRCA (Breast adenocarcinoma)
- OV (Ovarian serous carcinoma)
- KIRC (Kidney renal clear cell carcinoma)
- UCEC (Uterine corpus endometrial carcinoma)
- GBM (Glioblastoma multiforme)
- COAD, READ (Colon and rectal carcinoma)
- HNSC (Head and neck squamous cell carcinoma
- BLCA (Bladder urothelial carcinoma)
- LUAD (Lung adenocarcinoma)
- LUSC (Lung squamous cell carcinoma)

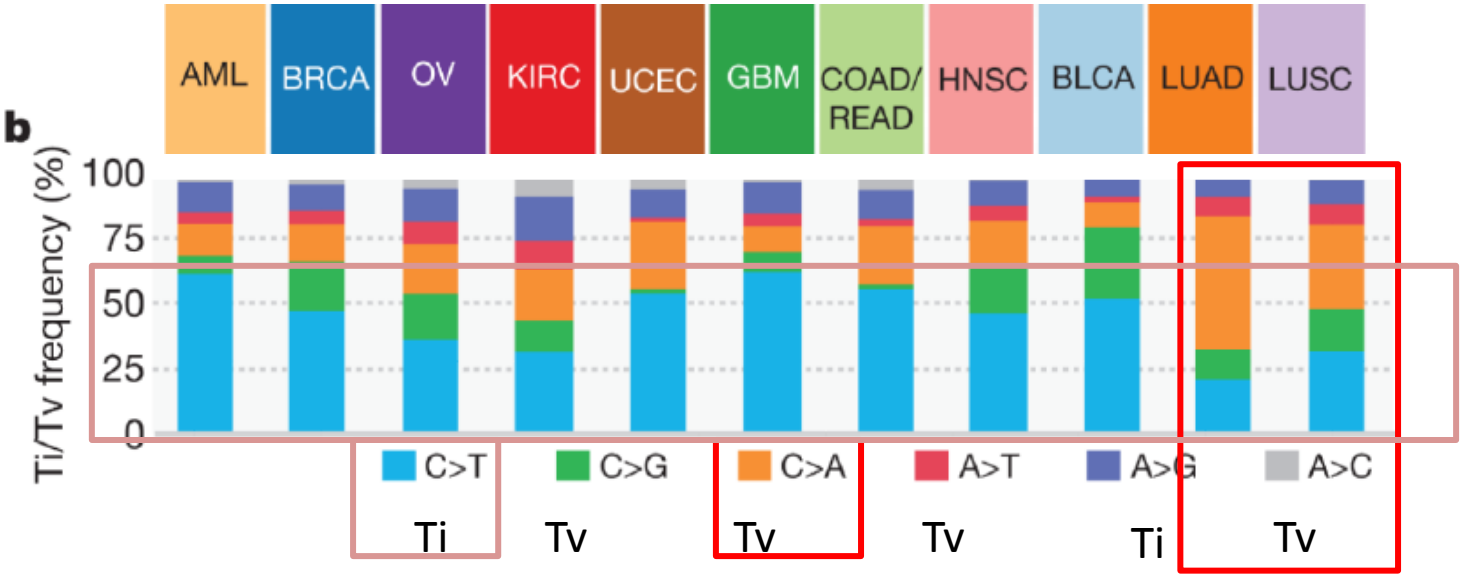
Kandoth et al.,Mutational landscape and significance across 12 major cancer types. *Nature, 2013. 502(7471): 333-9.*

Distribution of mutations in 127 SMGs across Pan-Cancer cohort

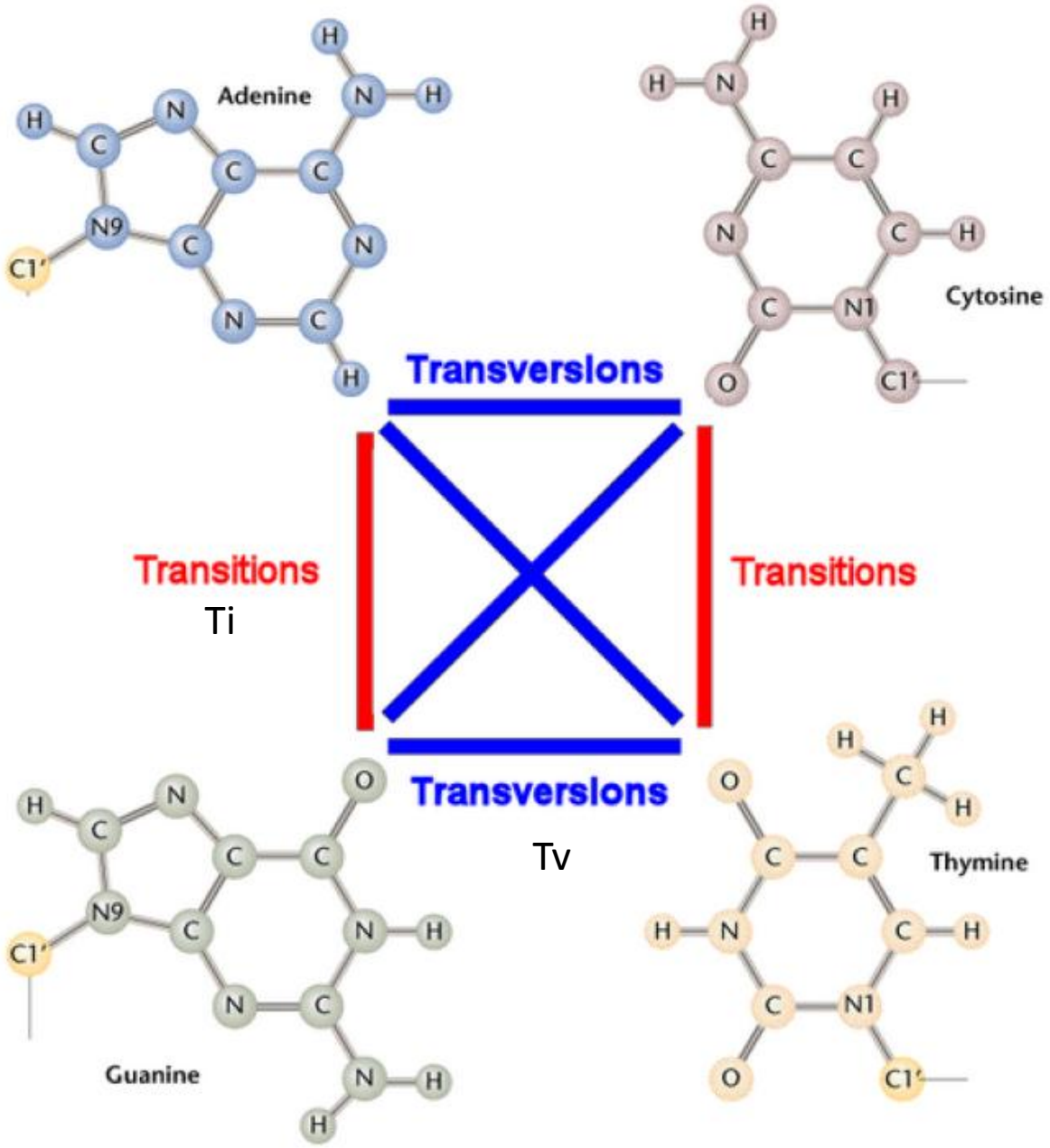


Box plot displays median numbers of non-synonymous mutations, with outliers shown as dots. In total, 3,210 tumours were used for this analysis (hypermutators excluded).

Mutation frequencies, spectra and contexts across 12 cancer types

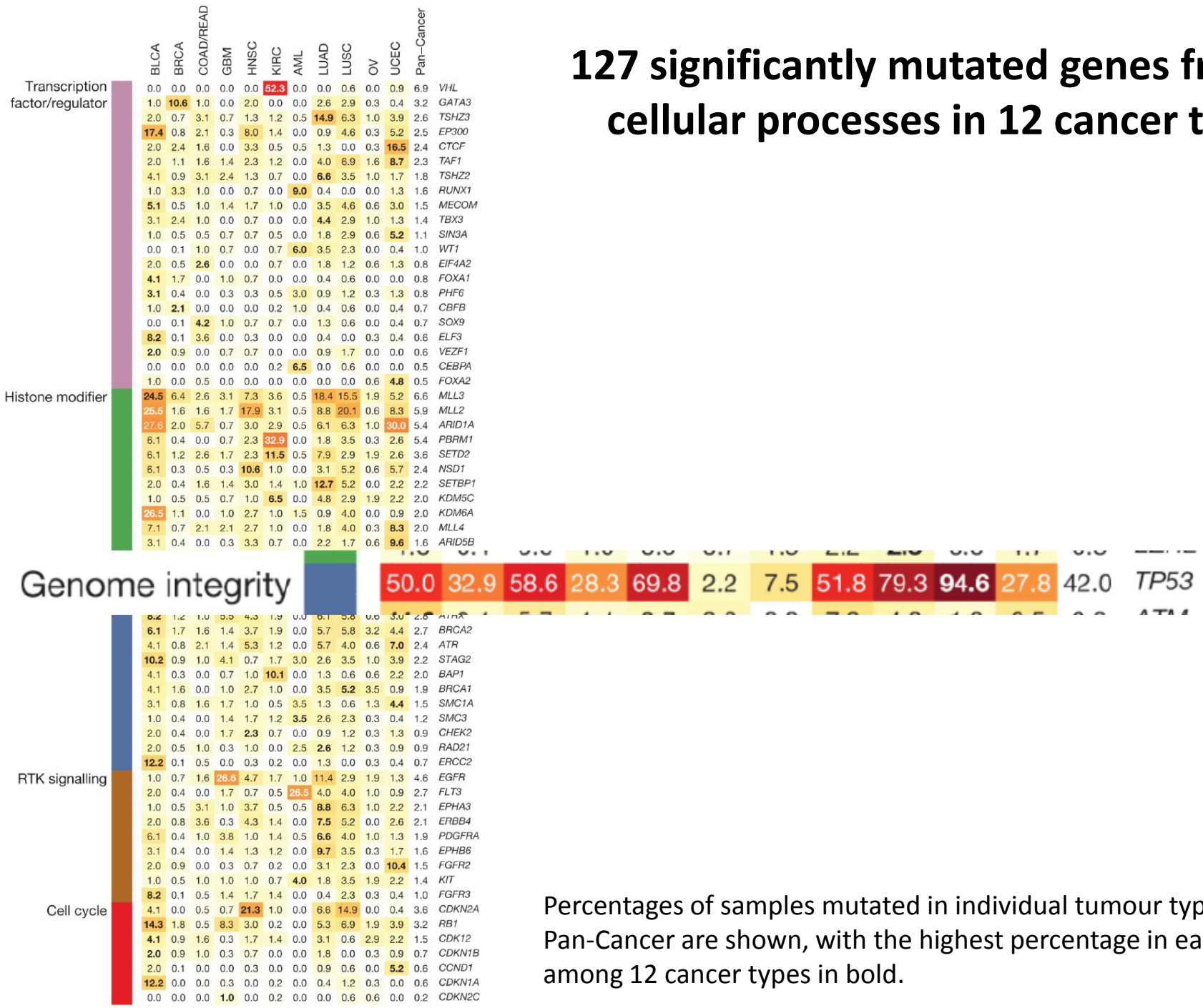


Mutation spectrum of six transition (Ti) and transversion (Tv) categories for each cancer type.

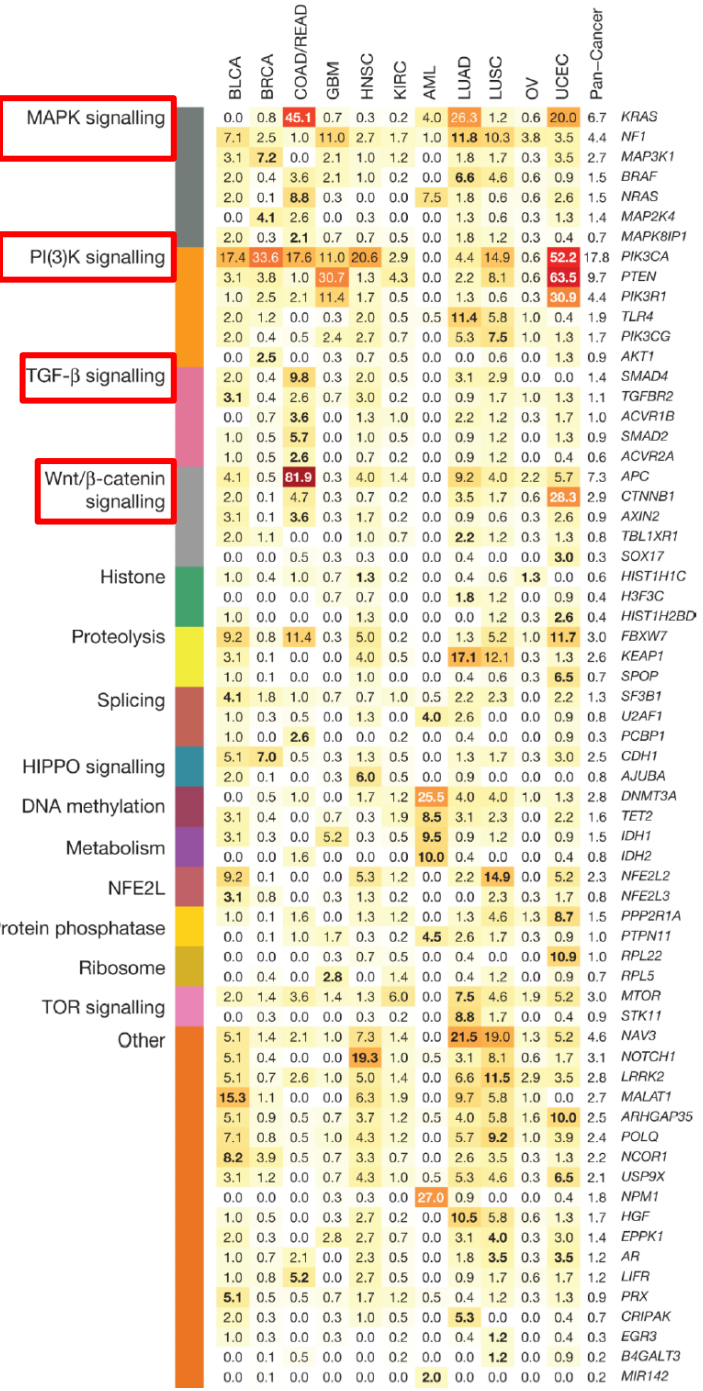


Transition *versus* Transversion mutations

127 significantly mutated genes from 20 cellular processes in 12 cancer types



Percentages of samples mutated in individual tumour types and Pan-Cancer are shown, with the highest percentage in each gene among 12 cancer types in bold.

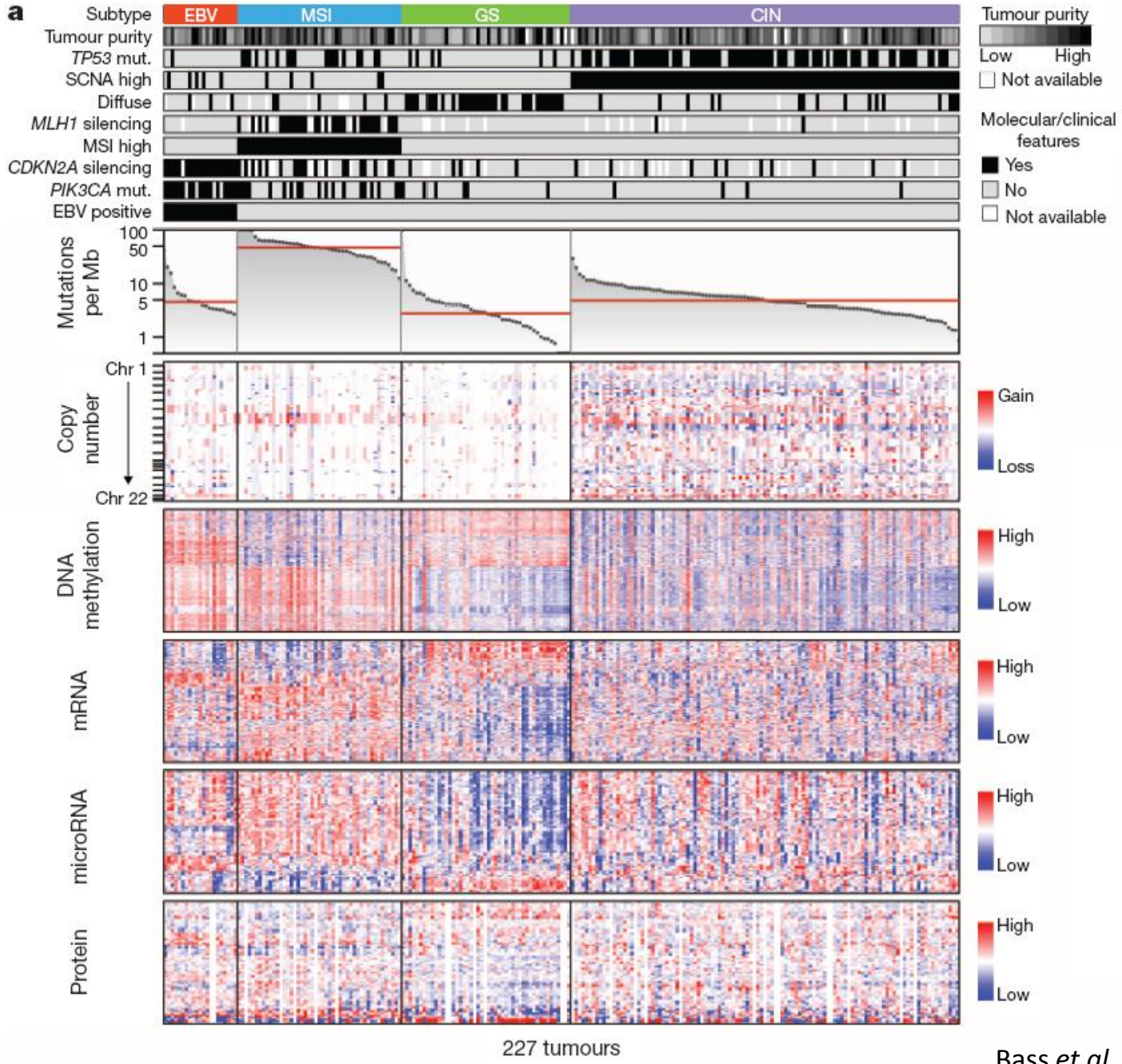


127 significantly mutated genes from 20 cellular processes in 12 cancer types

1. BRCA (Breast adenocarcinoma)
2. LUAD (Lung adenocarcinoma)
3. LUSC (Lung squamous cell carcinoma)
4. UCEC (Uterine corpus endometrial carcinoma)
5. GBM (Glioblastoma multiforme)
6. HNSC (Head and neck squamous cell carcinoma)
7. COAD, READ (Colon and rectal carcinoma)
8. BLCA (Bladder urothelial carcinoma)
9. KIRC (Kidney renal clear cell carcinoma)
10. OV (Ovarian serous carcinoma)
11. LAML, AML (Acute myeloid leukaemia)
12. Pan-Cancer

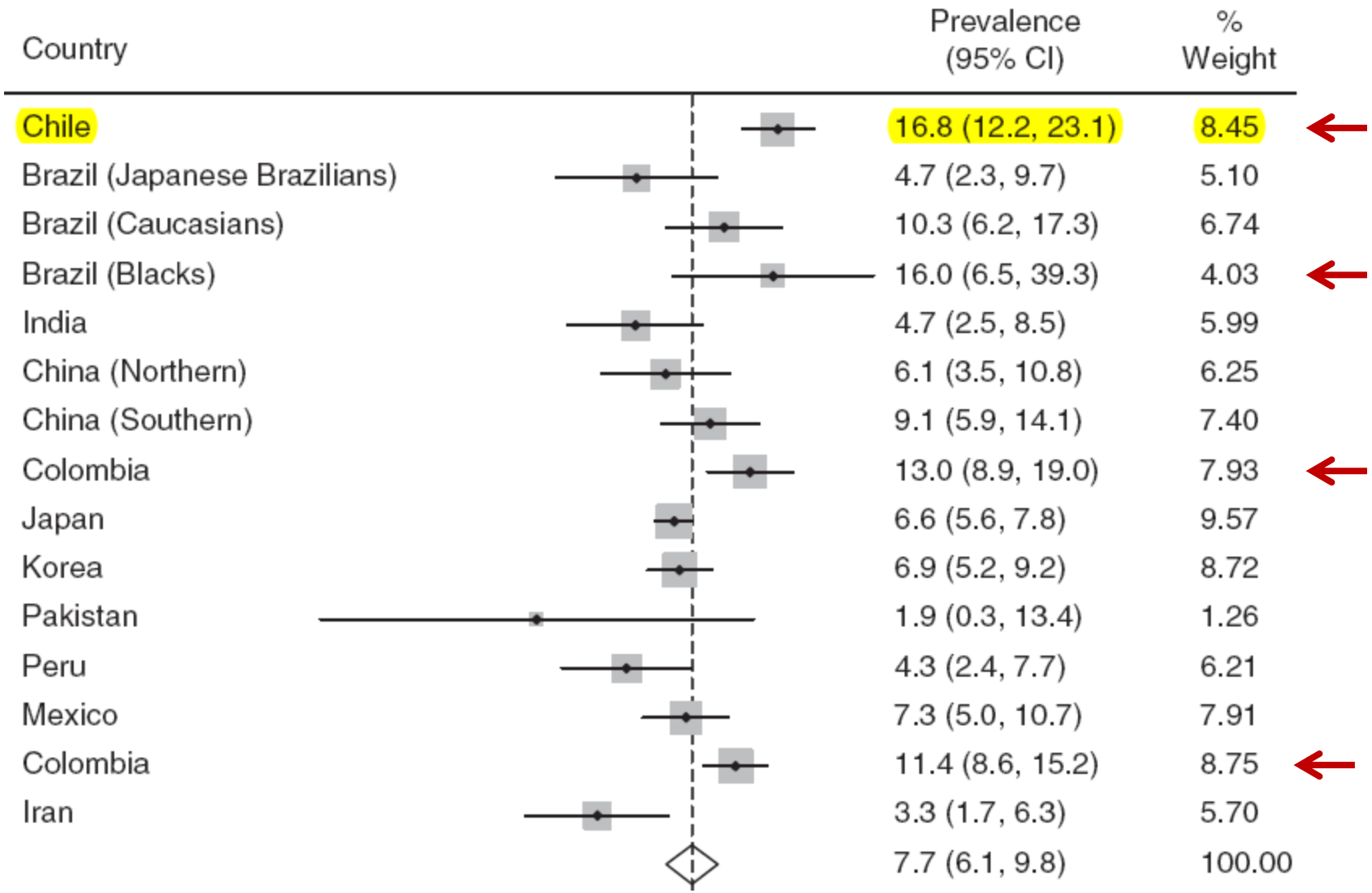
Percentages of samples mutated in individual tumour types and Pan-Cancer are shown, with the highest percentage in each gene among 12 cancer types in bold.

Comprehensive molecular characterization of gastric adenocarcinoma



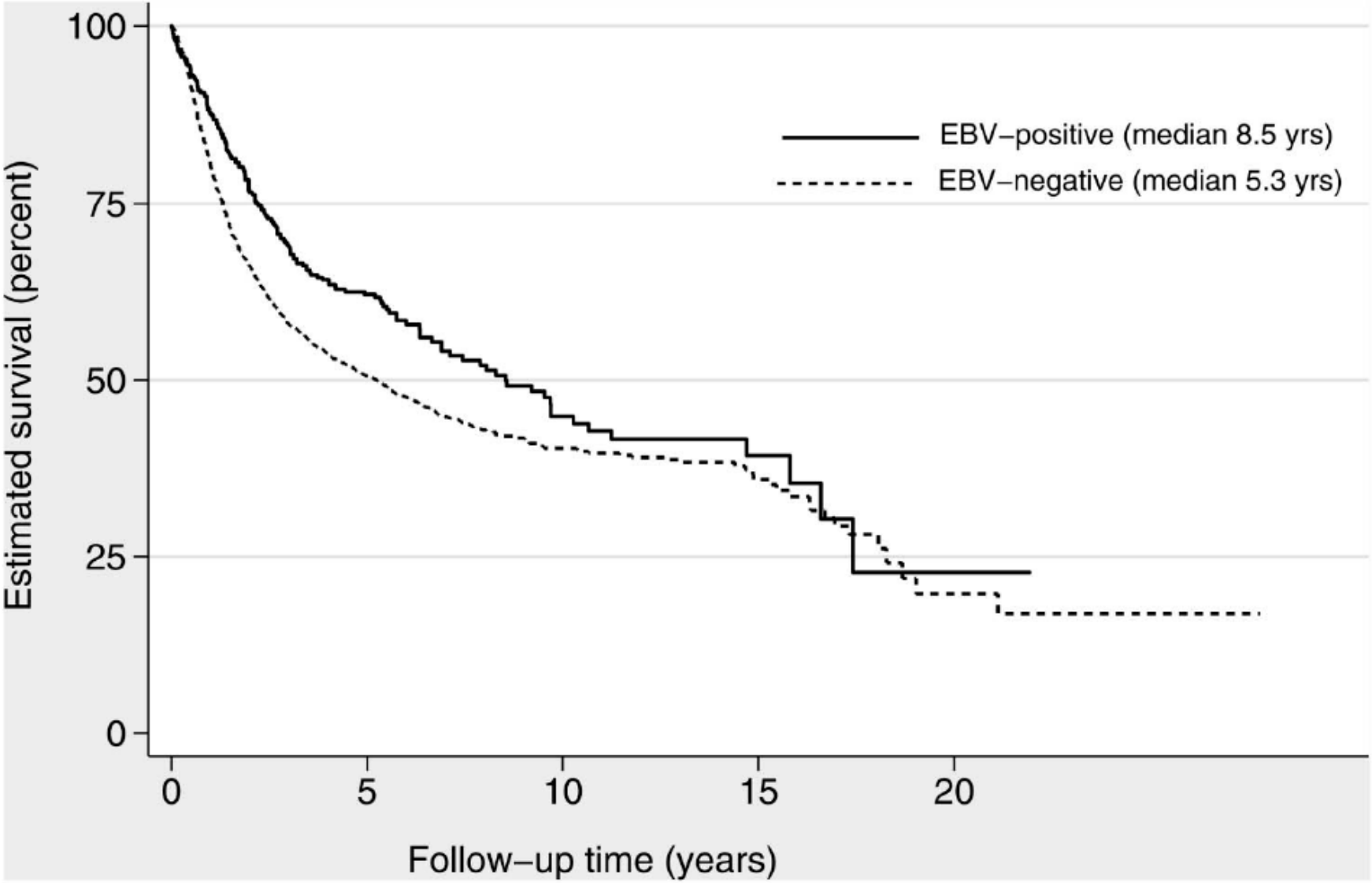
Bass *et al.*, Nature 2014

Determinants of Epstein-Barr virus-positive gastric cancer: an international pooled analysis



Camargo *et al.,* Br J Cancer 2011

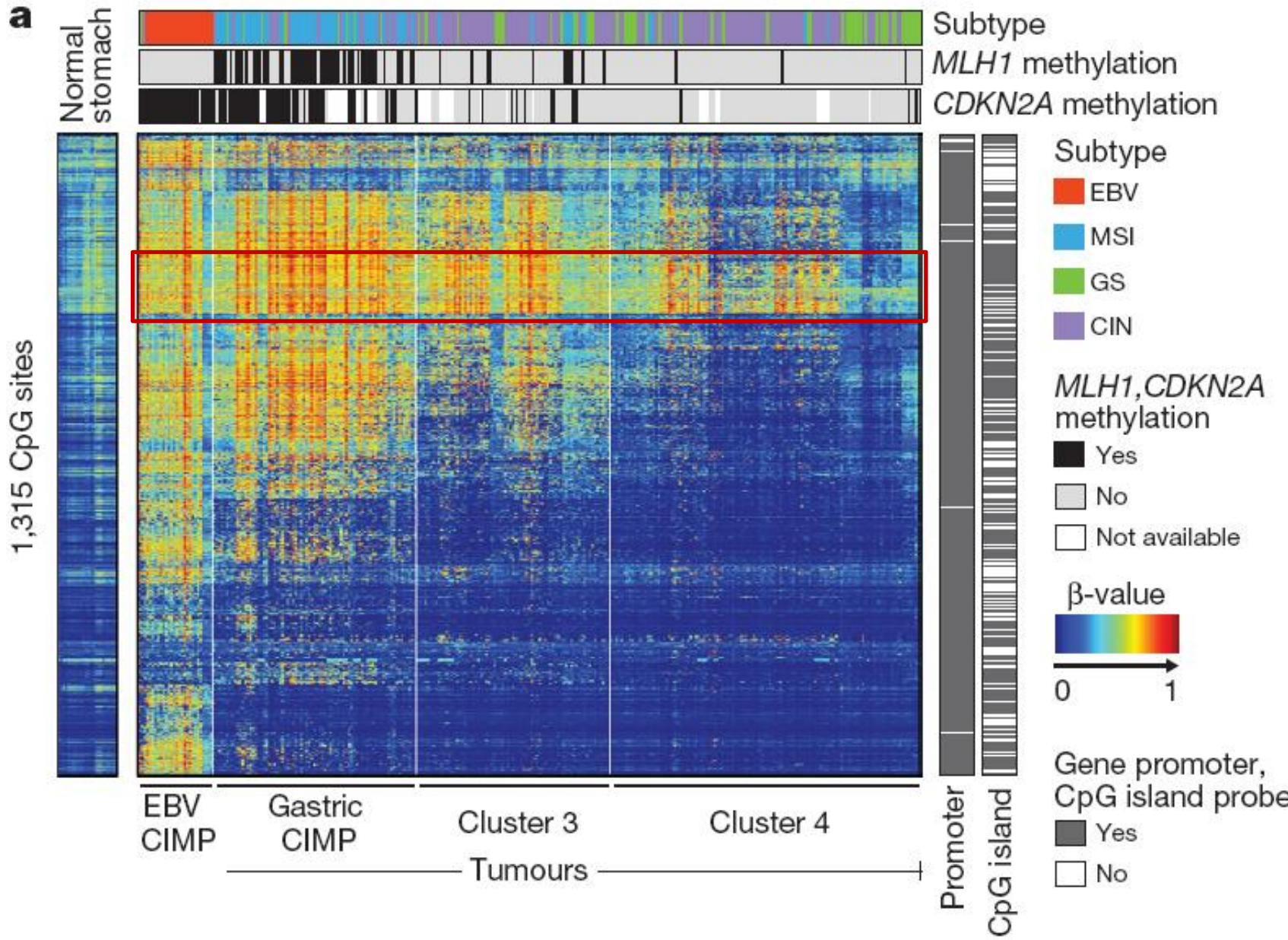
Improved survival of gastric cancer with tumour Epstein-Barr virus positivity: an international pooled analysis



Camargo *et al.,* Gut 2014

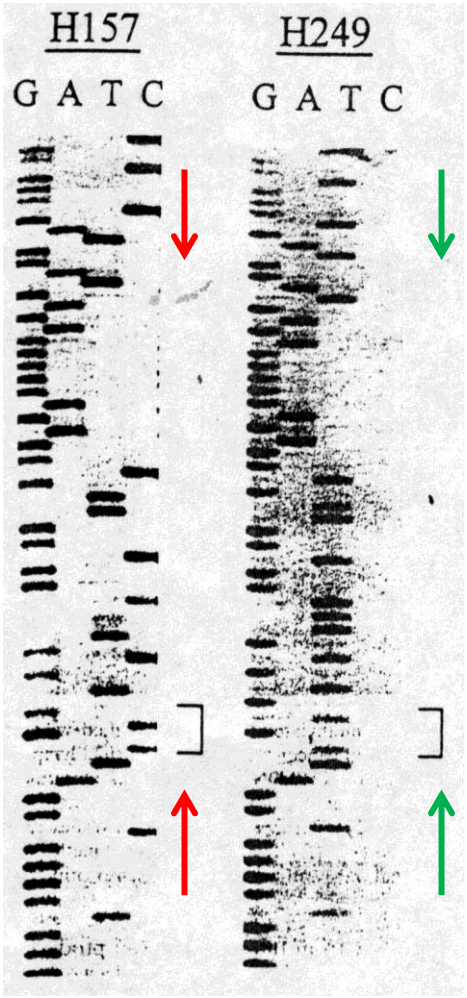
Comprehensive molecular characterization of gastric adenocarcinoma

The Cancer Genome Atlas Research Network*



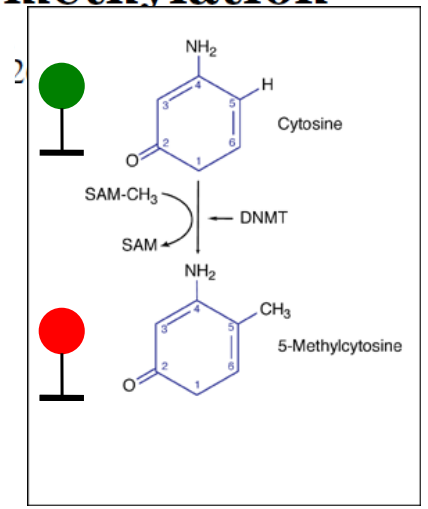
Methylation-specific PCR: A novel PCR assay for methylation status of CpG islands

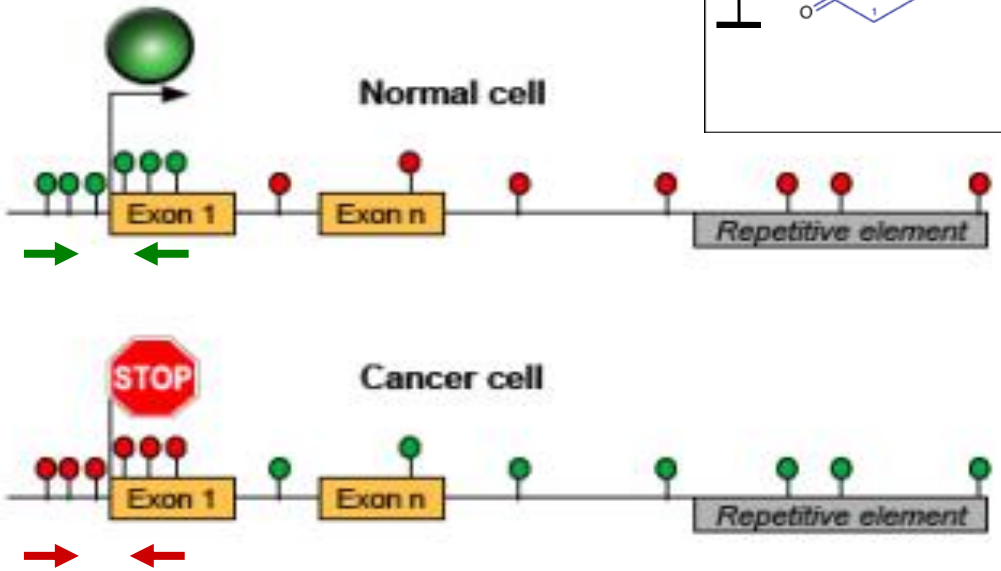
(DNA methylation/tumor suppressor genes/*p16*/*p15*)

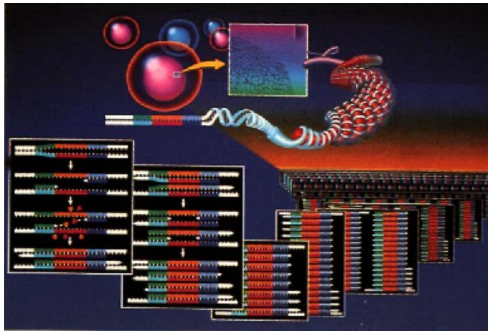


Methylated Unmethylated

BISULFITE CONVERSION



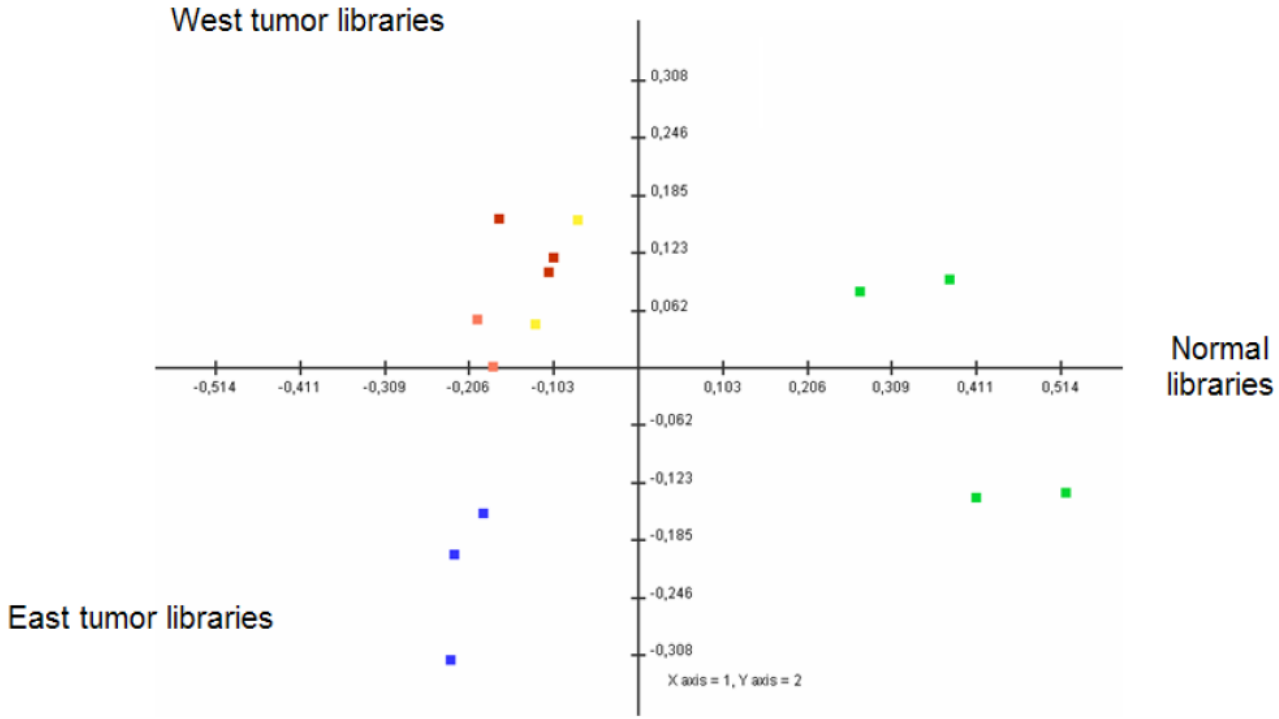




In silico analysis of gastric carcinoma **Serial Analysis of Gene Expression** (SAGE) libraries reveals different profiles associated with ethnicity

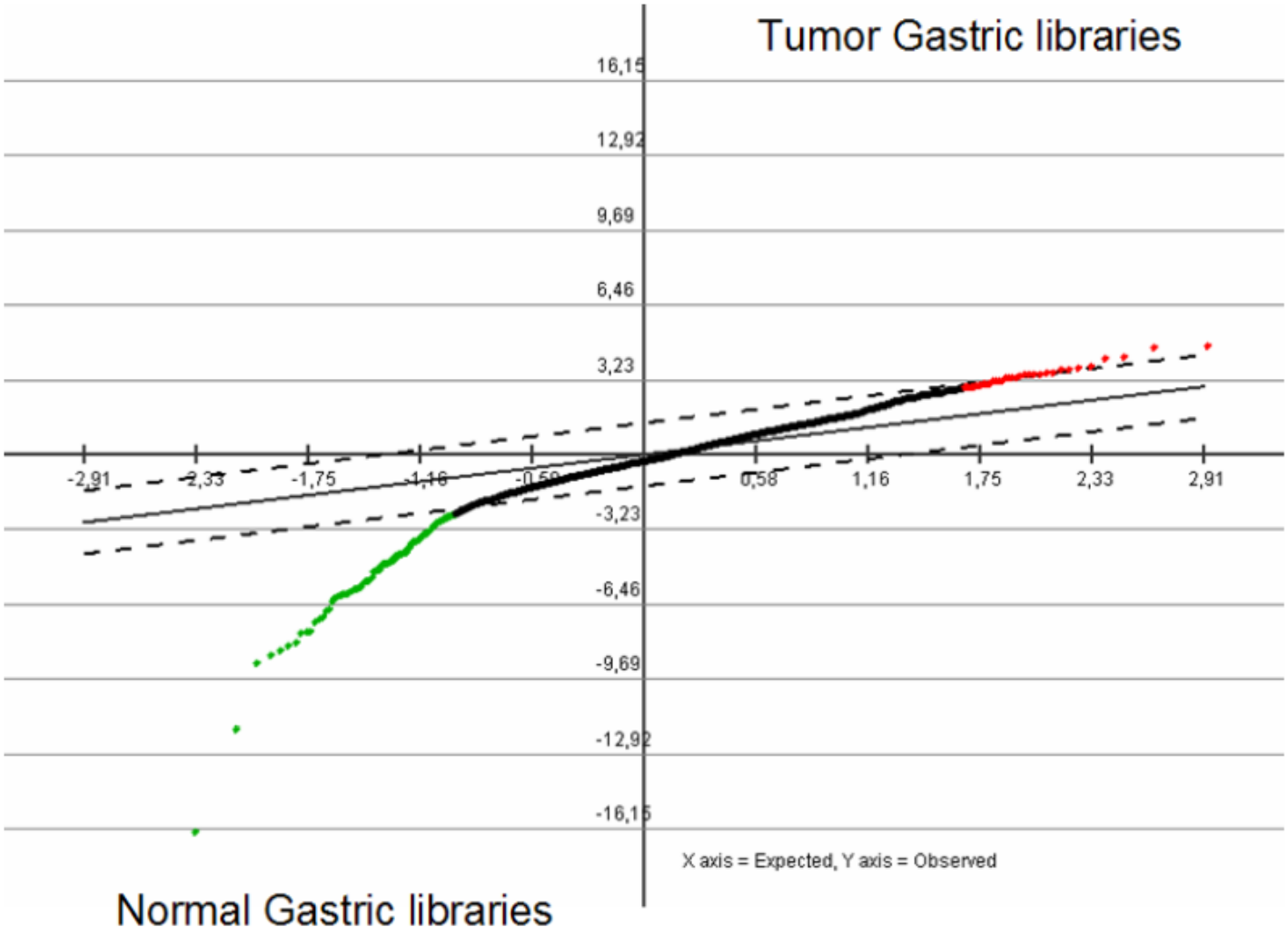
El-Rifai W
Vandebilt U. USA
East Tumor Libraries

Yasui W
Hiroshima U. Japan
West Tumor Libraries



Ossandon *et al.*, *Mol Cancer, 2008*

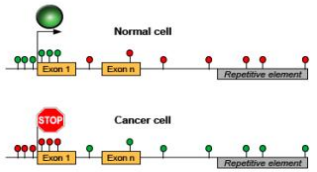
In silico analysis of gastric carcinoma Serial Analysis of Gene Expression libraries reveals different profiles associated with ethnicity



ASAH1
ACAA2
ATP4A
ATP4B
CCT3
CD9
CLIC1
CLIC6
CTGF
DKK1
DRD5
EIF4A1
ENO1
ESRRG
FYN
GMDS
GOLGA3
GPRC5A
HMGB1
HSPB1
ITGB4BP
KLK10
MACF1
MAML2
MBD3
NDUFA11
NPC2
PCSK1N
PFKP
PPAP2B
STAT1
STRAP
TENC1
TFF2
TIMP1
TM7SF3
TUBB
YWHAB

Ossandon *et al.*, *Mol Cancer, 2008*

DNA methylation profile in Gastric Cancer
32 gastric cancer cases / 24 genes



cases

genes

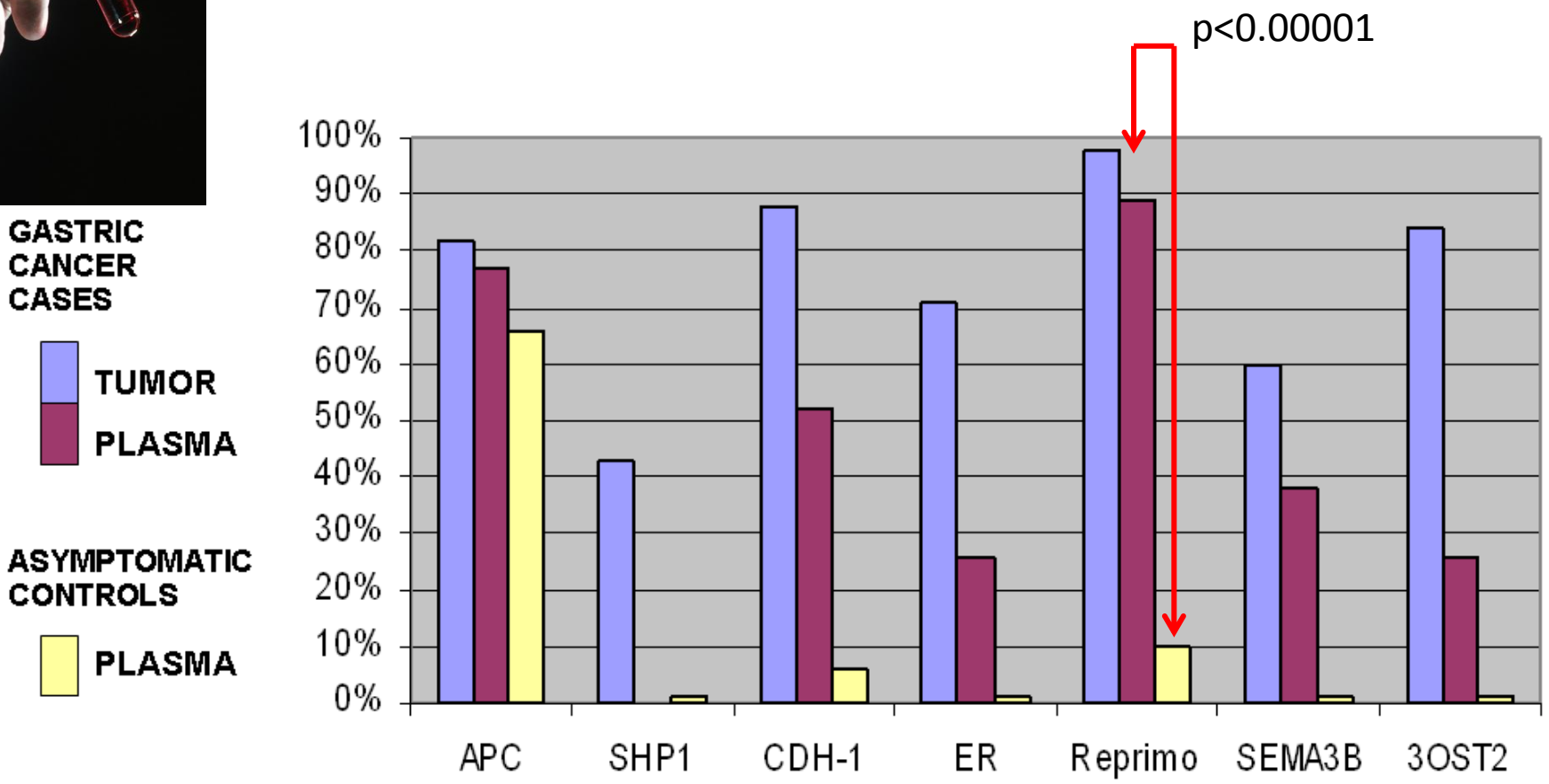
	CB6	CB8	CB12	CB13	CB14	CB15	CB17	CB18	CB21	CB22	CB25	CB26	CB27	CB29	CB30	CB33	CB34	CB35	CB36	CB37	CB38	CB39	CBCG2	CBCG4	CBCG5	KS4T	KS6T	KS11T	KS12T	KS16T	KS17T	KS18T	%
APC																																	87.5%
SHP1																																	78.1%
CDH1																																	71.9%
ER																																	71.9%
Reprimo																																	68.8%
SEMA3B																																	65.6%
3OST2																																	62.5%
p14																																	56.3%
p15																																	56.3%
DAPK																																	53.1%
p16																																	53.1%
p73																																	43.8%
BLU																																	40.6%
FHIT																																	40.6%
RUNX3																																	40.6%
BRCA1																																	34.4%
PTEN																																	34.4%
MGMT																																	28.1%
hMLH1																																	25.0%
RARB																																	25.0%
TIMP3																																	25.0%
RIZ1																																	21.9%
COX2																																	9.4%
GSTp1																																	0.0%
SOCS																																	0.0%

Unmethylated

Methylated

→ novel genes

PROSPECTIVE ANALYSIS
43 gastric cancer cases / 31 asymptomatic controls
7 candidate biomarkers



Histogram representing the percentage of positive cases for Reprimo and other genes (APC, SHP1, CDH-1, ER, SEMA3B and 3OST2) in 43 prospectively collected gastric cancer cases and 31 asymptomatic age- and gender-matched controls. Only Reprimo shows significative differences in plasma between gastric cancer and asymptomatic controls ($p<0.001$).

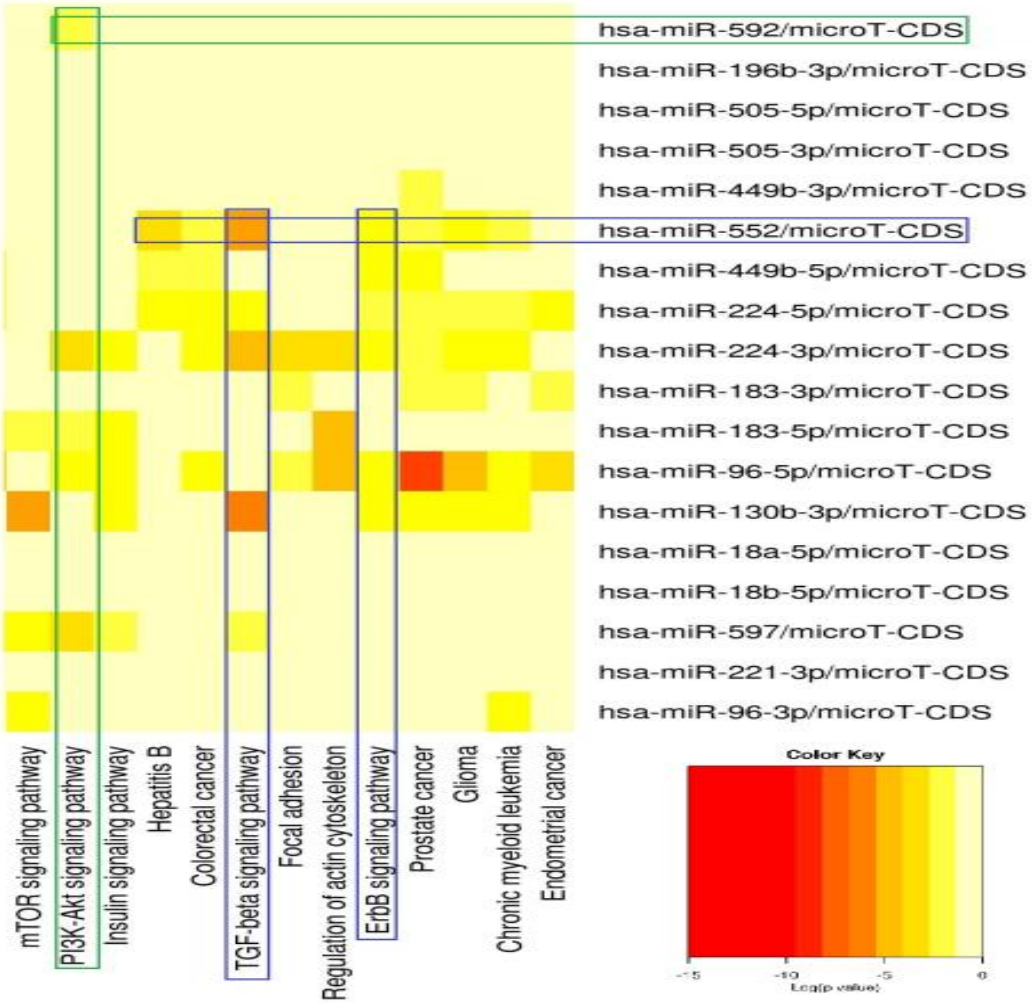
Bernal et al., Clin Cancer Res. 2008;14:6264-9

USO DE HERRAMIENTAS BIOINFORMÁTICAS PARA EL MODELAMIENTO Y PREDICCIÓN DE PROCESOS TUMORALES

Wichmann I. [1,2], Artigas R.[1,2], Corvalan A. [1,2,3]
[1]Laboratorio de Oncología UC, Pontificia Universidad Católica de Chile, Santiago, Chile.
[2]Centro de Estudios de Enfermedades Crónicas (ACCDiS) y [3]Centro UC Investigación en Oncología (CITO), Pontificia Universidad Católica de Chile, Santiago,

miRNAs vs Vías Moleculares

Heatmap generado utilizando mirPath 2.0 (Diana Tools)



USO DE HERRAMIENTAS BIOINFORMÁTICAS PARA EL MODELAMIENTO Y PREDICCIÓN DE PROCESOS TUMORALES

miRNAs en TCGA

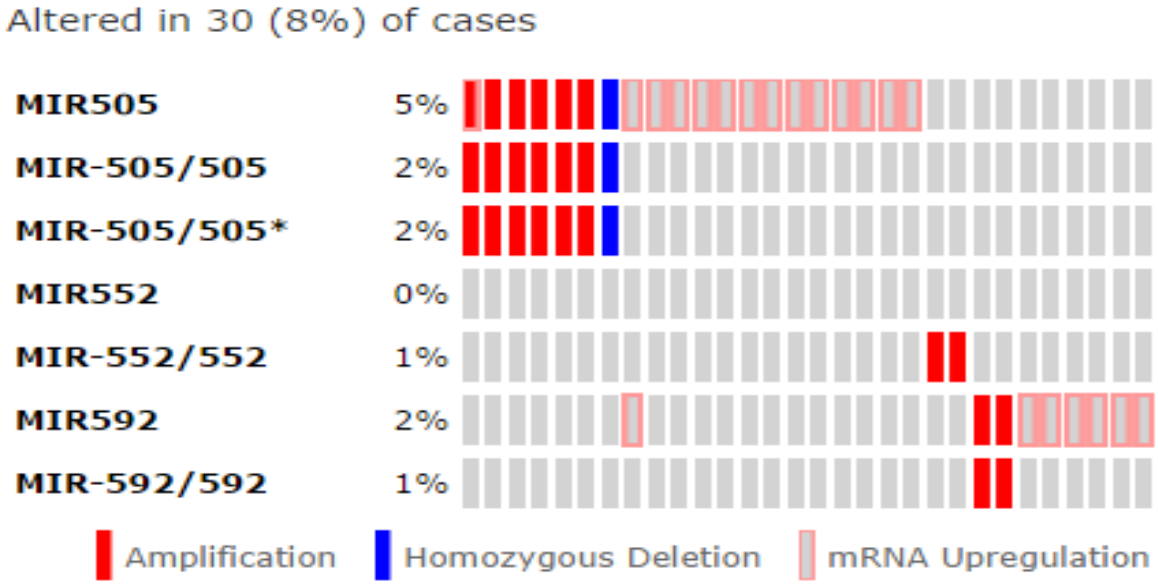
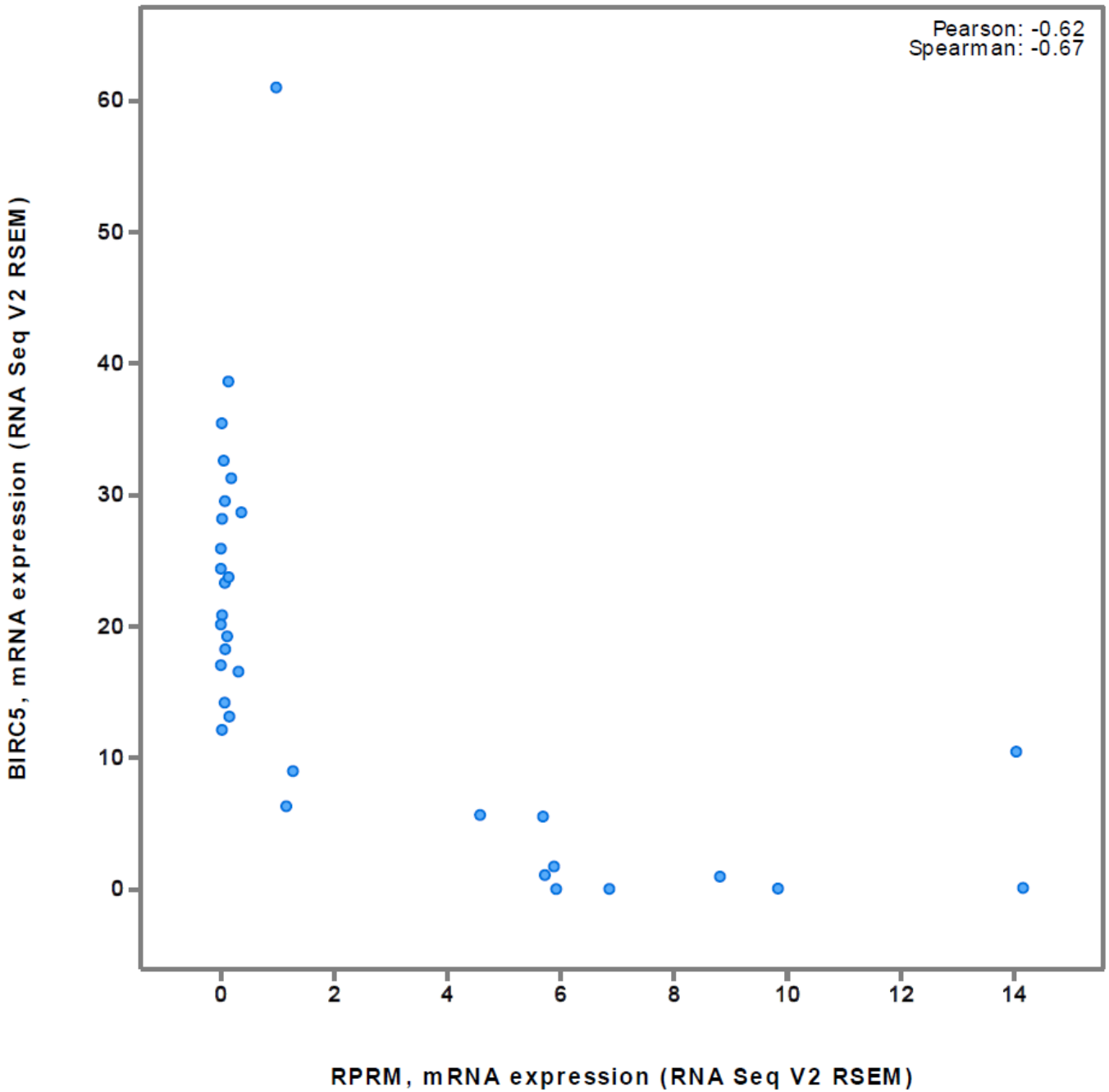


Tabla 1: Vías oncogénicas y genes blanco

	p-value	Target Genes
TGF-Beta (miR-552)	0,002	RPS6KB1, SMAD3.
Erbβ (miR-552)	0,006	MAP2K1, RPS6KB1, TGFA.
PI3K-AKT (miR-592)	0,04	IGF1, LAMC1, IFNAR1, ITGB6, PIK3CA, PPP2R2D, EIF4E, BRCA1, FOXO3, CREB3L3.

Vías oncogénicas relacionadas a miRNAs-505, -552 y 592
Valor-p calculado utilizando Diana Tools mirPath 2.0


Pearson: -0.62
Spearman: -0.67
BIRC5, mRNA expression (RNA Seq V2 RSEM)
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
RPRM, mRNA expression (RNA Seq V2 RSEM)

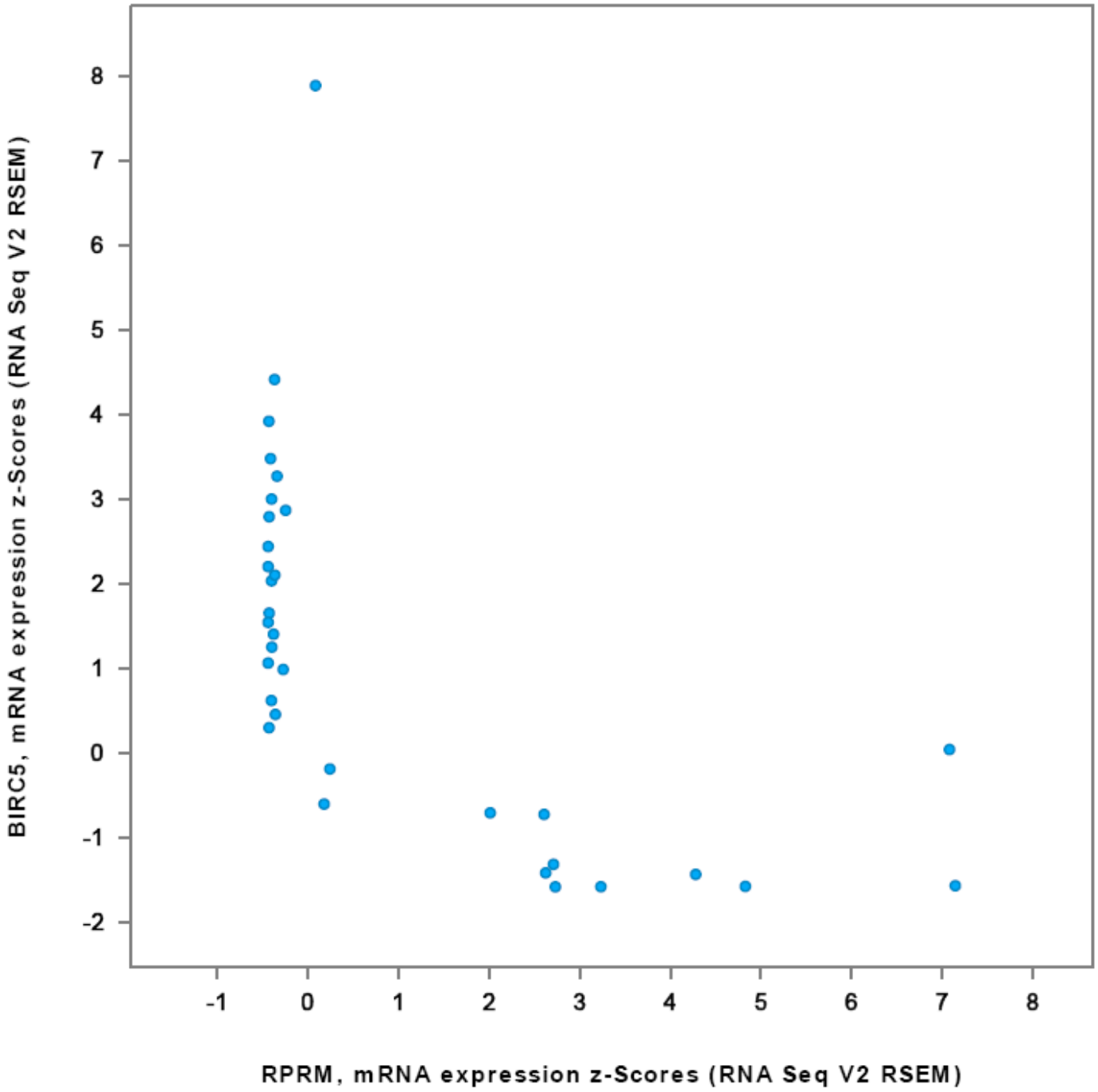

BIRC5, mRNA expression z-Scores (RNA Seq V2 RSEM)
8
7
6
5
4
3
2
1
0
-1
-2
-1
0
1
2
3
4
5
6
7
8
RPRM, mRNA expression z-Scores (RNA Seq V2 RSEM)

Fig.1

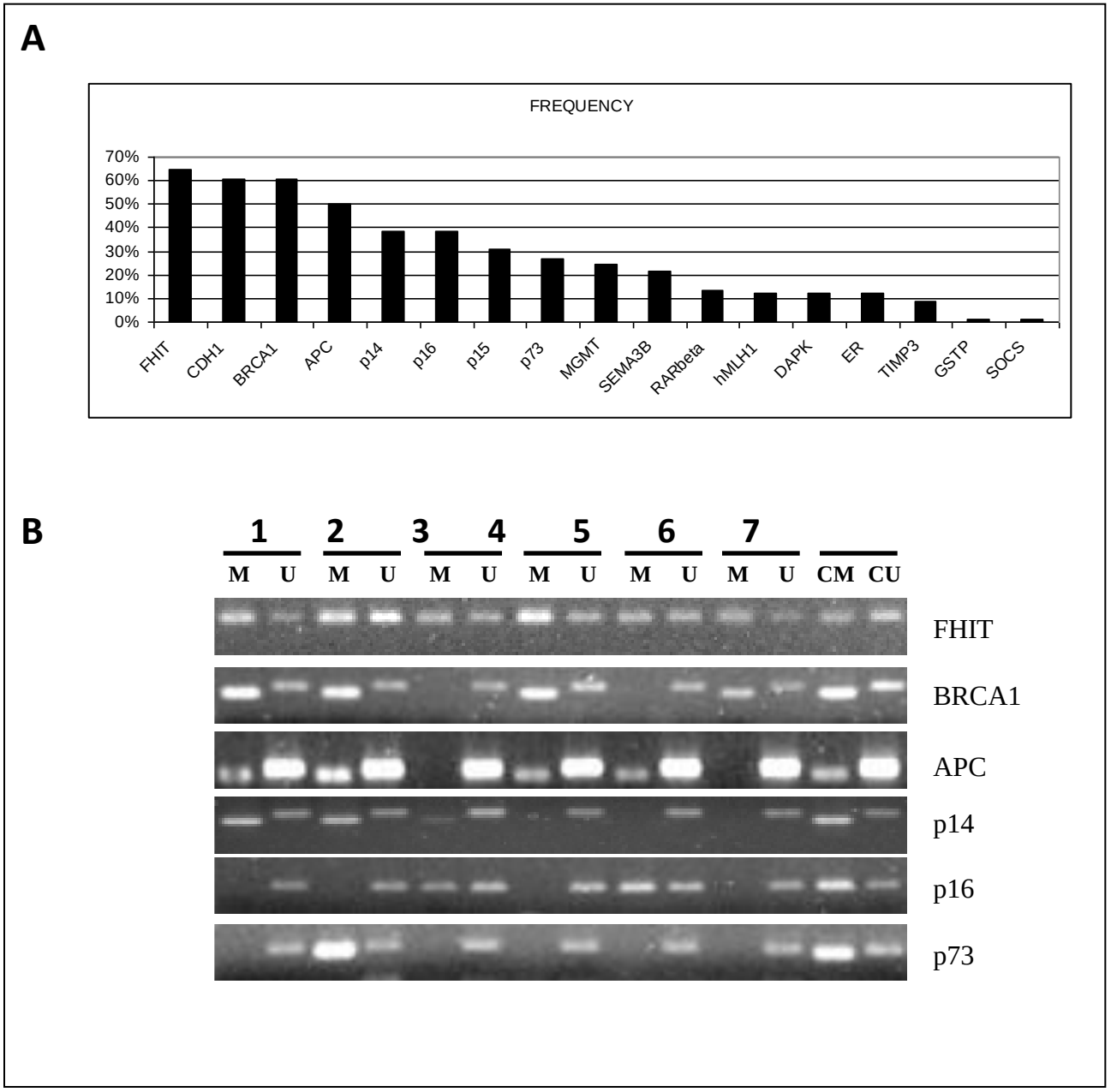

A
FREQUENCY
70%
60%
50%
40%
30%
20%
10%
0%
FHIT
CDH1
BRCA1
APC
p14
p16
p15
p73
MGMT
SEMA3B
RARbeta
hMLH1
DAPK
ER
TIMP3
GSTP
SOCS
B
1
2
3
4
5
6
7
M U M U M U M U M U M U CM CU
FHIT
BRCA1
APC
p14
p16
p73

Fig.2

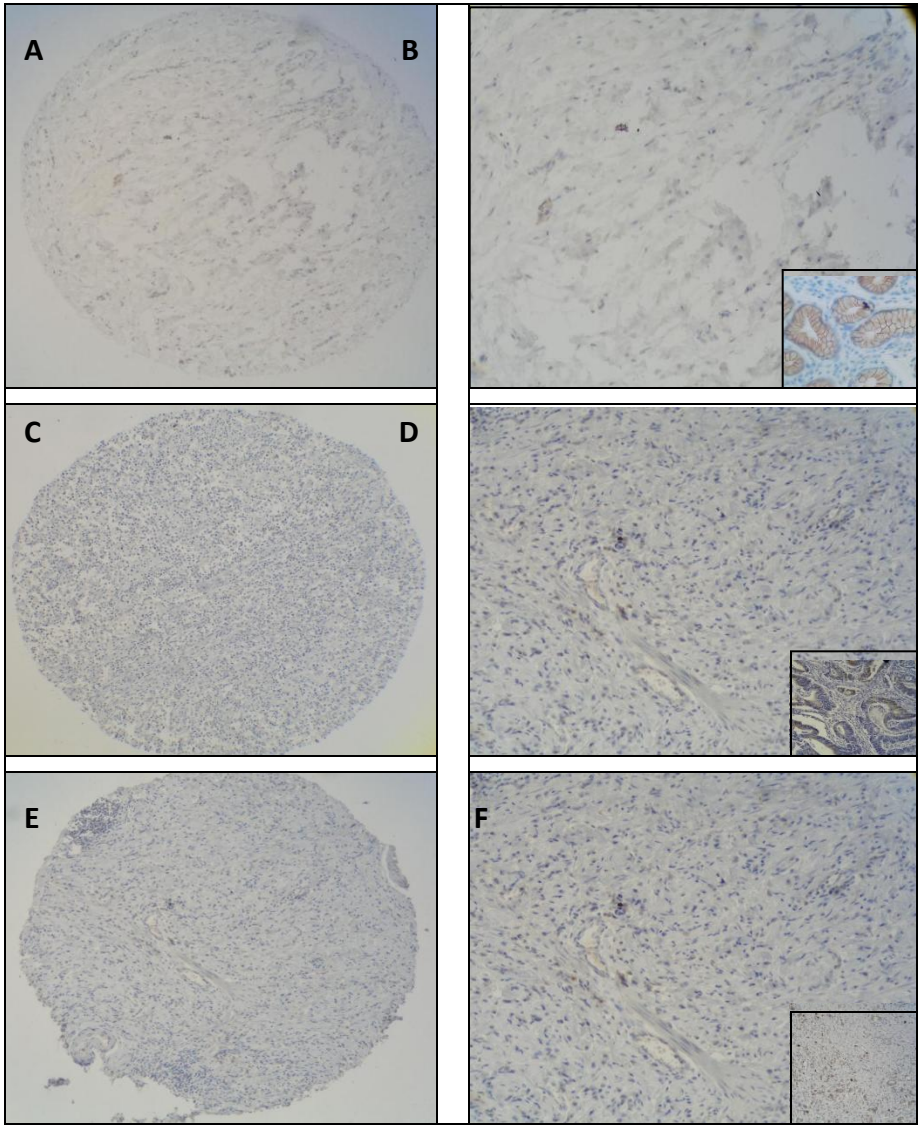
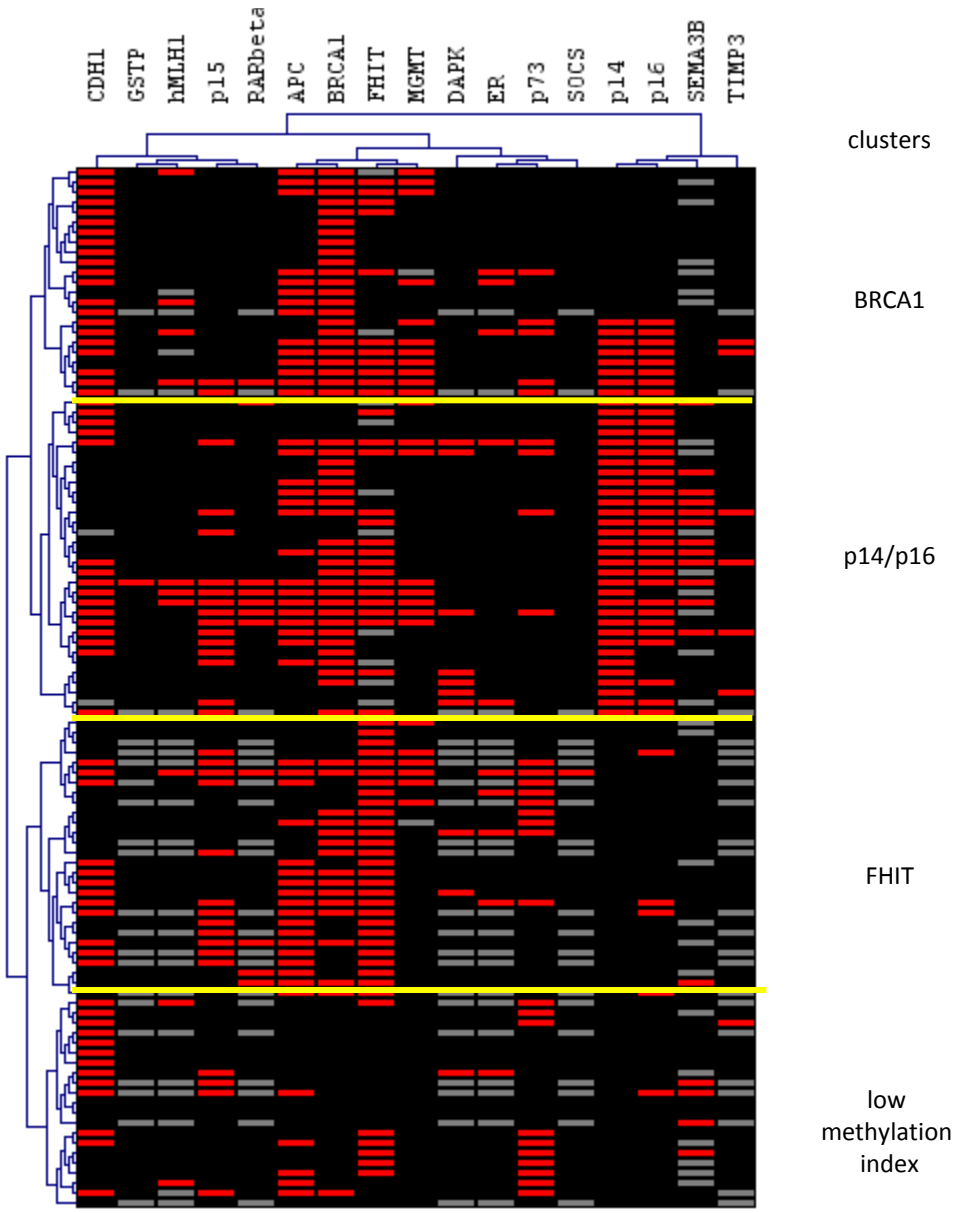
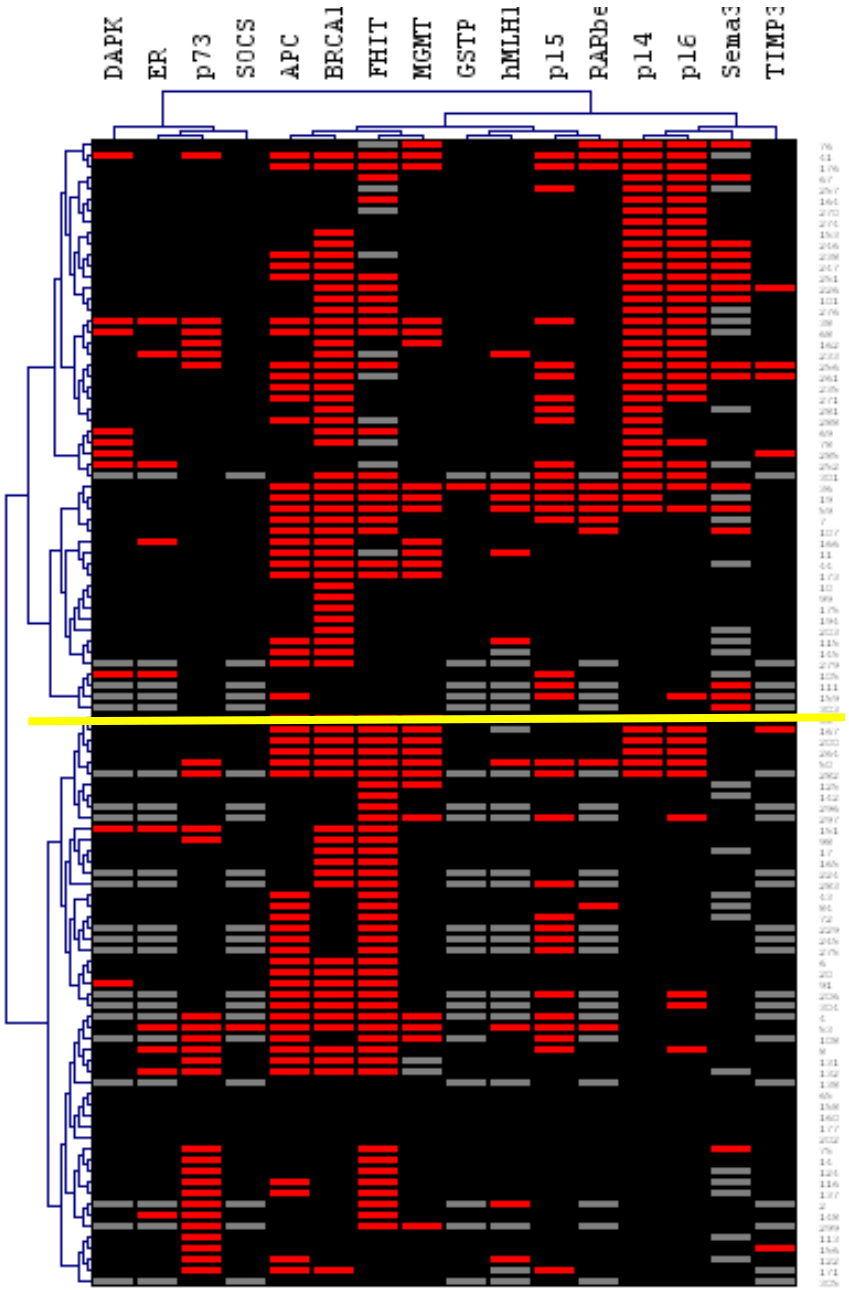


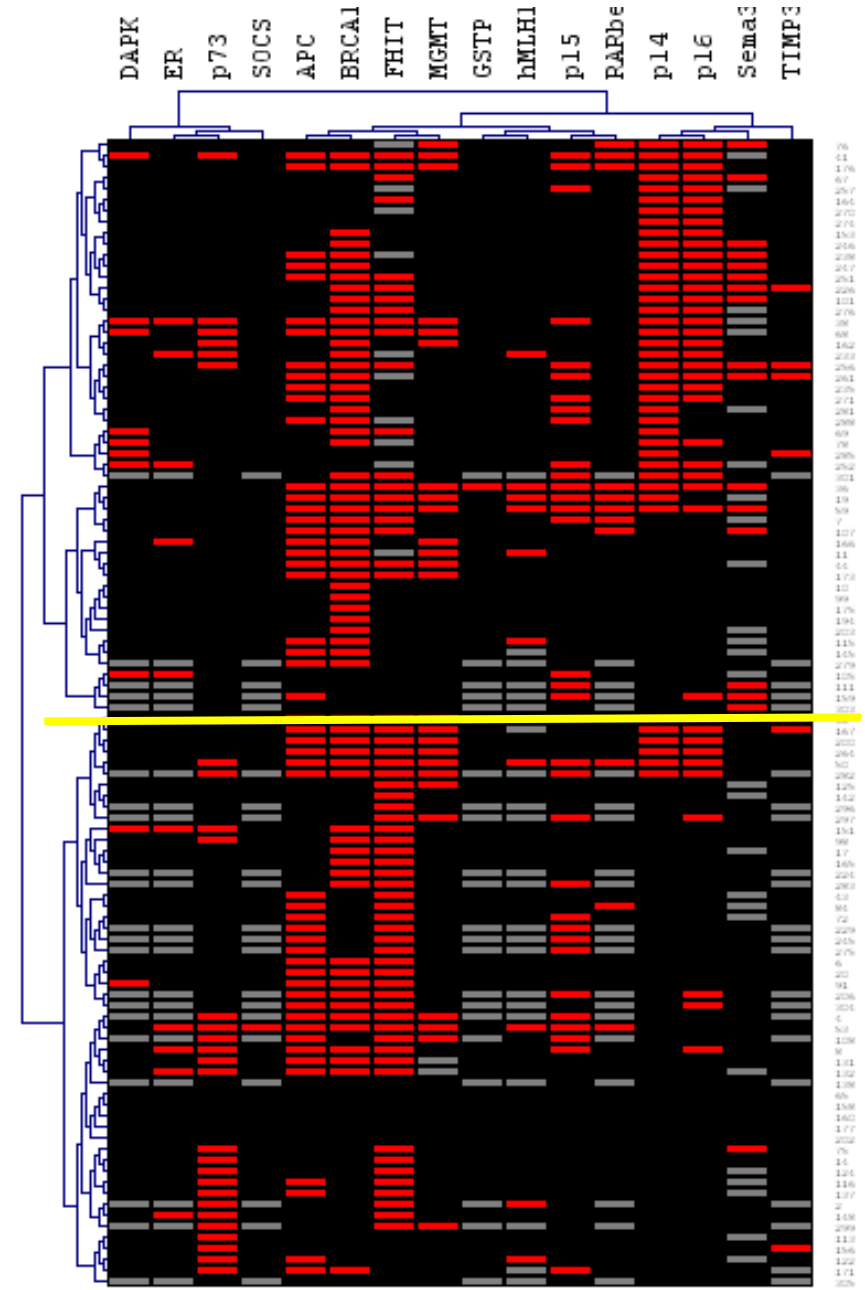
Fig.3


CDH1
GSTP
hMLH1
p15
RARbeta
APC
BRCA1
FHIT
MGMT
DAPK
ER
p73
SOCS
p14
p16
SEMA3B
TIMP3
clusters
BRCA1
p14/p16
FHIT
low
methylation
index

Cluster Analysis of methylation status of 16 genes in 104 cases of sporadic-diffuse gastric carcinoma



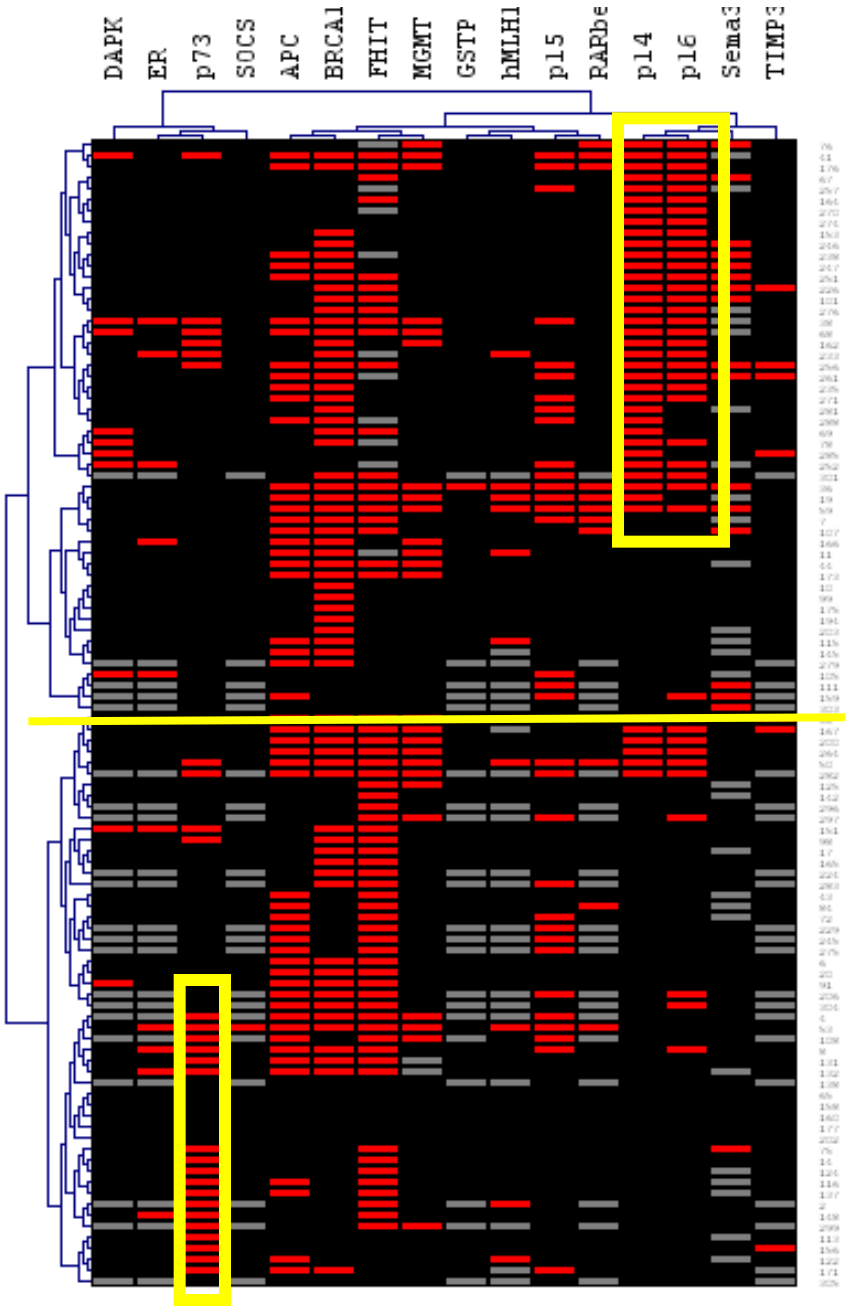
Cluster Analysis of methylation status of 16 genes in 104 cases of sporadic-diffuse gastric carcinoma



cluster A

cluster B

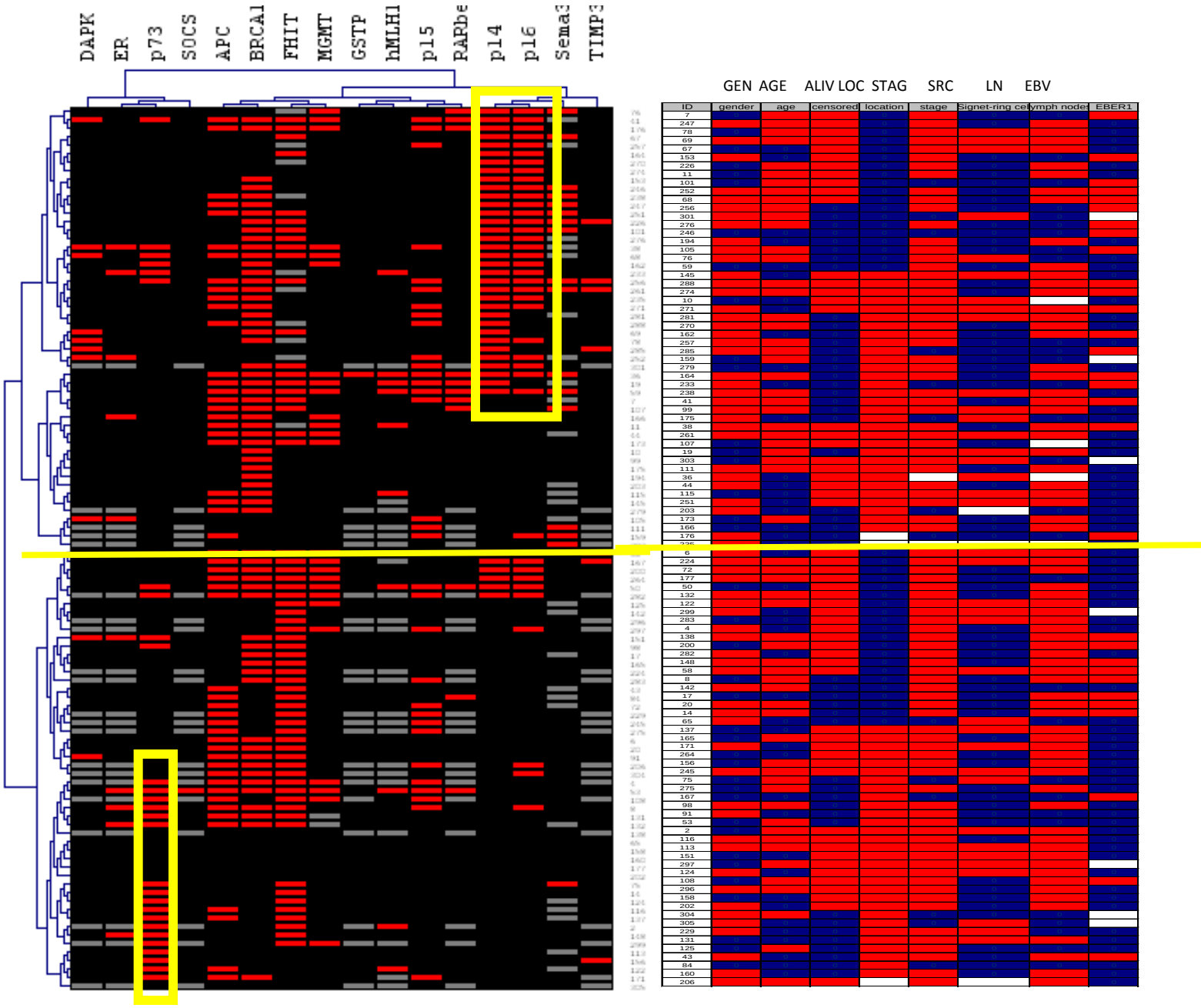
Cluster Analysis of methylation status of 16 genes in 104 cases of sporadic-diffuse gastric carcinoma



cluster A
p14/p16
34/52 (65.4%)
30/52(57.7%)

cluster B
p73
22/52 (42.3%)
p<0.001

Cluster Analysis of methylation status of 16 genes in 104 cases of sporadic-diffuse gastric carcinoma



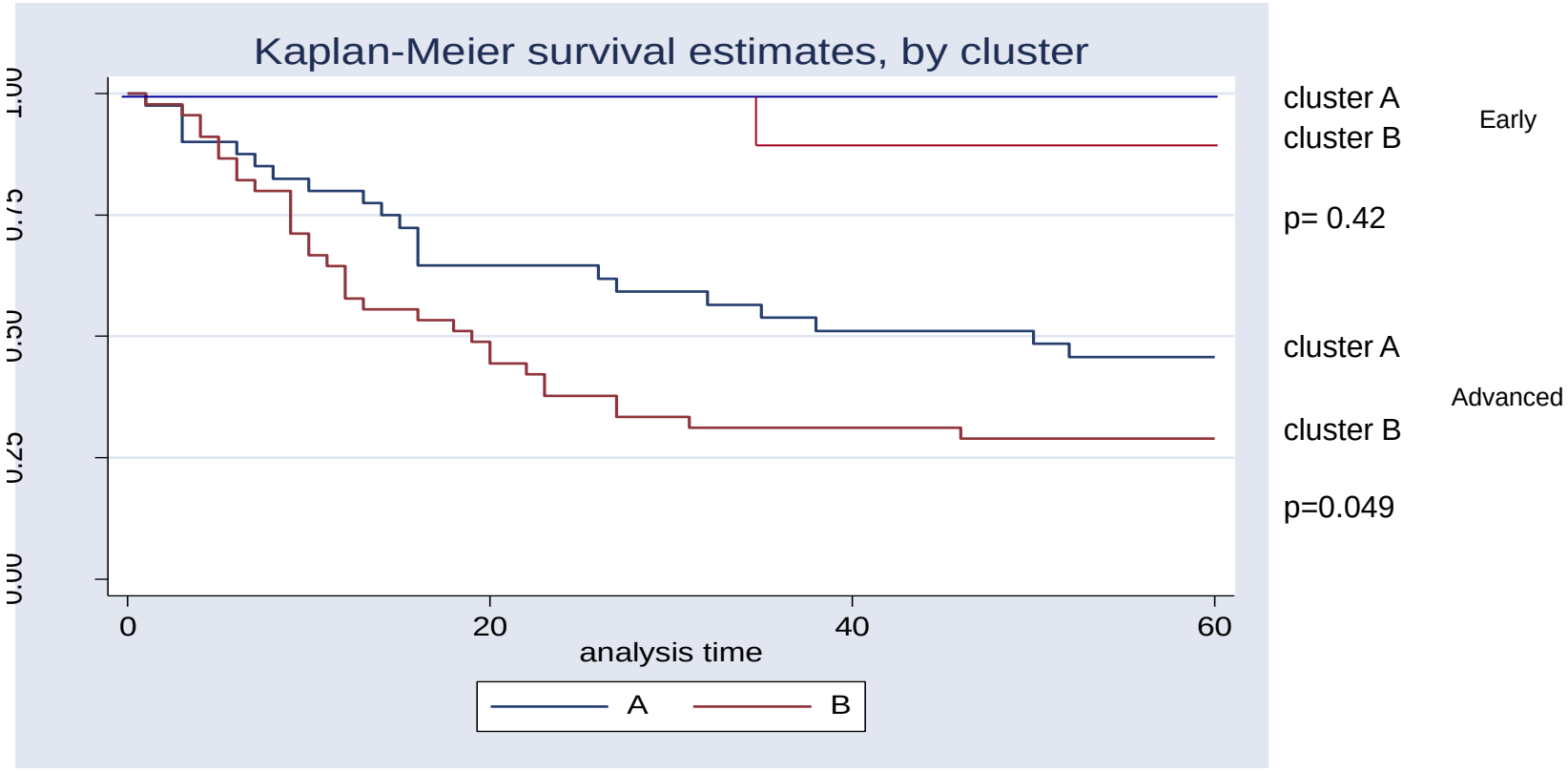
cluster A
p14/p16
34/52 (65.4%)
30/52(57.7%)

cluster B
p73
22/52 (42.3%)
p<0.001

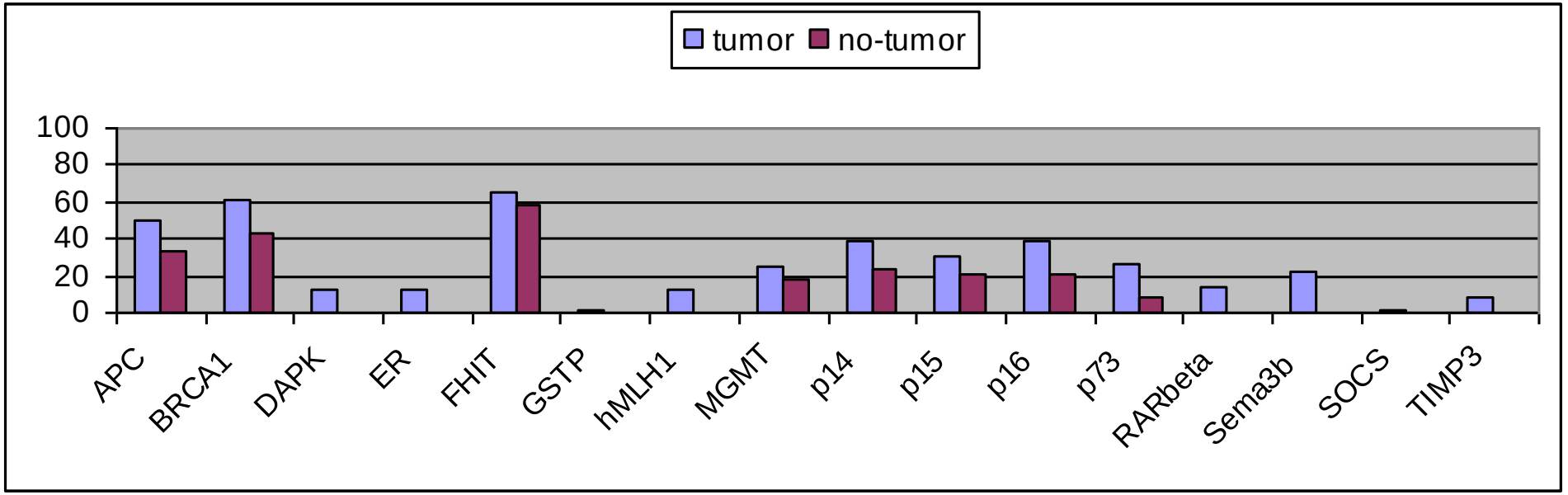
Table 1. Clinico-pathological correlation of clusters A (BRCA1, p14/p16 genes) and B (p73 gene).

		cluster A		cluster B		p
		N	%	N	%	
gender						
	female	17	32.7%	21	40.4%	0.116
	male	35	67.3%	31	59.6%	
age						
	<58	20	38.5%	23	44.2%	0.132
	>58	32	61.5%	29	55.8%	
censored						
	alive	24	46.2%	20	38.5%	0.115
	dead	28	53.8%	32	61.5%	
location						
	cardia	19	38.0%	21	41.2%	0.152
	corpus	18	36.0%	11	21.6%	
	antral	13	26.0%	19	37.3%	
stage						
	early	8	16.0%	6	11.5%	0.183
	advanced	42	84.0%	46	88.5%	
Signet-ring cell						
	no	32	64.0%	32	62.7%	0.162
	yes	18	36.0%	19	37.3%	
lymph nodes						
	negative	17	35.4%	12	23.1%	0.07
	positive	31	64.6%	40	76.9%	
Epstein-Barr virus						
	negative	30	61.2%	37	77.1%	0.042
	positive	19	38.8%	11	22.9%	

Fig. 2


Kaplan-Meier survival estimates, by cluster
1.00
0.75
0.50
0.25
0.00
0
20
40
60
analysis time
A
B
cluster A
cluster B
p= 0.42
Early
cluster A
cluster B
p=0.049
Advanced

Hypermethylation of 16 genes in 104 cases in diffuse-type gastric carcinoma

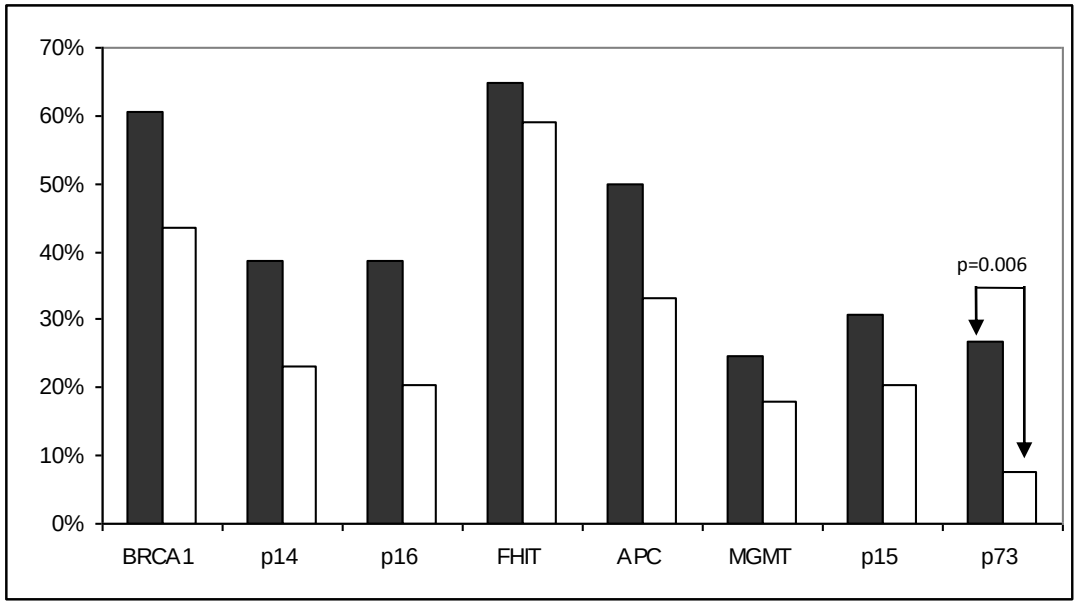


FONDECYT 1030130

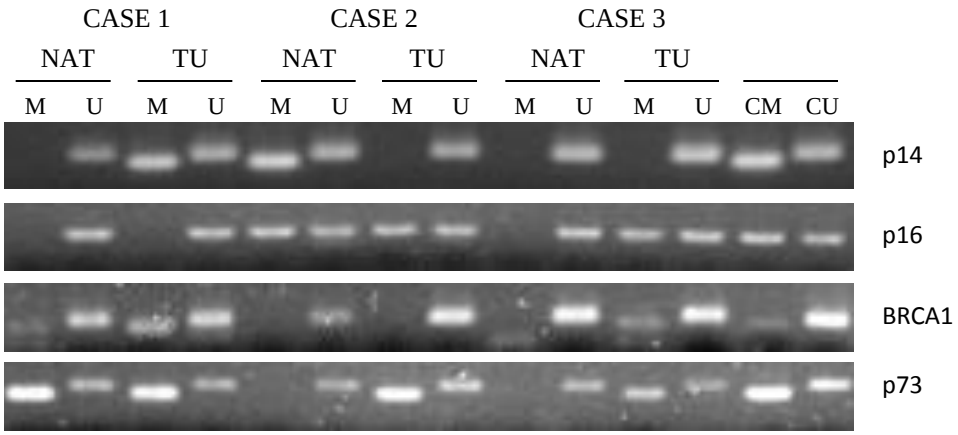
PATRON DE METILACIÓN DE GENES SUPRESORES DE TUMORES EN LA PATOGÉNESIS DEL CANCER GÁSTRICO DIFUSO

Fig.4

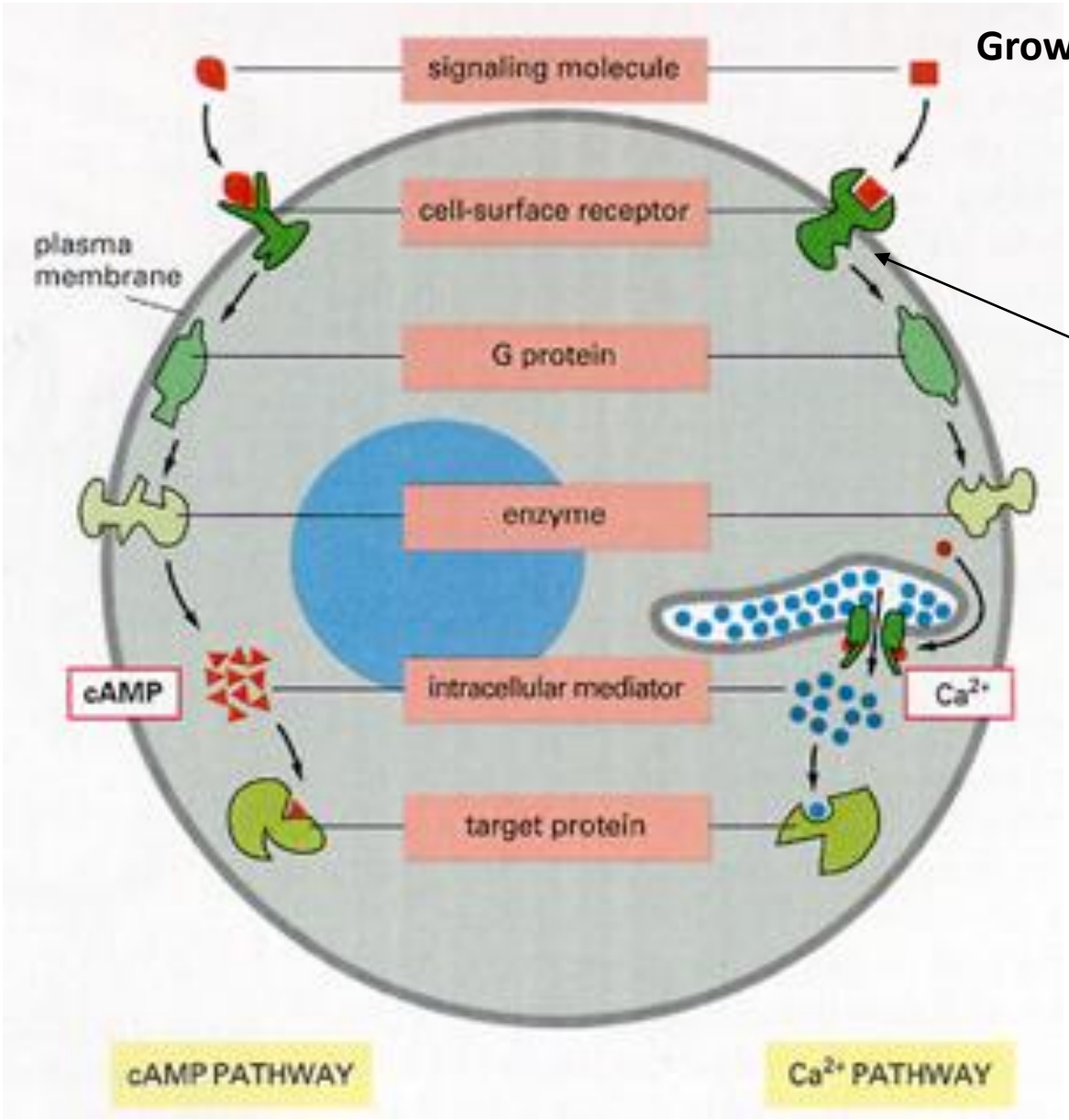
A


70%
60%
50%
40%
30%
20%
10%
0%
p=0.006
BRCA1
p14
p16
FHIT
APC
MGMT
p15
p73

B


CASE 1
CASE 2
CASE 3
NAT
TU
NAT
TU
NAT
TU
M U M U M U M U M U M U CM CU
p14
p16
BRCA1
p73

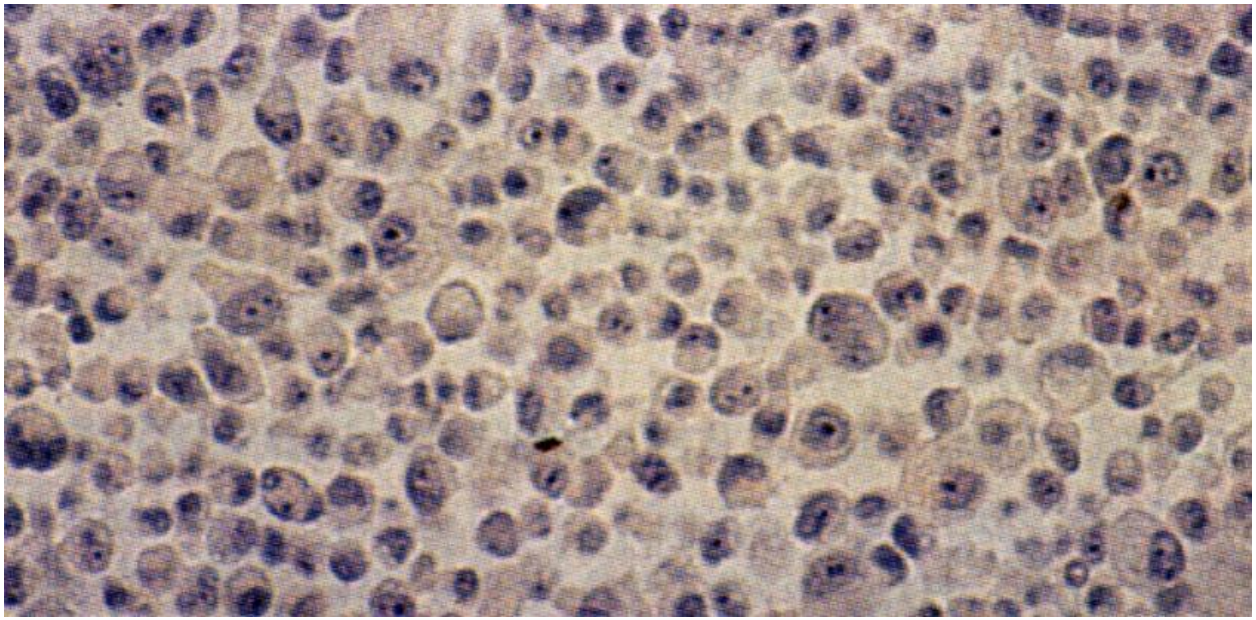
c-erbB2 oncogene



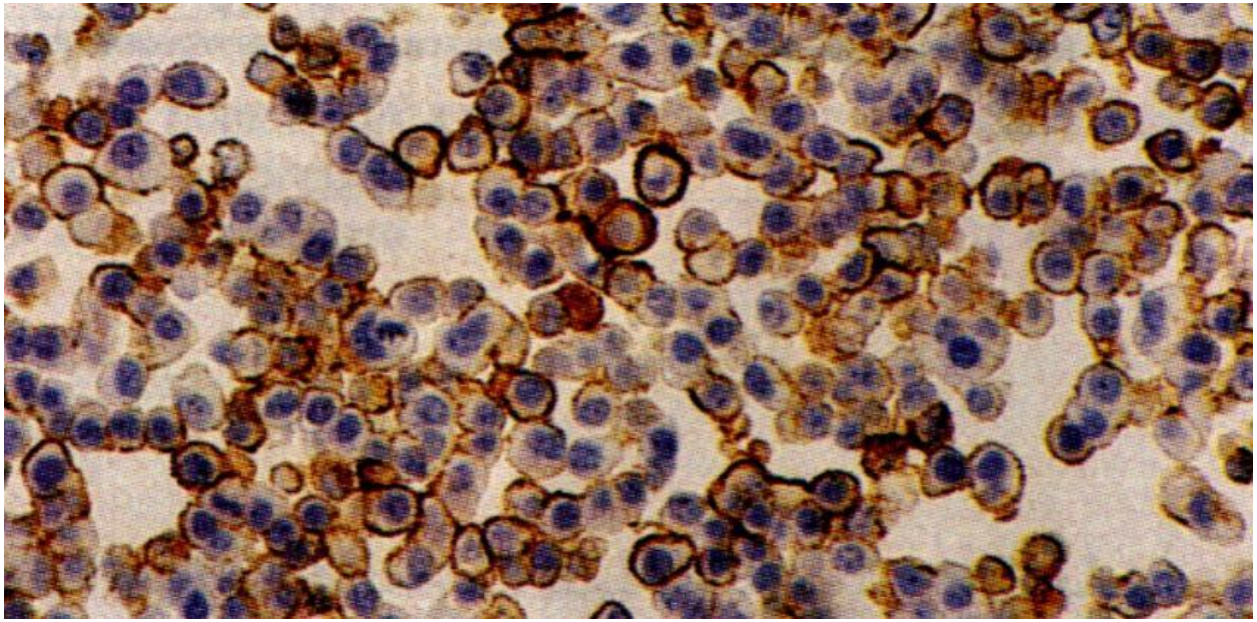
Growth factor

Receptor growth factor

Amplification of c-erbB2 oncogene detected by immunohistochemistry

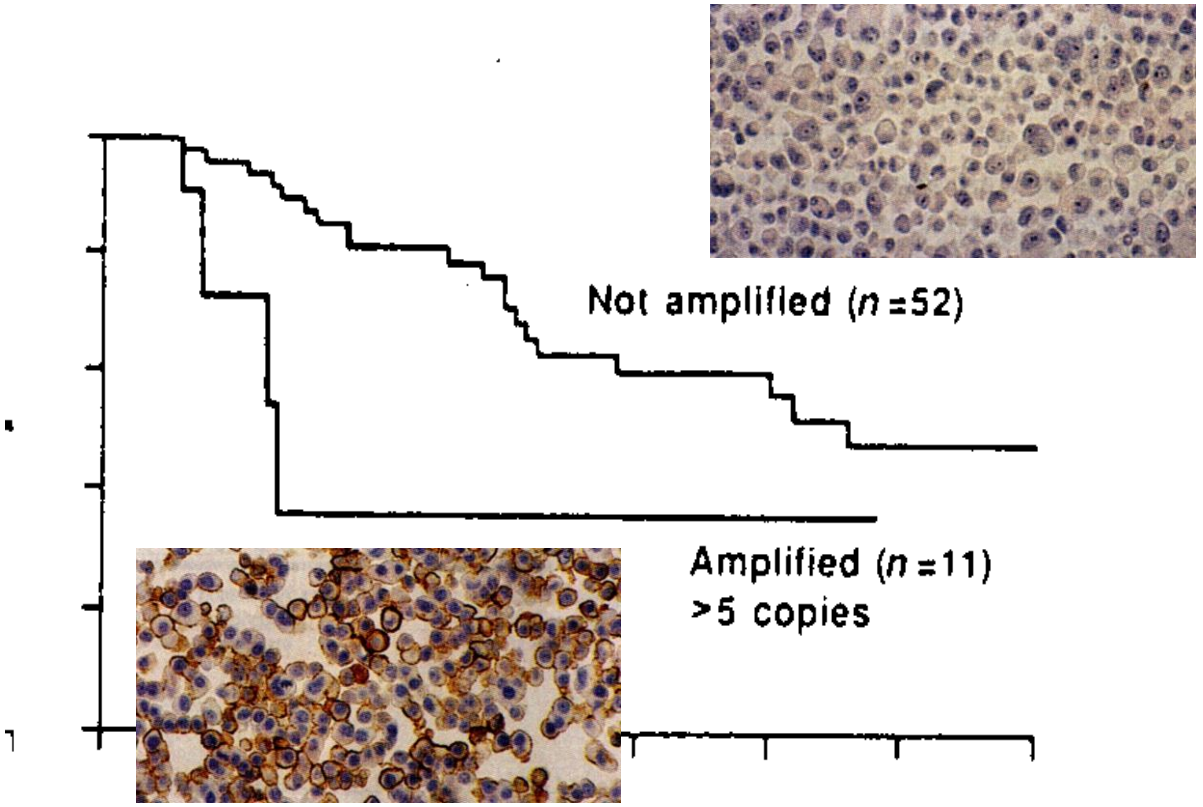


No amplification
c-erbB2



Amplification
c-erbB2

c-erbB2 oncogene amplification & tumor progression in breast carcinoma

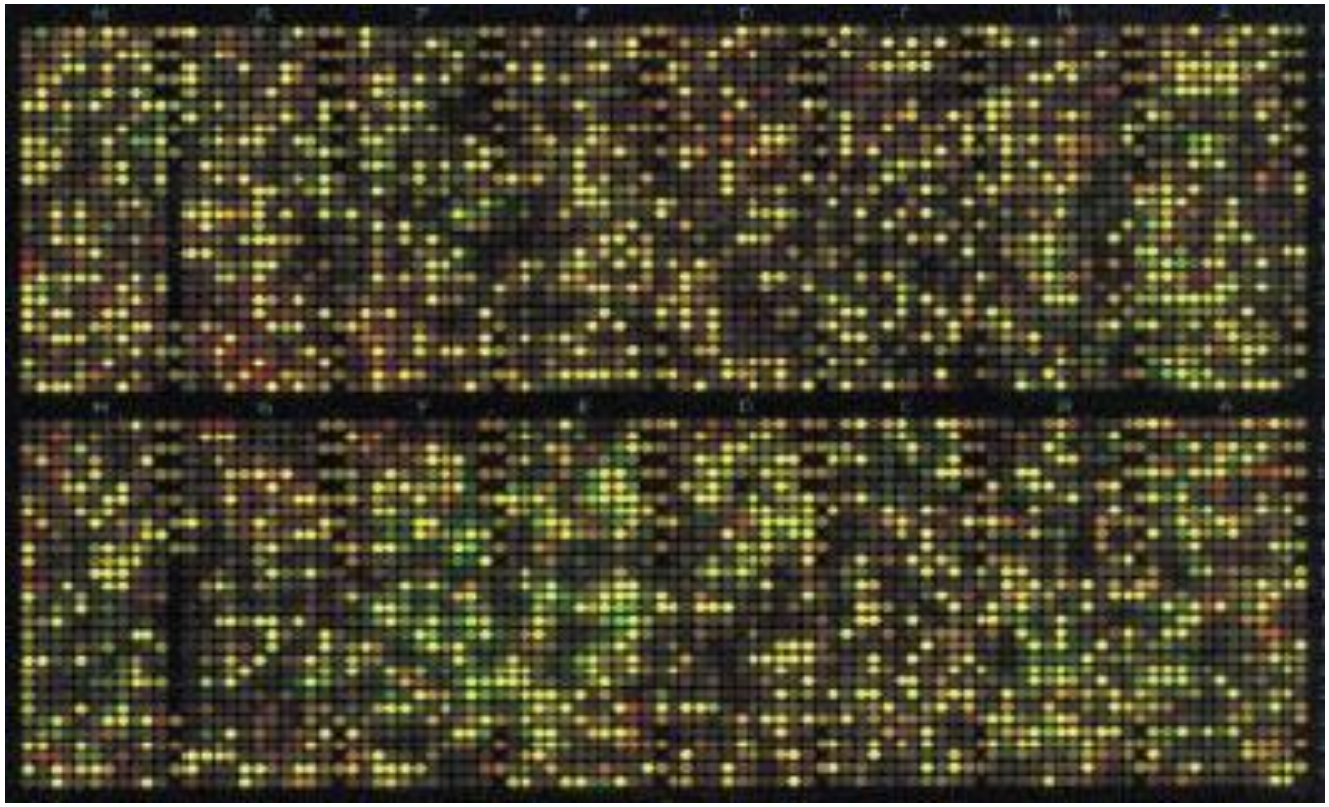


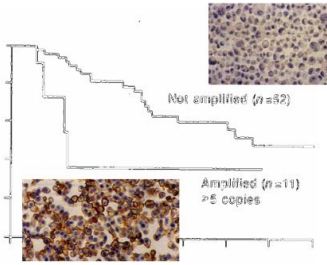
Slamon *et al.*,
Science 1987;235:177-82

Differential gene expression patterns in HER2/neu-positive and -negative breast cancer cell lines and tissues.

HER2/neu-positive

HER2/neu-negative

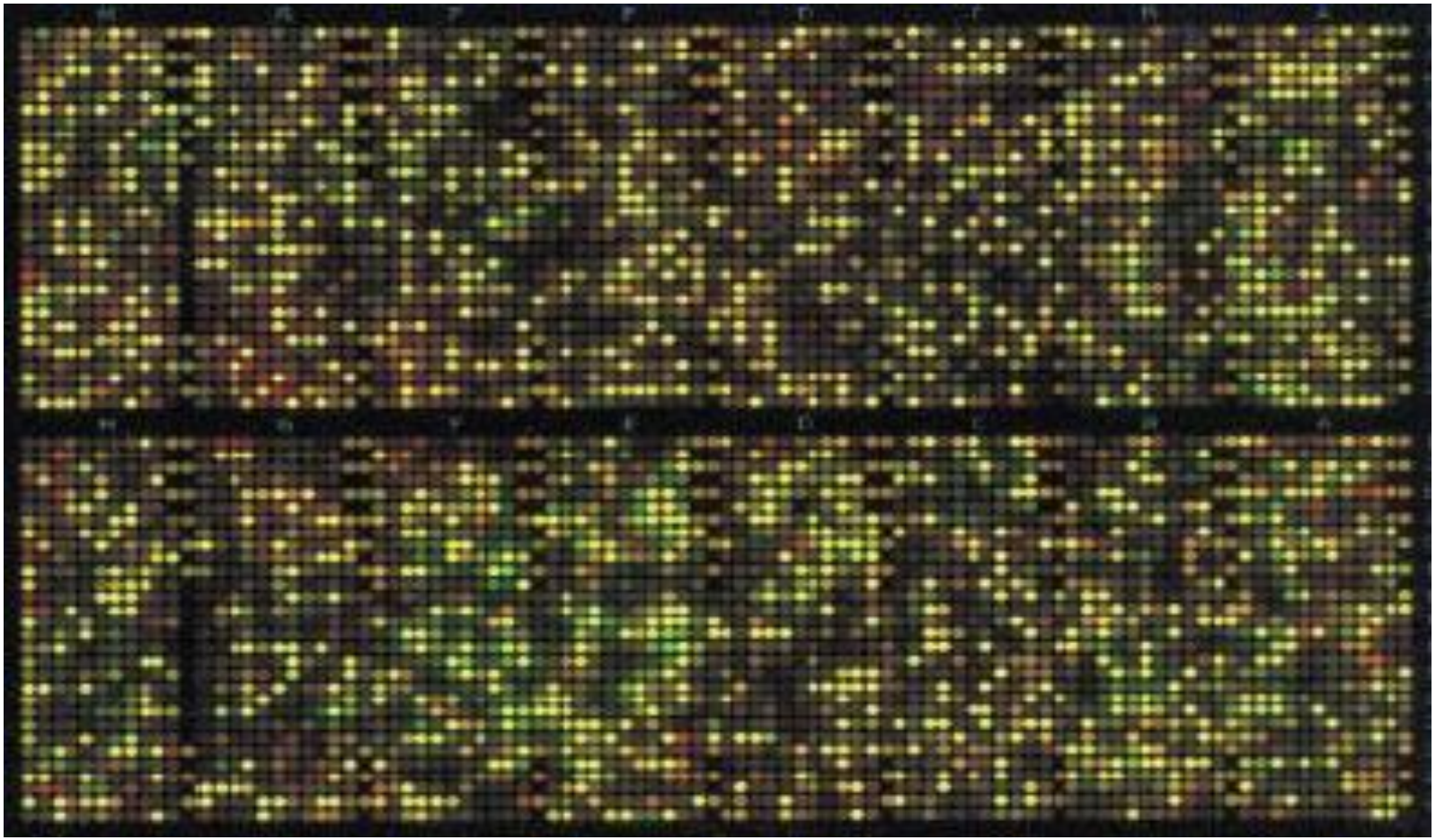




Green spots genes expressed in HER2/neu-negative breast cancers.
Red spots genes expressed in HER2/neu-positive breast cancers.
Yellow spots genes expressed at similar levels in both breast cancers types.

Wilson *et al.,* (2002) Am J Pathol. 161:1171-85

Differential gene expression patterns in
HER2/neu-positive and -negative breast cancer cell lines and tissues.



HER2/neu positive breast carcinomas - 5184 genes
40 genes (0.8%) up-regulated
219 genes (4.2%) down-regulated
259 genes (5%) total genes

Conclusiones

The most important cancer-related cell surface receptor types are signaling through G-protein-coupled cell-surface receptors (GPCRs) and enzyme-coupled receptors (TRK).

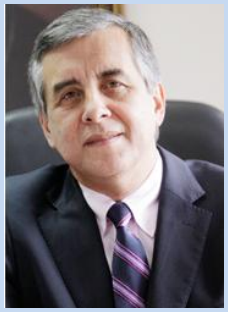
In both type of cell-surface receptors, the binding of the extracellular signal molecule activates five parallel intracellular signaling pathways (PKA, PKC, MAP kinase, Akt kinase and CaM kinase). These signaling activates gene transcription.

Other types of signaling pathways exists dependant on regulated proteolysis of latent gene regulatory proteins (Nothc, wnt/b-cateinin and TNFa/NFKbeta).

In human cancer multiple somatic mutations activates these pathways mainly causing disruption of negative-feedback mechanisms.

Advanced Center for Chronic Diseases

BASIC CORE



Sergio Lavandero
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Marcelo Kogan
PI
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EPIDEMIOL CORE

Catterina Ferréccio
Deputy Director
Epidemiology-Cancer

CLINICAL CORE

Alejandro Corvalan
PI
Cancer

Pablo Castro
PI
Cardiovasc Dis

+ 14 Associated Investigators (AIs)

♀ 40% ♂ 60%

Average age 48 yrs

25% foreigners

= 20

12	38	5	9	10	13	= 87
Postdocs	PhDs	MSc	Undergraduate students	Professionals	Technicians	

Previous collaborative interactions:

***Grants*: AQ-SL (FONDAP CEMC, Ring), CF-AC (FONDEF grant), SL-PC (FONDECYTs), etc.**

***Papers:* High level productivity (last 5 years): 215 papers in peer-reviewed journals, 23 joint papers between two groups. 47 in 10% top journals, average impact factor: 4.5.**