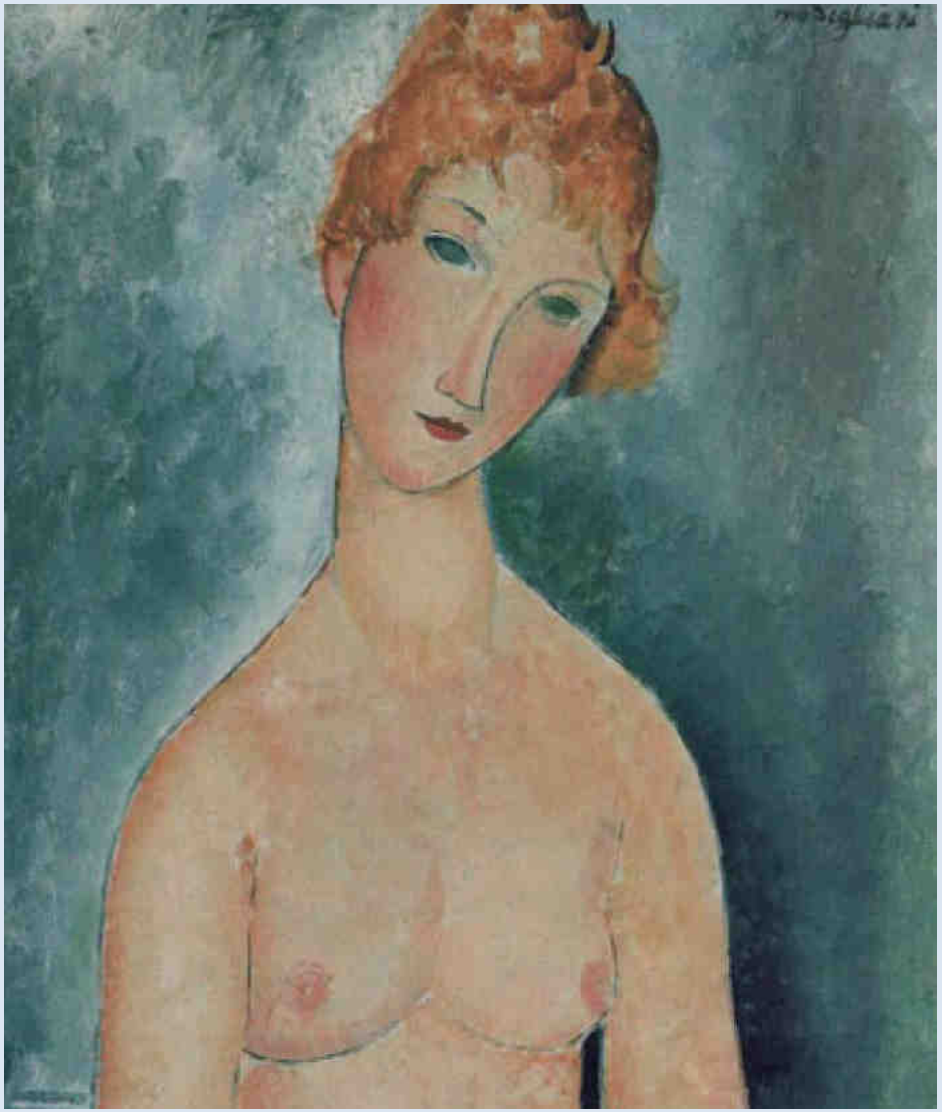


Hacia la personalización en el tratamiento del cáncer de mama

¿Qué aportan los biomarcadores en la actualidad?

Segunda Parte

Federico Rojo

XVI Jornada sobre el Cáncer de Mama:
Personalización en el Cáncer de Mama
Barcelona, 22 Febrero 2013

Proliferation (Ki67) and prognosis in breast cancer

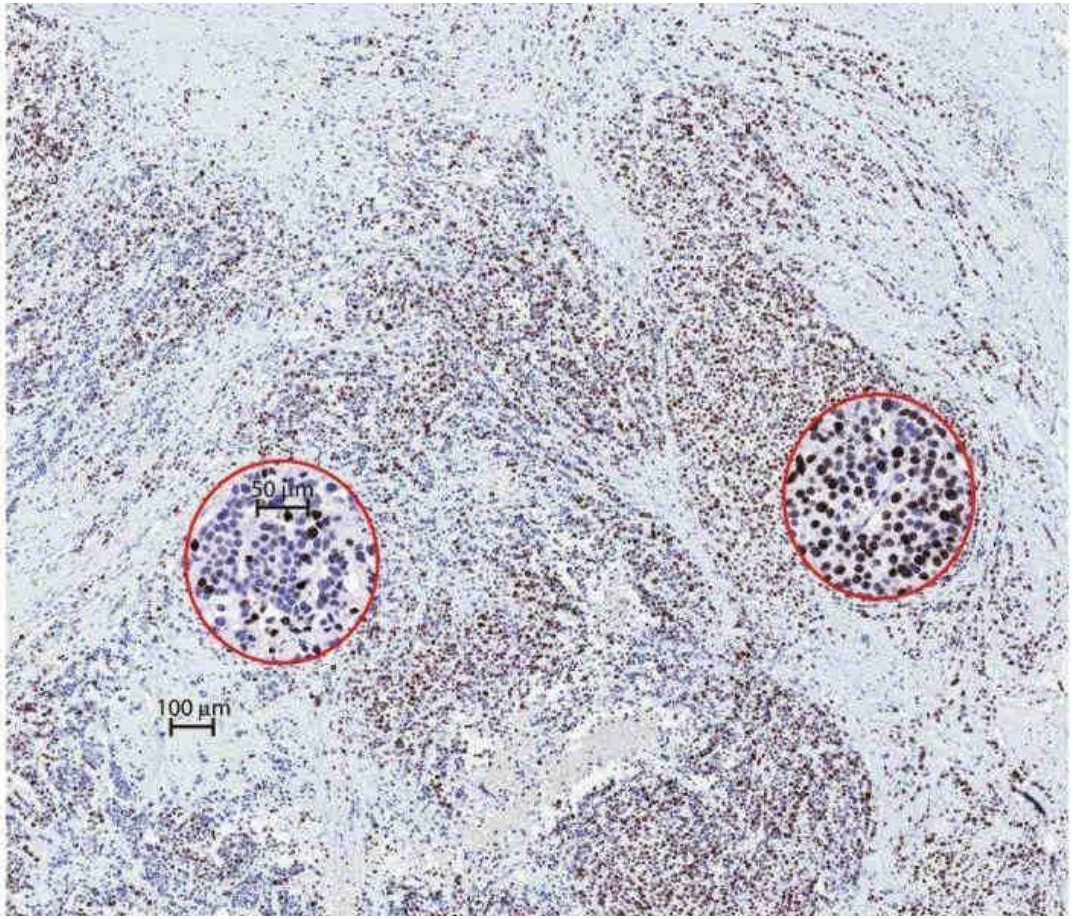
A limited prognostic use

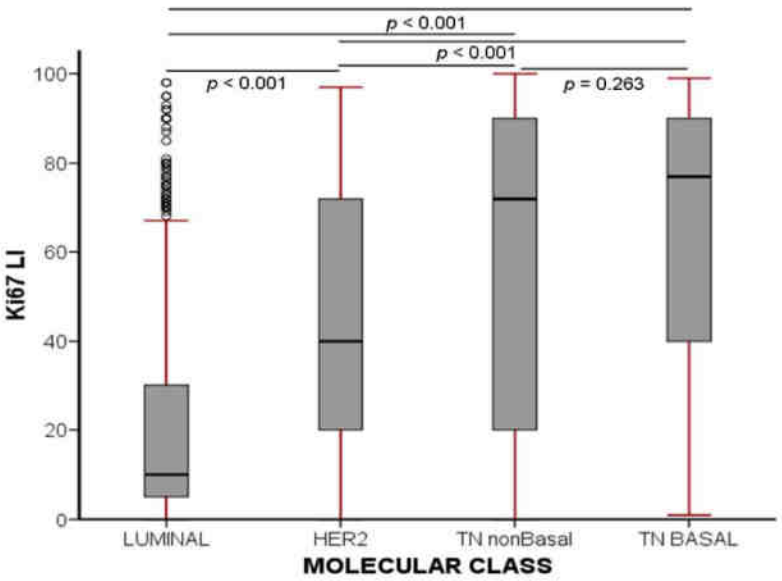
Table 1. Correlation Between Baseline Ki-67 and Prognosis

Author	No. of Patients	Follow-Up (years)	Ab	C-O %	Node Negative				Node Positive				Mixed Node Status			
					DFS		OS		DFS		OS		DFS		OS	
					Univ	Mutiv	Univ	Multiv	Univ	Multiv	Univ	Multiv	Univ	Multiv	Univ	Multiv
Liu[46]	791/16.3	16.3	Mib-1	17.8									P	N	P	N
Seshadri[57]	740	5.5	Mib-1	10	P	N	P	P	P	P	P	P				
Billgren[58]	732	5.7	Ki/Mib	15	P	P			P	P			P	P		
Brown[17]	674	5	Ki-67	5	P	P	N									
Joensuu[59]	496	9.5	MM-1	20	P											
Haerslev[34]	487	10	Mib-1	1			P	N			P	N			P	N
Thor[26]	486	5.2	Mib-1	28.6	P	N	P	P	N	N	P	N	P	N	P	P
Iacopetta[60]	422	6.1	Mib-1	10	N	N	N	N								
Rudolph[61]	356	8.2	Ki-S5	25	P	P	P	P								
Molino[52]	322	5.0	Ki-67	Any > 5									P	P	P	P
Rudolph[62]	273	8.2	Ki-S5	25	P	P	P	P								
Rudolph[63]	261	8.0	Ki-65	15	P	P	P	P								
Railo[18]	212	8.3	Ki-67	10	P	P										
Weikel[54]	568	< 2.0	Ki-67	10 and 20	N		N		P		N		P		P	
Weikel[64]	549	3.4	Ki-67	10 and 20	N		N		P		P		P		P	
Trihia[28]	434	NR	Mib-1	9.5				P				P				
Clahsen[27]	441	3.4	Mib-1	20	P	P										
Gaglia[65]	353	2.5	Ki-67	9	P	P			N				P	P		

Urruticoechea, A. et al. J Clin Oncol 2005

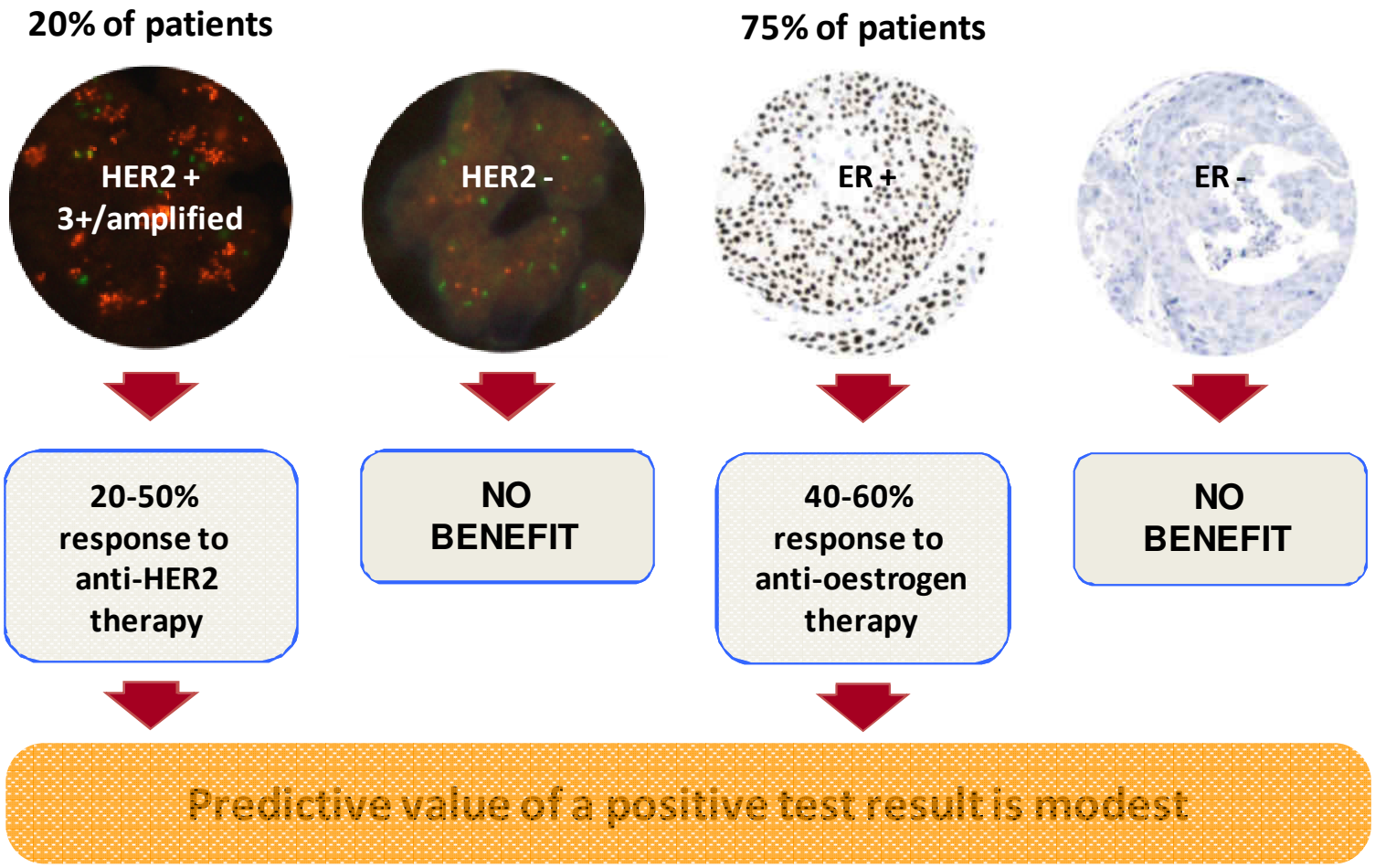
Proliferation in breast cancer: Strong evidence for prognostication?





Aleskandarany, MA. Breast Cancer Res 2012

Importance of biomarker assays in breast cancer: Current molecular assays to select patients for targeted therapies



Resistance mechanisms to endocrine therapy in breast cancer: emerging efficacy biomarkers

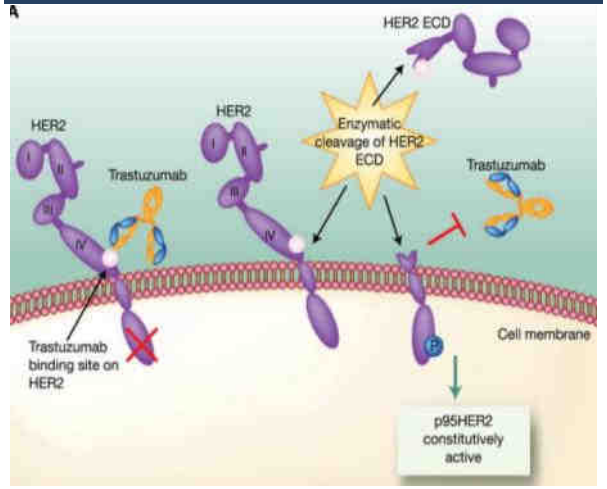
Table 2 | Biomarkers for resistance to adjuvant endocrine therapy in women with ERα-positive breast cancer

Marker*	Menopausal status	LOE‡	Agent-specific resistance
Nuclear receptors			
Low ERα phosphorylation at Ser118[25]	Premenopausal	II-B(+)	Unknown
Low expression of PR (<75% tumour cells PR-positive)[45]	Premenopausal	II-B(+)§	Unknown
Low ERα protein expression[18‖]	Premenopausal Postmenopausal	I-B(+) I-B(+)	Unknown Broad¶#
Low *ESR1* mRNA[21]	Postmenopausal	II-B(+)	Broad¶#
ERα modifications			
ERα phosphorylation at Ser305[36]	Premenopausal	II-B(+)**	Specific for tamoxifen resistance‡‡
PAK-1 expression and/or phosphorylation of ERα at Ser305 and PKA[37]	Premenopausal	II-B(+)	Specific for tamoxifen resistance‡‡
ERα phosphorylation at Ser305 and expression of PAK-1[38]	Postmenopausal	II-B(+)§	Specific for tamoxifen resistance‡‡
Variation in cofactor expression			
Low SRC-3 expression[50]	Premenopausal	II-B(+)	Unknown
High SRC-3 expression[49]	Postmenopausal	II-B(+)§	Unknown
Additional activated growth factor pathways			
High EGFR expression[56]	Premenopausal	II-B(+)	Unknown
Nuclear PAK-1 expression[88]	Premenopausal	II-B(+)	Unknown
HER2 protein overexpression[59]	Postmenopausal	II-B(+)**	Broad¶#‡‡
PAK1 amplification[87]	Postmenopausal	II-B(+)	Unknown
PIK3CA mutations with Akt activation[73§§]	Postmenopausal	II-B(+)**	Broad¶#‡‡
Cell cycle regulation			
CCND1 amplification[90]	Premenopausal	II-B(+)	Unknown
Low $p27^{Kip1}$ expression[95]	Premenopausal	II-B(+)§	Unknown
High *HOXB13* expression[103]	Postmenopausal	II-B(+)	Unknown
Oestrogen and drug metabolism			
Low endoxifen levels[112]	Premenopausal Postmenopausal	III-C(+)‖‖ III-C(+)‖‖	Specific for tamoxifen resistance Specific for tamoxifen resistance
High 17β-HSD 1 expression[113]	Premenopausal	II-B(+)§	Unknown
High 17β-HSD 1 to 17β-HSD 2 ratio[114]	Postmenopausal	II-B(+)§	Unknown

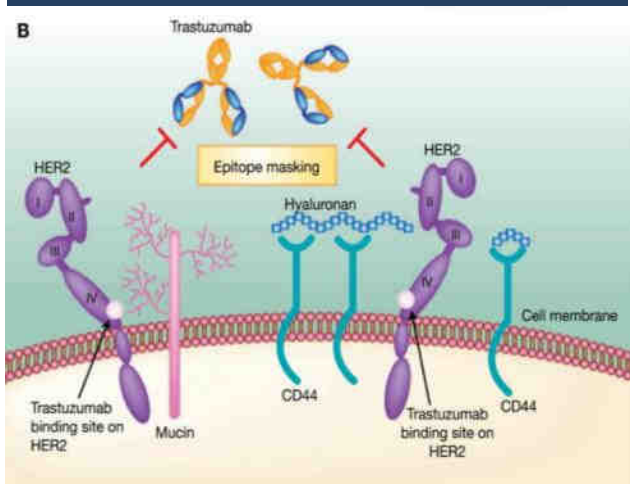
Beelen, K. et al. Nat. Rev. Clin. Oncol. 2012

Resistance mechanisms to anti-HER2 therapy in breast cancer

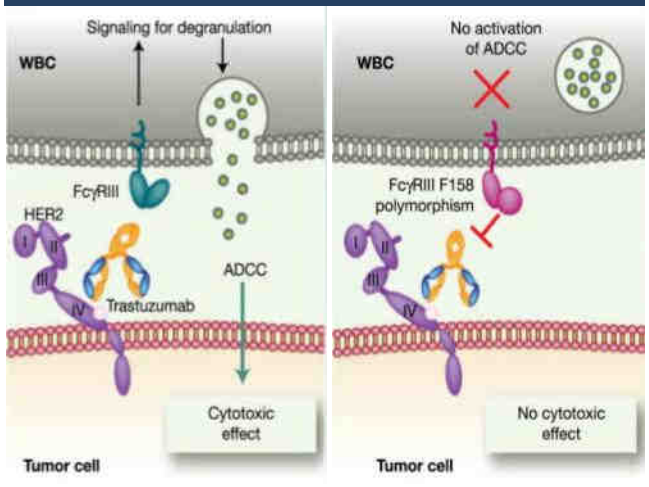
Constitutively active truncated HER2



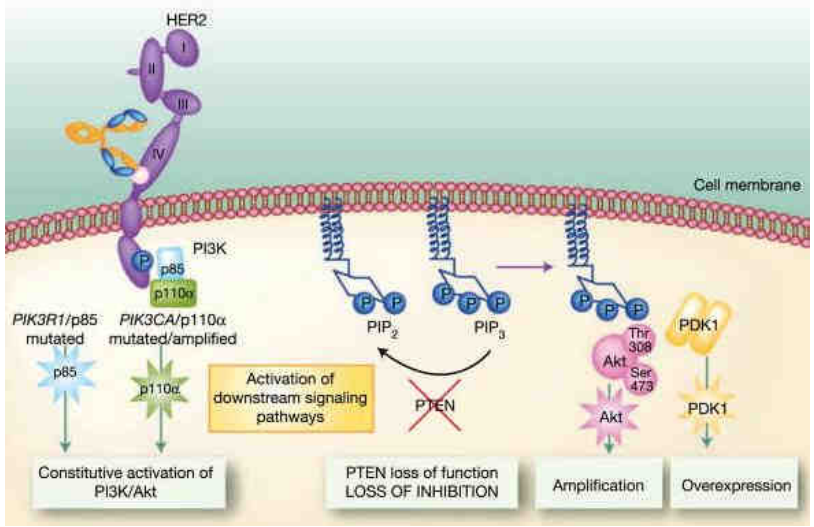
Epitope masking by MUC4 or CD44/ polymeric hyaluronan complex



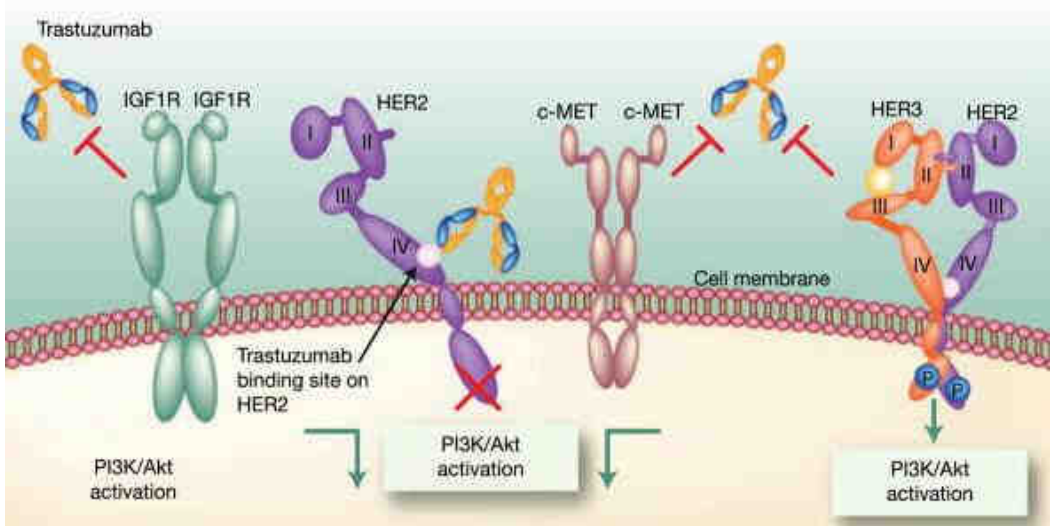
Failure to trigger immune-mediated mechanisms



Upregulation of HER2 downstream signaling pathways



Signaling through an alternate receptor and/or pathway



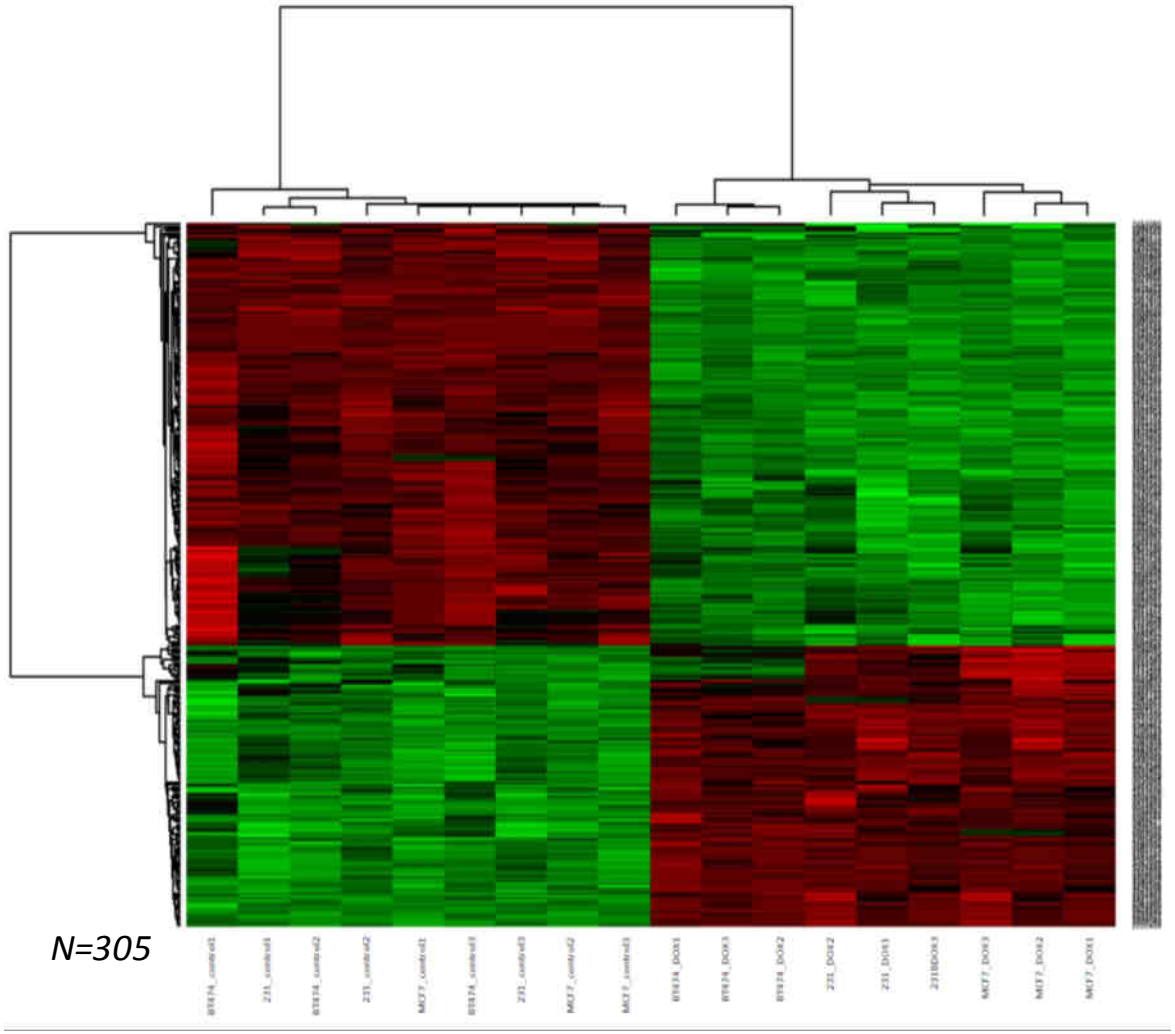
Resistance mechanisms to anti-HER2 therapy in breast cancer: emerging efficacy biomarkers

Mechanism of resistance	Level of evidence	Role in intrinsec resistance	Role in acquired resistance	Frequency in HER2 breast cancer
p95HER2	IIB	Yes	Unknown	~25%
PI3K pathway				
PTEN loss	IIB	Yes	Unknown	~35%
PI3KCA mutations	IIB	Yes	Possible	~25%
AKT amplification	In vitro	Yes	Unknown	Unknown
PDK1 overexpression	In vitro	Yes	Unknown	Unknown
Alternative signaling				
HER3	III	Yes	Unknown	Unknown
IGF1R	III	Yes	Unknown	Unknown
EGFR	IIB	Yes	Yes	Unknown
MET	In vitro	Yes	Unknown	Unknown
VEGFR	In vitro	Yes	Unknown	Unknown
Epitope masking				
MUC4	III	Yes	Unknown	Unknown
HSP90	In vitro	Yes	Unknown	Unknown
CD44	In vitro	Yes	Unknown	Unknown
Immune mechanisms	In vitro	Yes	Unknown	Unknown

New approaches in the therapy of patients with HER2 breast cancer

Strategies and drugs	Stage of development	Reference or ClinicalTrials.gov identifier
Optimization of trastuzumab antibody structure		
Ertumaxomab (trifunctional, bispecific mAb targeting HER2 and CD3)	Phase II (terminated)	Kiew *et al.* (2008),[79] Jäger *et al.* (2009),[80] Kiewe *et al.* (2006)[81]
Conjugation of HER2-targeted agents with toxins		
Trastuzumab–DM1 (trastuzumab conjugated to the maytansine derivative DM1)	Phase III	Krop *et al.* (2009)[160]
Targeting HER1		
Pelitinib (irreversible HER1 TKI)	Phase I–II (suspended)	Ocaña *et al.* (2009)[107]
Targeting HER3		
MM-121 (HER3-targeted mAb)	Phase I–II	Schoeberl *et al.* (2010),[161] NCT01097460, NCT00911898
MM-111 (HER2/HER3 bispecific antibody)	Phase I–II	Huhalov *et al.* (2010),[162] NCT00911898, NCT01097460
Targeting HER2		
Pertuzumab (mAb, HER2 dimerization inhibitor)	Phase III	Baselga *et al.* (2010)[93]
Broad-spectrum TKIs		
Neratinib (irreversible HER1/HER2 TKI)	Phase III‡	Burstein *et al.* (2010)[108]
BIBW-2992 (irreversible HER1/HER2 TKI)	Phase II	Hickish *et al.* (2009)[163]
Inhibition of PI3K (class I)		
XL147 (pan-PI3K inhibitor [all class I isoforms])	Phase I–II	Shapiro *et al.* (2009),[115] NCT01042925, NCT01082068
BGT226 (p110α-selective PI3K inhibitor)	Phase I–II	NCT00600275, NCT00742105
Inhibition of mTOR		
Everolimus	Phase III	Ellard *et al.* (2009),[129] Baselga *et al.* (2009),[164]
Inhibition of IGF-1R pathway		
Figitumumab (mAb against IGF-1R)	Phase II	Gualberto (2010),[165] NCT00635245
Cixutumumab (mAb against IGF-1R)	Phase II	McKian & Haluska (2009),[166] NCT00699491, NCT00728949
AVE1642 (mAb against IGF-1R)	Phase II (terminated, company decision)	NCT0074878
Dalotuzumab (mAb against IGF-1R)	Phase I–II (completed)	NCT00759785
AMG479 (mAb targeting IGF-1R)	Phase II	NCT00626106
OSI-906 (IGF-1R inhibitor)	Phase I–II	NCT01013506
Inhibition of HSP90		
Alvespimycin	Phase I–II (phase II in HER2+ BC completed)	Miller *et al.* (2007)[137]
Retaspimycin	Phase II	Hanson *et al.* (2009),[138] NCT00817362
BIIB021	Phase I–II	Lundgren *et al.* (2009),[140] NCT00412412
AUY922	Phase I–II	NCT00526045
Vaccines and immunotherapy		
E75 (peptide vaccine based on extracellular domain of HER2)	Phase II	Peoples *et al.* (2008),[167] Mittendorf *et al.* (2008),[168] Patil *et al.* (2010),[169] Holmes *et al.* (2008)[170]
GP2 (peptide vaccine based on transmembrane domain of HER2)	Phase II	Carmichael *et al.* (2010)[171]
AE37 (II-key hybrid HER2 peptide vaccine)	Phase II	Holmes *et al.* (2008)[172]
HER2 intracellular-domain peptide vaccine	Phase I–II	NCT00343109, NCT00791037, NCT00363012
HER2 protein AUTOVAC (PX104.1.6)	Phase I–II (discontinued)	NCT00068614
dHER2 (a modified HER2 protein) with AS15 adjuvant	Phase I–II	NCT00058526, NCT00952692
Allogeneic GM-CSF-secreting whole-cell breast-cancer vaccine	Phase II	NCT00399529, NCT00095862, NCT00847171, NCT00971737, NCT00397371
Autologous dendritic-cell vaccines (dendritic cells are loaded with HER2 peptides or genetically manipulated to express HER2)	Phase I–II	Morse *et al.* (2007),[173] NCT00266110, NCT00228358
PG13-4D5-D12 (anti-HER2 CAR; autologous peripheral blood lymphocytes transduced with a retroviral vector)	Phase I–II	NCT00924287
Multitarget kinase and angiogenesis inhibitors		
Bevacizumab (mAb against VEGF-A)	Phase III§	Pegram *et al.* (2006)[144]
Pazopanib (inhibitor of VEGFR, PDGFR and c-kit; inhibits cross-talk between HER2 and VEGFR pathways)	Phase II	Slamon *et al.* (2008)[174]
Sunitinib (inhibitor of VEGFR, PDGFR, c-Kit, RET, FLT3, and CSF-1R)	Phase II§	Burstein *et al.* (2008)[175]

Efectos de la doxorubicina en cáncer de mama a nivel transcripcional



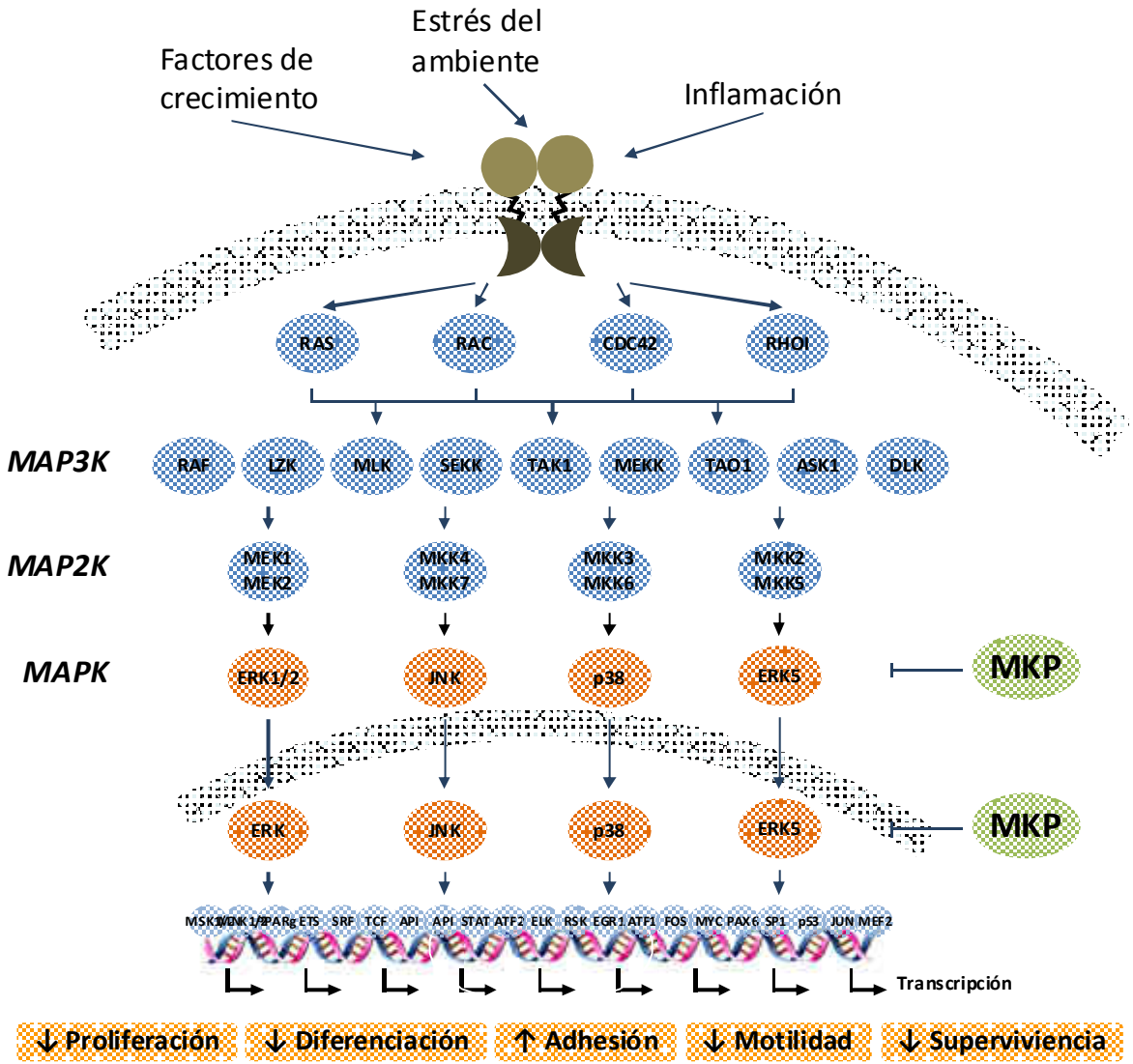
N=305

Doxorubicina 5uM (IC50), 24h

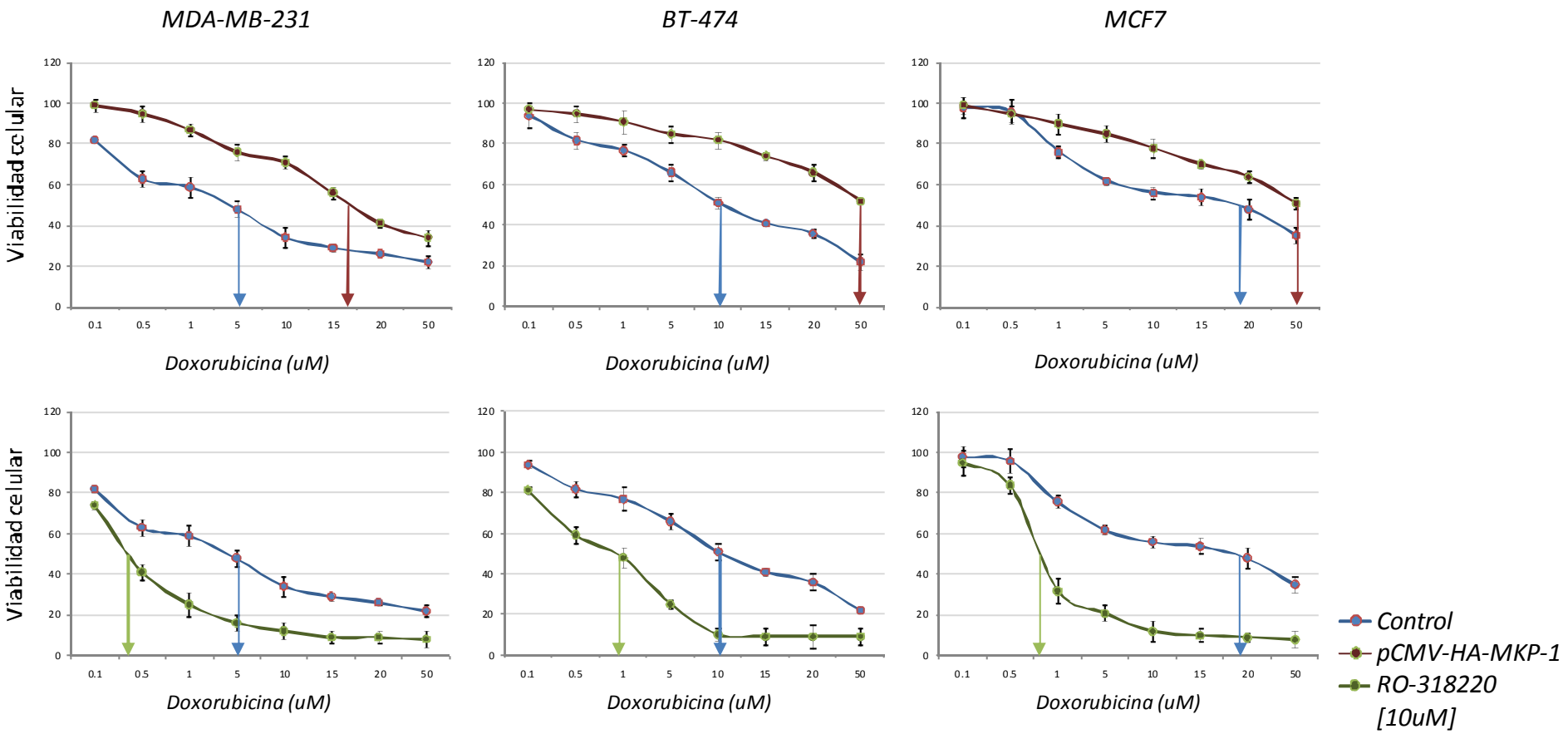
Affymetrix Human Genome U133 Array

Análisis de resultados mediante IPA

El control de la señalización mediada por las MAPK: Las MKP (DUSP)

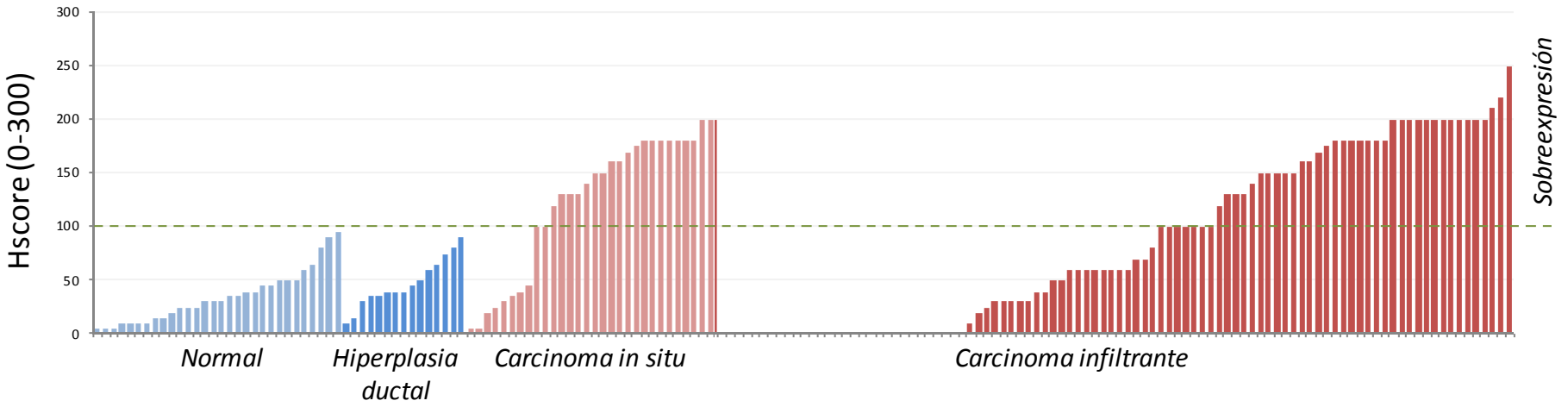


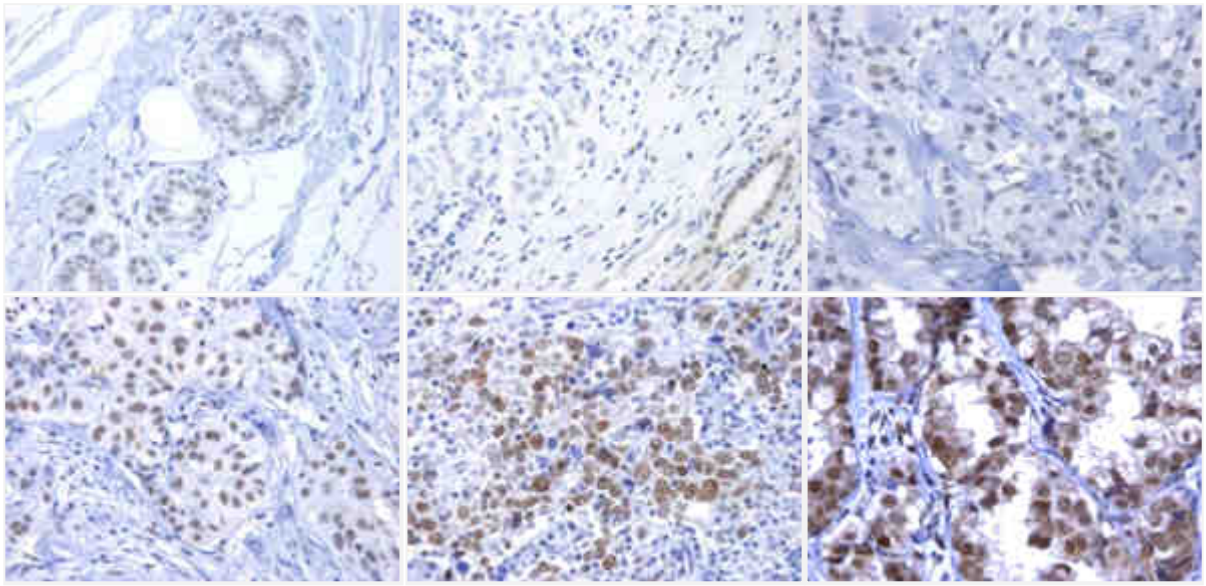
Resultados VIII:
Efectos de la modulación de MKP-1 sobre la sensibilidad a la doxorubicina

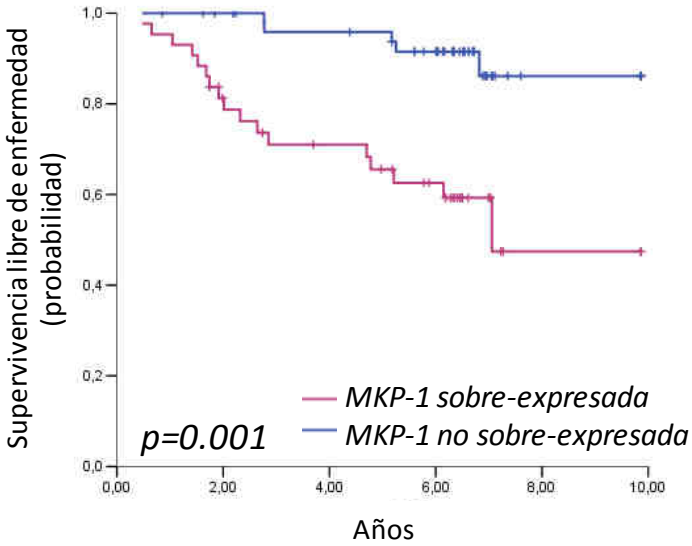


MTS, 48h

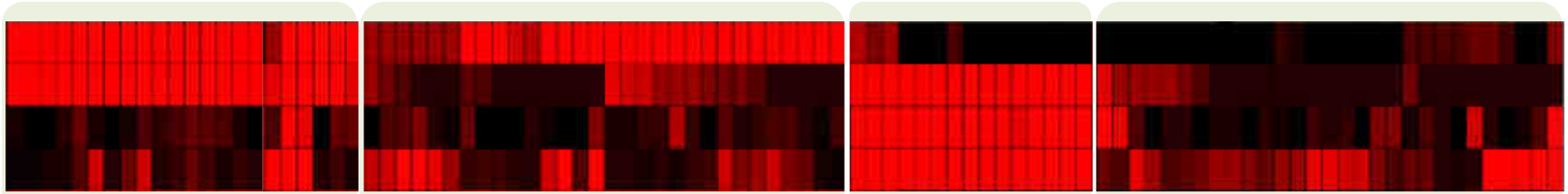
Expresión de MKP1 en parénquima mamario y carcinoma de mama







Asociación de MKP-1 y las MAPK en cáncer de mama

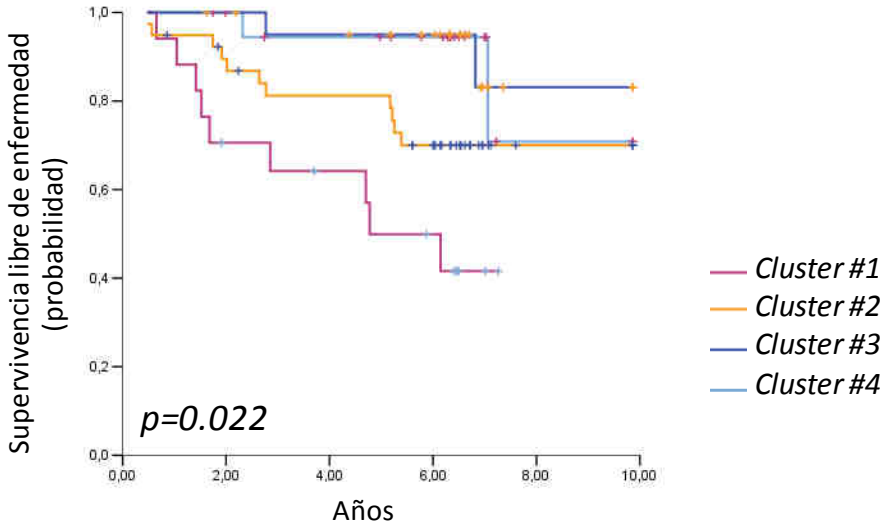


Cluster #1
↑ MKP-1
↑ p-ERK1/2
↓ p-JNK
↓ p-p38

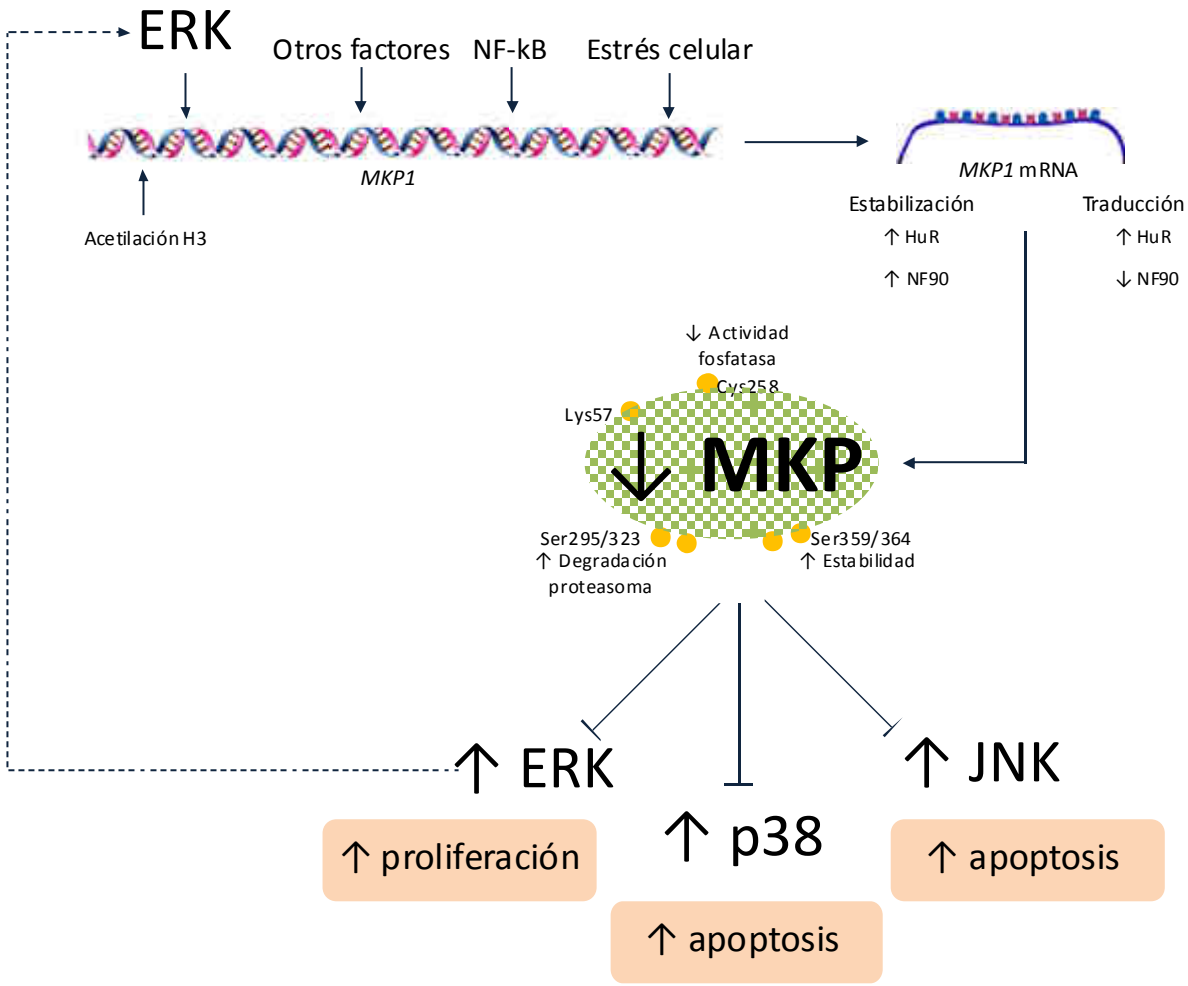
Cluster #2
↑ MKP-1
↓ p-ERK1/2
↓ p-JNK
↓ p-p38

Cluster #3
↓ MKP-1
↑ p-ERK1/2
↑ p-JNK
↑ p-p38

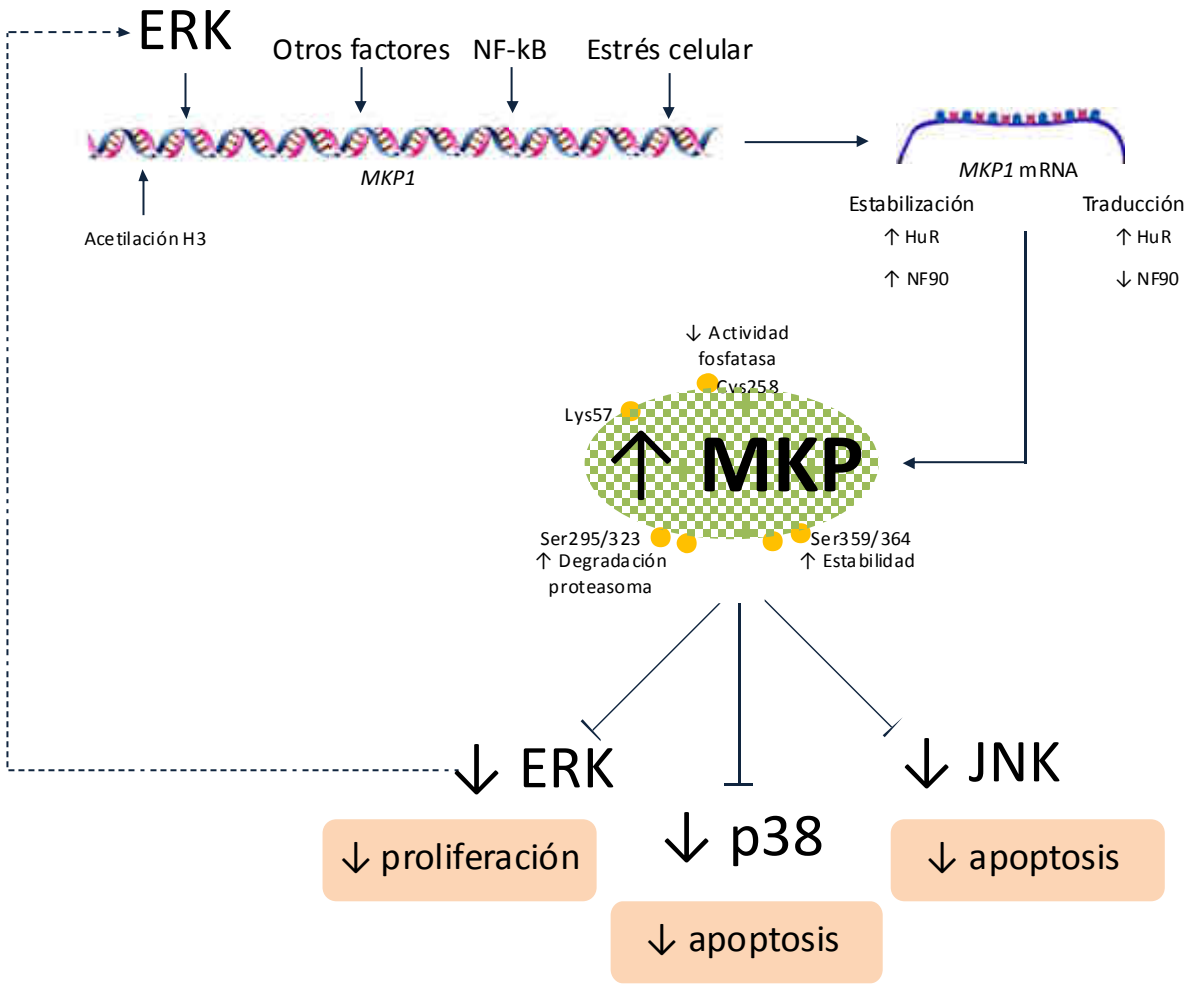
Cluster #4
↓ MKP-1
↓ p-ERK1/2
↓ p-JNK
↓ p-p38



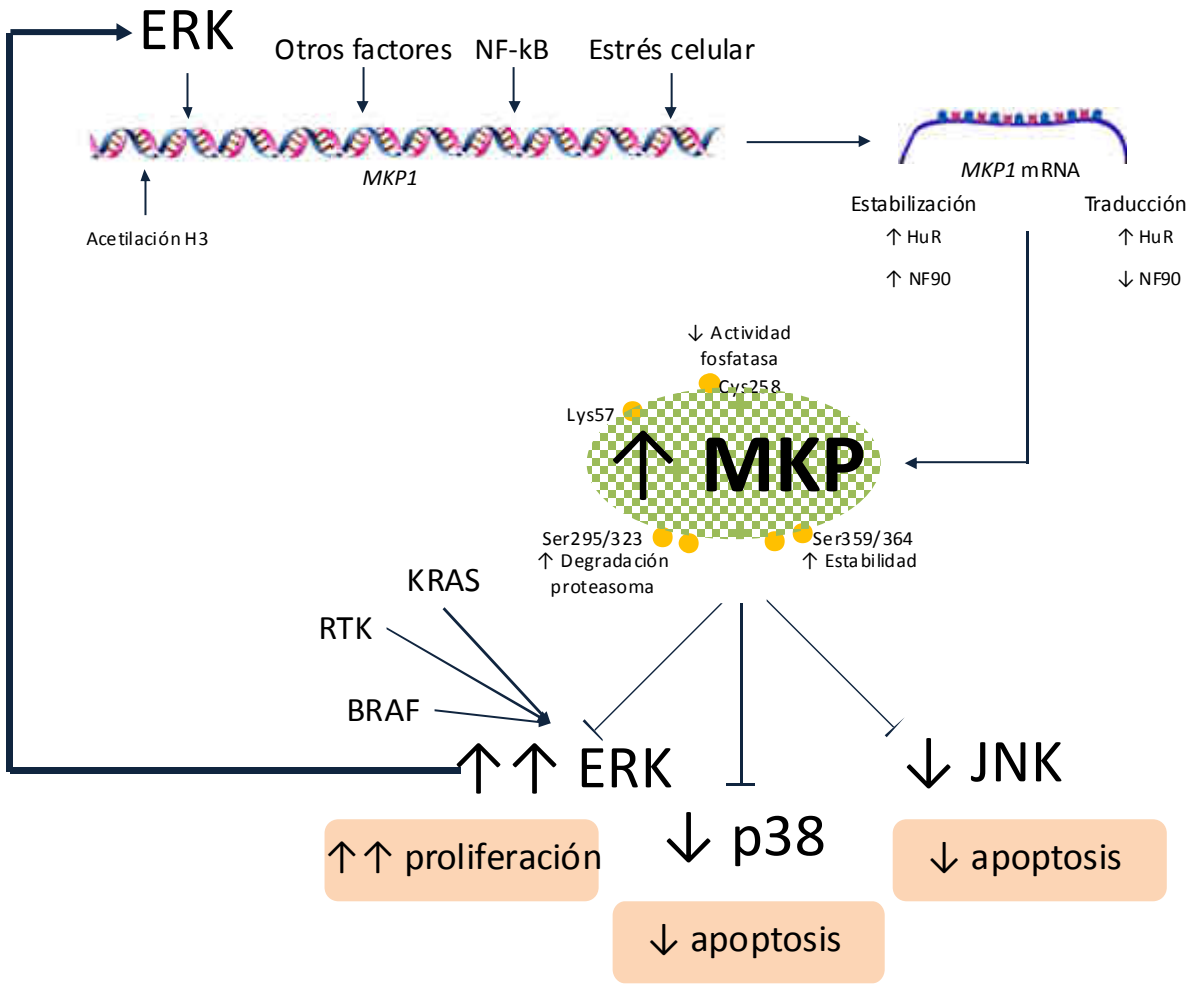
Regulación de MKP-1 y MAPK en cáncer de mama: efecto sobre quimiosensibilidad



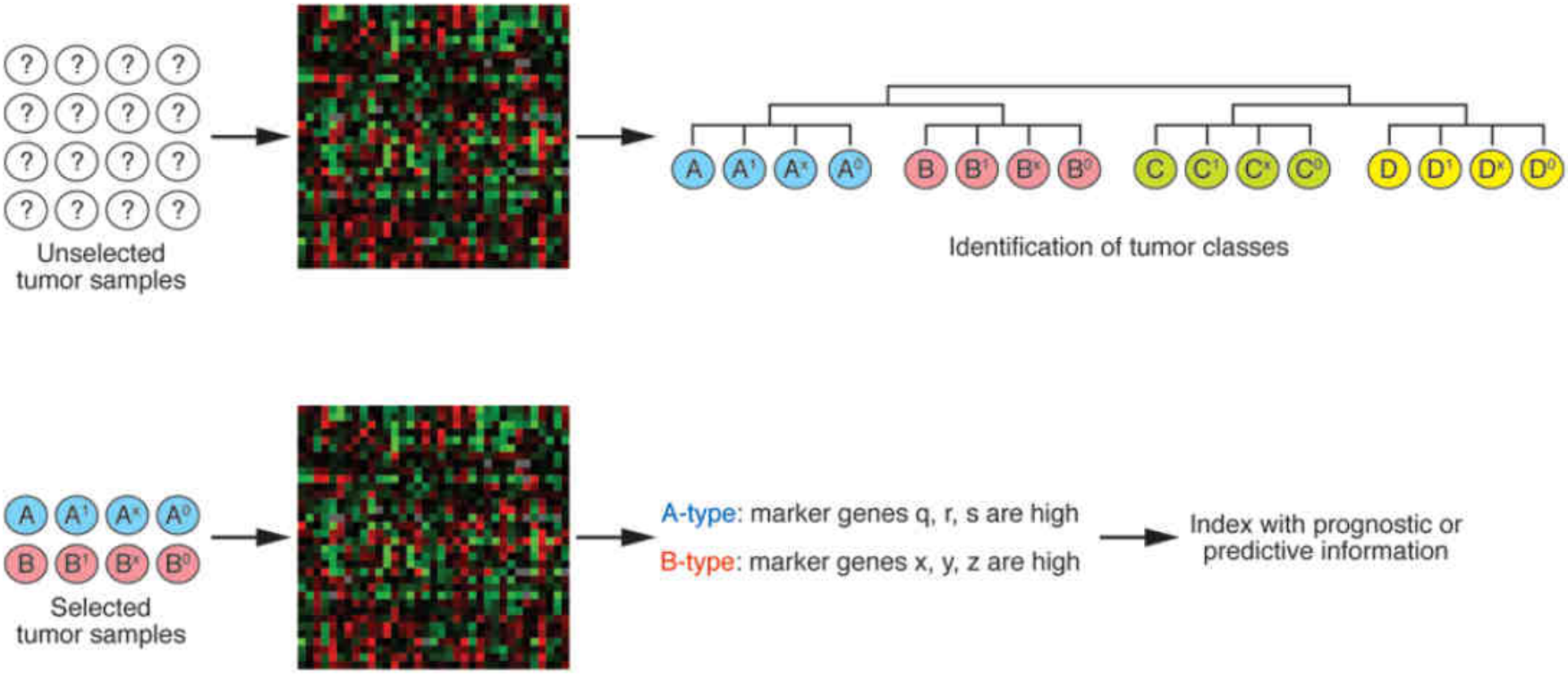
Regulación de MKP-1 y MAPK en cáncer de mama: efecto sobre quimiosensibilidad



Regulación de MKP-1 y MAPK en cáncer de mama: efecto sobre quimiosensibilidad



A new paradigm in breast cancer management
Massive target profiling

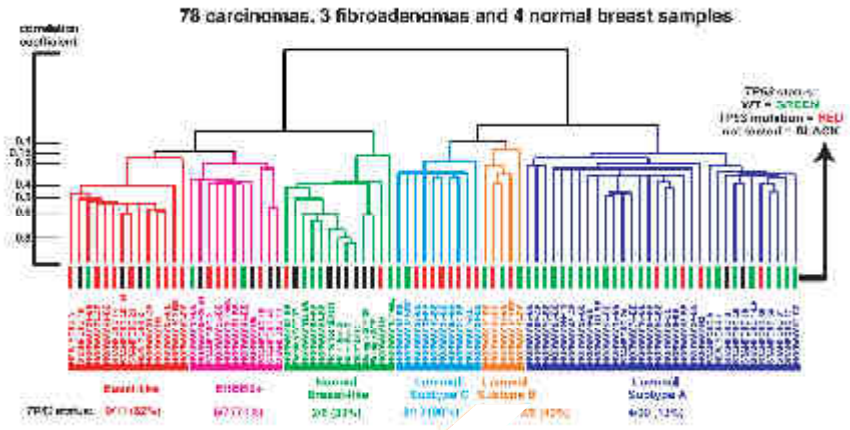


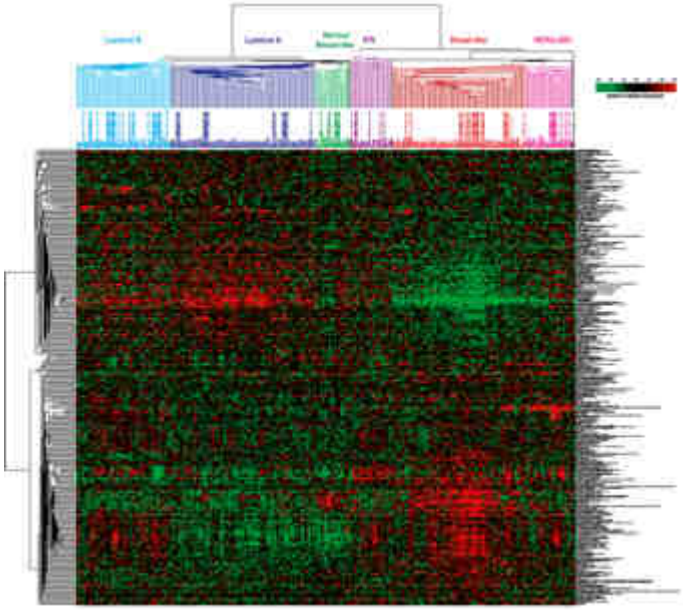
Molecular classification in breast cancer: The intrinsec subtypes

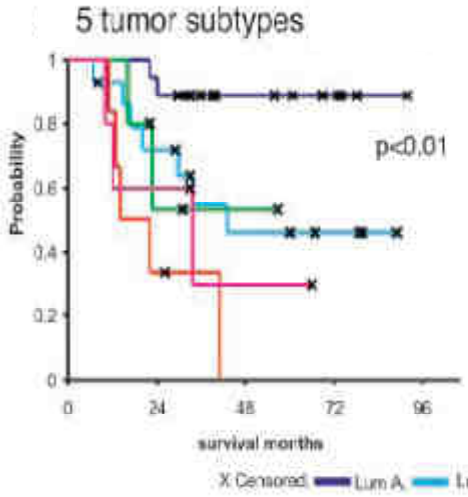
letters to nature

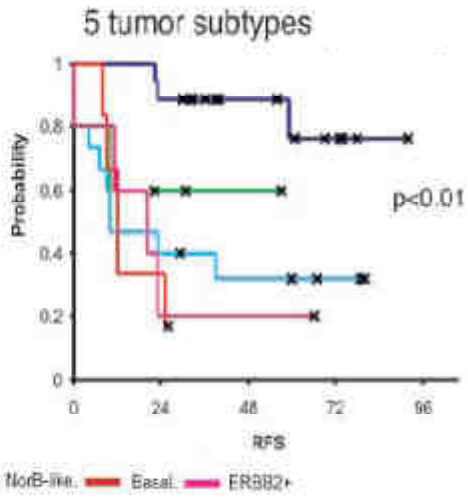
Molecular portraits of human breast tumours

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***









X Censored Lum A Lum B+C NorB-like Basal ERBB2+

Sorlie, T et al. PNAS, 2001
Perou, CM et al. Nature, 2000
Perreard, L et al. Breast Cancer Res, 2006

Clinico-pathological features of intrinsic subtypes

	IHC markers*	Histological grade*	Proliferation cluster	Other markers	Outcome*	Benefit from chemotherapy*
Luminal A	ER+: 91–100% PR+: 70–74% HER2+: 8–11% Ki67: low Basal markers: –	GI/II: 70–87% GIII: 13–30%	Low	*FOXA1* high	Good	Low (0–5% pCR)
Luminal B	ER+: 91–100% PR+: 41–53% HER2+: 15–24% Ki67: high Basal markers: –	GI/II: 38–59% GIII: 41–62%	High	*FGFR1* and *ZIC3* amp	Intermediate or poor‡	Intermediate (10–20% pCR)
Basal-like	ER+: 0–19% PR+: 6–13% HER2+: 9–13% Ki67: high Basal markers: +	GI/II: 7–12% GIII: 88–93%	High	*RB1*: low/– *CDKN2A*: high *BRCA1*: low/– *FGFR2*: amp	Poor	High (≥40% pCR)
HER2-enriched	ER+: 29–59% PR+: 25–30% HER2+: 66–71% Ki67: high Basal markers: –/+	GI/II: 11–45% GIII: 55–89%	High	*GRB7*: high	Poor	Intermediate (25–40% pCR)
Normal breast-like	ER+: 44–100% PR+: 22–63% HER2+: 0–13% Ki67: low/ intermediate Basal markers: –/+	GI/II: 37–80% GIII: 20–63%	Low/ intermediate	..	Intermediate	Low (0–5% pCR)
Claudin-low	ER+: 12–33% PR+: 22–23% HER2+: 6–22% Ki67: intermediate Basal markers: +/–	GI/II: 62–23% GIII: 38–77%	Intermediate/ high	*CDH1*: low/– Claudins: low/–§	Intermediate	Intermediate (25–40% pCR)
Molecular apocrine	ER– PR– HER2 +/– Ki67: high‡ Basal markers: –/+	Predominantly GII/GIII	High	Androgen receptor: +	Poor	Not examined

Reis-Filho, JS & Pusztai, L. Lancet 2011

Main features of commercially available multigene signatures in breast cancer

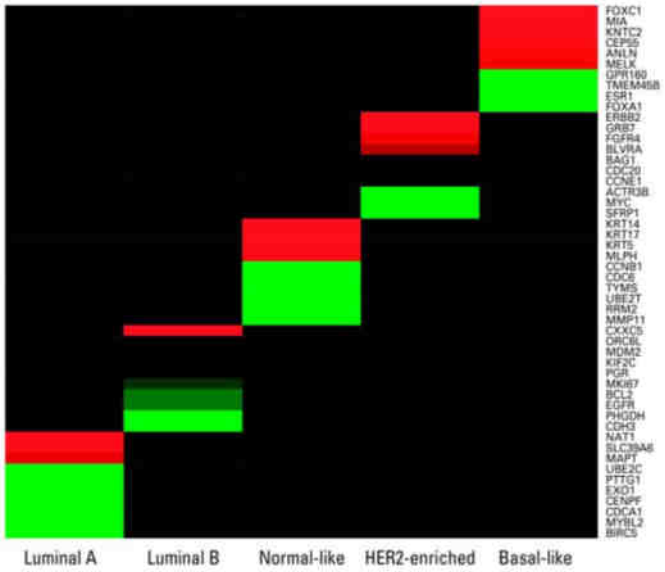
Table 1 | Main features of the commercially available multi-gene signatures in breast cancer

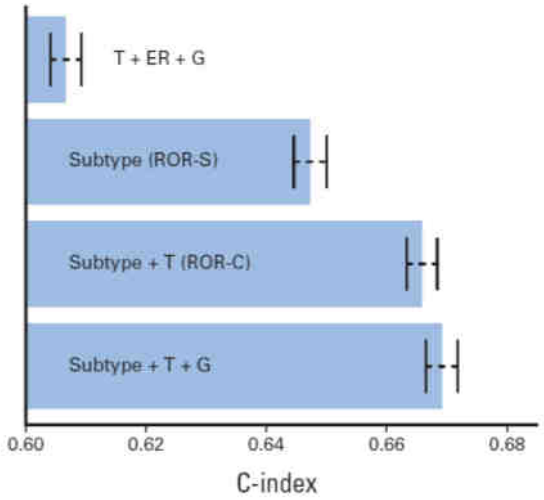
Assay name	Genes (*n*)	Source	Platform	Training dataset	Output data
Biology driven					
PAM50 subtype-predictor	55*	FFPE/FF	qRT-PCR/ microarray/ nCounter	Breast cancer-based cohort	Luminal A Luminal B HER2-E Basal-like Normal-like
Survival driven					
PAM50 risk of relapse (ROR)	55*	FFPE/FF	qRT-PCR/ microarray/ nCounter	RFS; ER+/ER–/node– breast cancer patients receiving no adjuvant systemic treatment	Continuous Variable Low–medium–high
Oncotype DX®	21	FFPE	qRT-PCR	Survival: largely ER+/node– breast cancer patients receiving tamoxifen-only adjuvant treatment	Continuous Variable Low–intermediate–high
MammaPrint®	70	FF	Microarray	DRFS: largely ER+/node– breast cancer patients receiving no adjuvant systemic treatment	Continuous Variable Good–bad
Pathology driven					
MapQuant Dx™	97	FF	Microarray	Grade 1 vs 3 in ER+ patients with breast cancer	Continuous Variable Low–high
Survival and pathology driven					
Breast Cancer Index	7	FFPE	qRT-PCR	MGI: grade 1 vs 3, HOXB13/IL17BR ratio DRFS: ER+ patients with breast cancer receiving tamoxifen-only treatment	Continuous Variable Low–intermediate–high

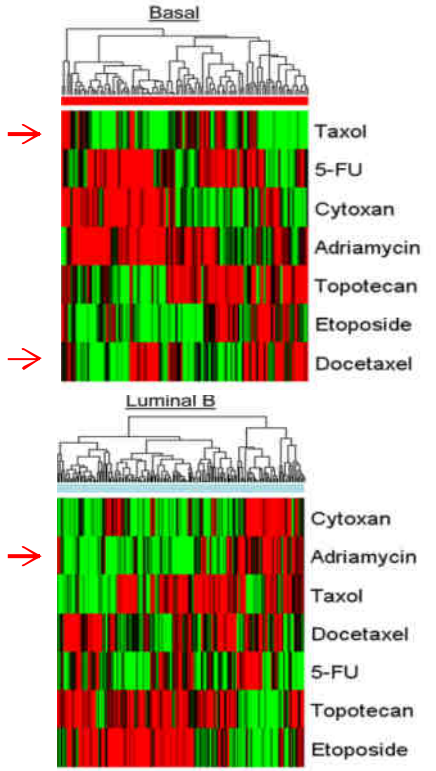
*5 genes included for expression normalization. Abbreviations: DRFS, distant relapse-free survival; FF, fresh-frozen; FFPE, formalin-fixed paraffin-embedded; MGI, molecular grade index; qRT-PCR, quantitative reverse transcription PCR; RFS, relapse-free survival.

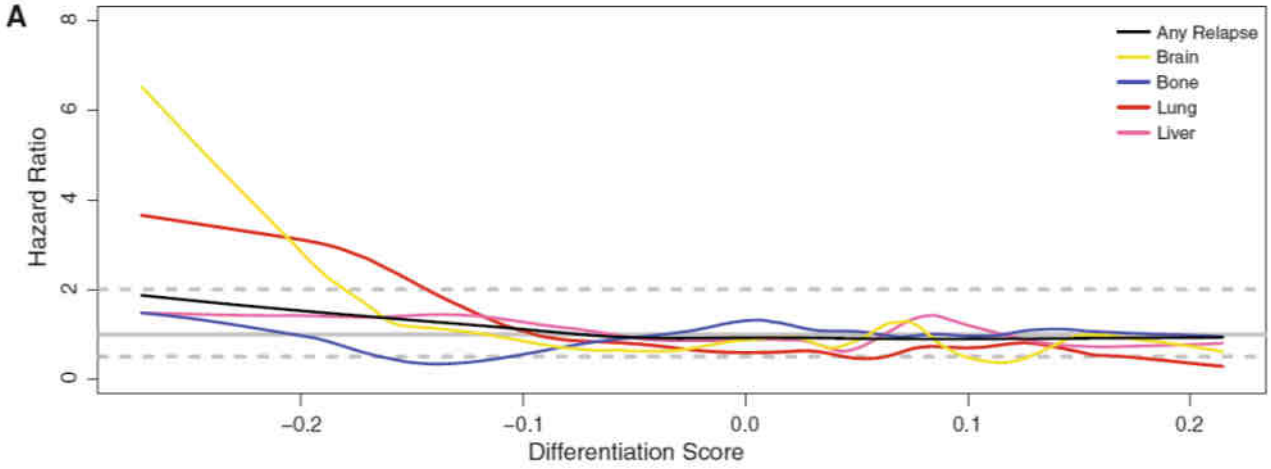
Prat, A. et al. Nat Rev Clin Oncol 2011

Prediction Analysis of Microarray (PAM) 50
Intrinsec subtypes are predictors in breast cancer

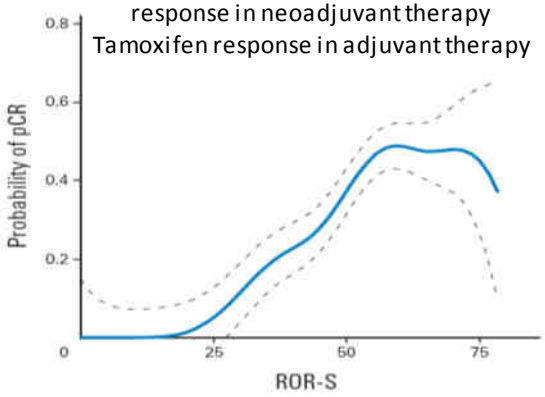








Paclitaxel, fluorouracil, doxorubicin and cyclophosphamide
response in neoadjuvant therapy
Tamoxifen response in adjuvant therapy



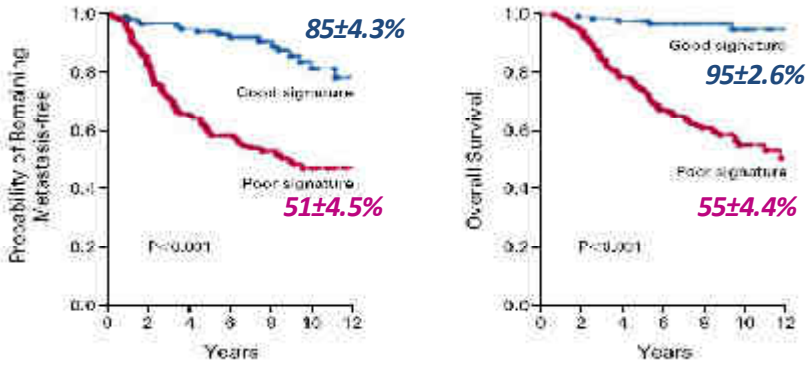
Parker, JS et al. J Clin Oncol 2009

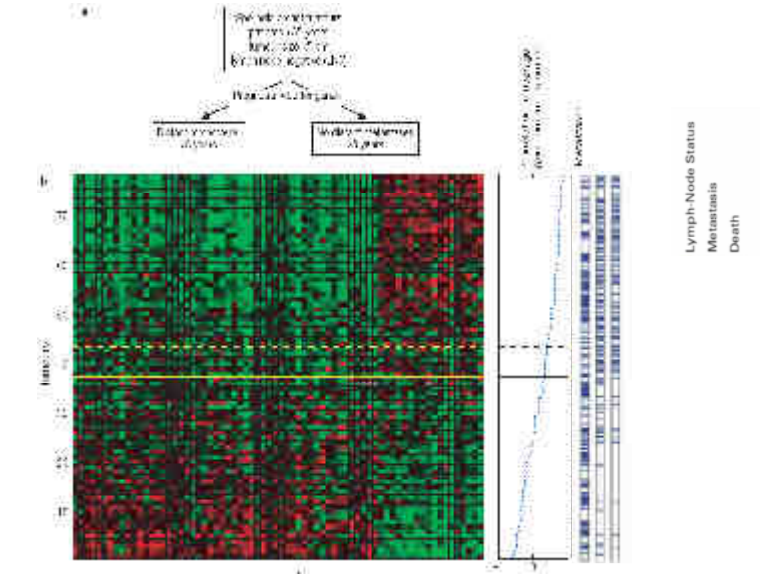
Mammaprint Breast Cancer Assay

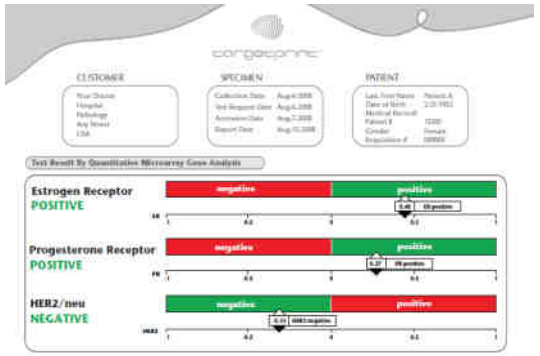

The New England Journal of Medicine

A GENE-EXPRESSION SIGNATURE AS A PREDICTOR OF SURVIVAL IN BREAST CANCER

- Prognostic test on frozen tissue
- 70-gene expression profile (Agilent-based) related to angiogenesis, invasiveness, cell cycle and signaling
- Independent prognostic factor in retrospective studies for tumor size <5cm, 0-3 positive lymph nodes, stage I-II ER+/-
- Define a poor prognosis signature candidate to adjuvant chemotherapy
- 91 % sensitivity, 73% specificity







Oncotype Dx Recurrence Score in ER+, N-, Tam+ patients

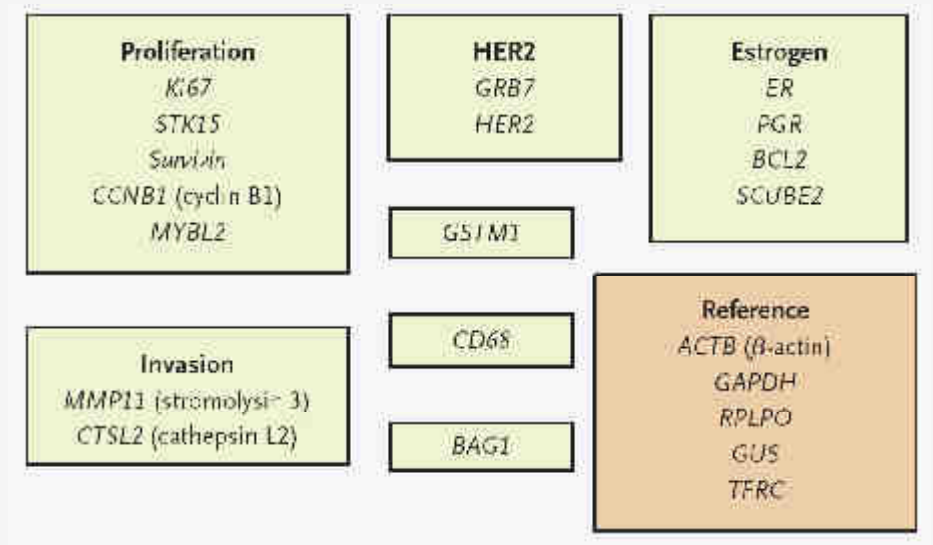
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer

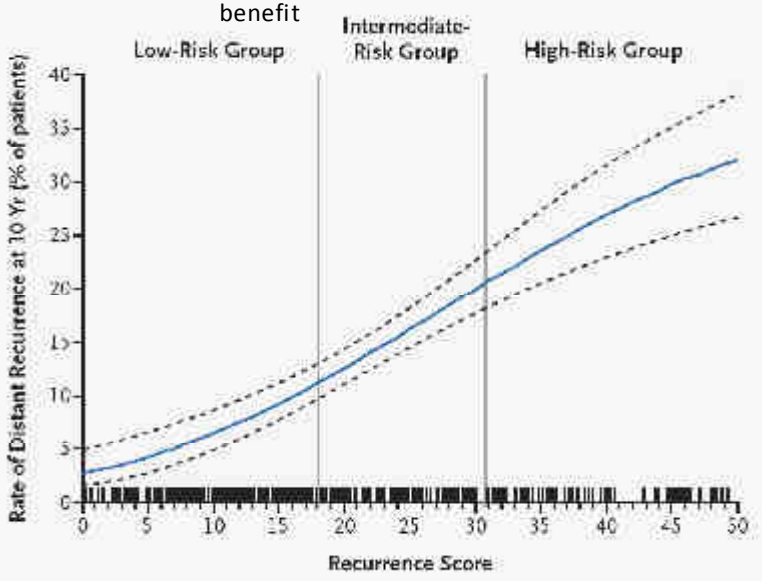
Soonmyung Paik, M.D., Steven Shak, M.D., Gong Tang, Ph.D., Chungyeul Kim, M.D., Joffre Baker, Ph.D., Maureen Cronin, Ph.D., Frederick L. Baehner, M.D., Michael G. Walker, Ph.D., Drew Watson, Ph.D., Taesung Park, Ph.D., William Hiller, F.T., Edwin R. Fisher, M.D., D. Lawrence Wickerham, M.D., John Bryant, Ph.D., and Norman Wolmark, M.D.

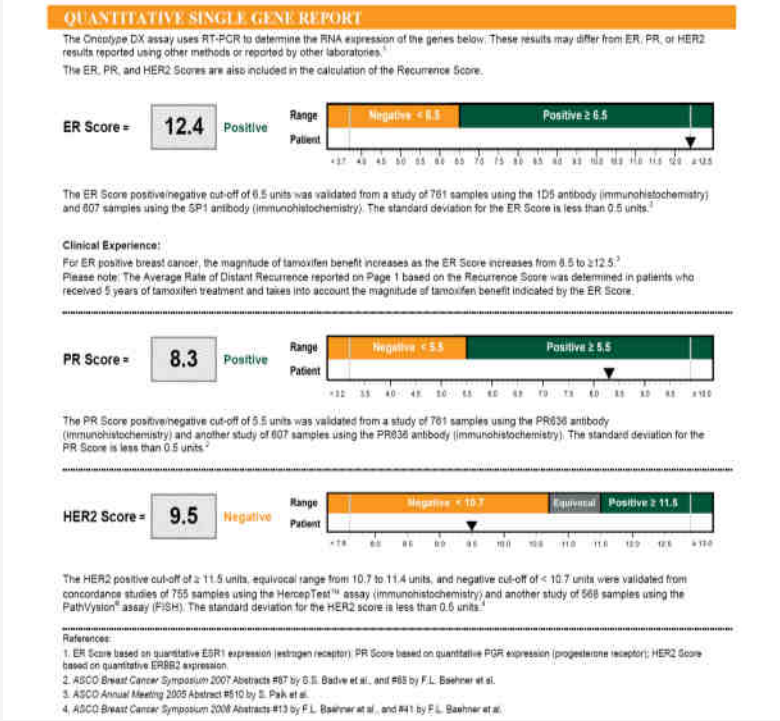
N Engl J Med 2004;351:2817-26



Lower likelihood of recurrence
Greater magnitude of TAM benefit
Minimal, if any, chemotherapy benefit

Greater likelihood of recurrence
Lower magnitude of TAM benefit
Clear chemotherapy benefit





QUANTITATIVE SINGLE GENE REPORT

The Oncotype DX assay uses RT-PCR to determine the RNA expression of the genes below. These results may differ from ER, PR, or HER2 results reported using other methods or reported by other laboratories.[1]

The ER, PR, and HER2 Scores are also included in the calculation of the Recurrence Score.

ER Score = 12.4 Positive — Range: Negative < 6.5 | Positive ≥ 6.5 — Patient

The ER Score positive/negative cut-off of 6.5 units was validated from a study of 761 samples using the 1D5 antibody (immunohistochemistry) and 607 samples using the SP1 antibody (immunohistochemistry). The standard deviation for the ER Score is less than 0.5 units.[2]

Clinical Experience:

For ER positive breast cancer, the magnitude of tamoxifen benefit increases as the ER Score increases from 6.5 to ≥12.5.[3]

Please note: The Average Rate of Distant Recurrence reported on Page 1 based on the Recurrence Score was determined in patients who received 5 years of tamoxifen treatment and takes into account the magnitude of tamoxifen benefit indicated by the ER Score.

PR Score = 8.3 Positive — Range: Negative < 5.5 | Positive ≥ 5.5 — Patient

The PR Score positive/negative cut-off of 5.5 units was validated from a study of 761 samples using the PR636 antibody (immunohistochemistry) and another study of 607 samples using the PR636 antibody (immunohistochemistry). The standard deviation for the PR Score is less than 0.5 units.[2]

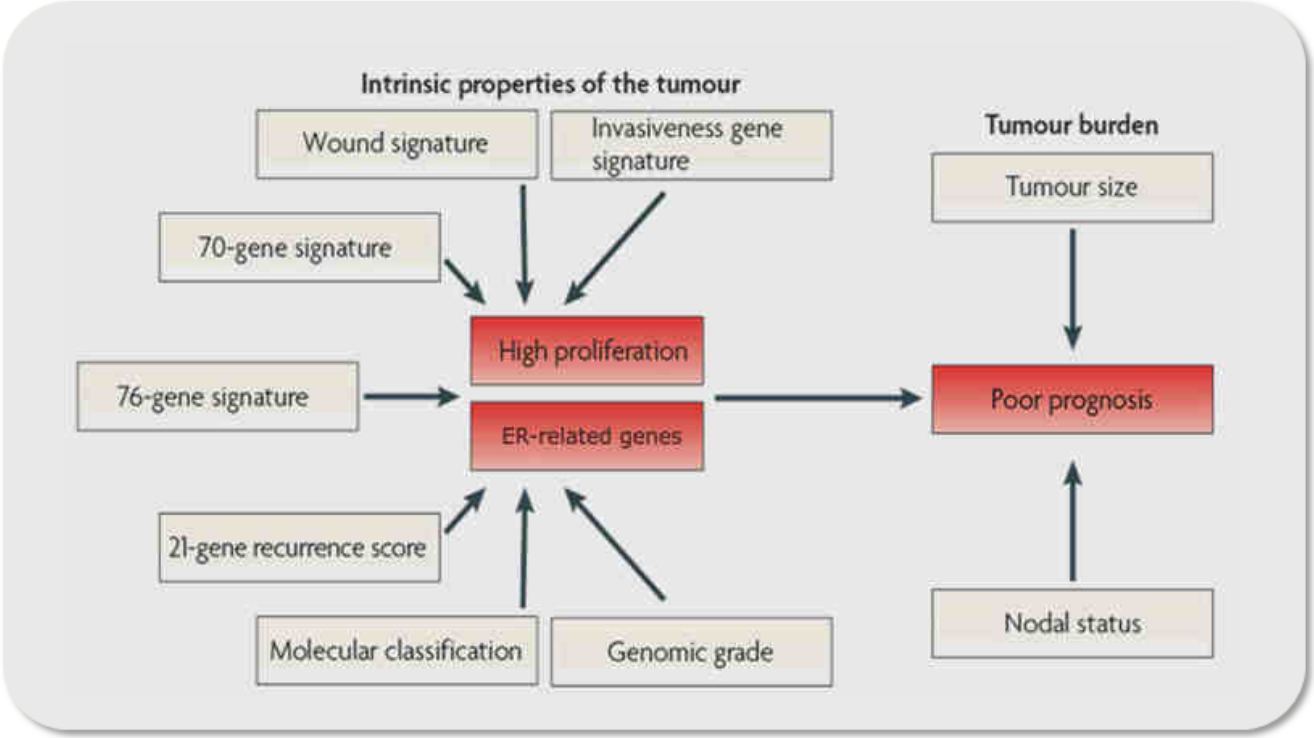
HER2 Score = 9.5 Negative — Range: Negative < 10.7 | Equivocal | Positive ≥ 11.5 — Patient

The HER2 positive cut-off of ≥ 11.5 units, equivocal range from 10.7 to 11.4 units, and negative cut-off of < 10.7 units were validated from concordance studies of 755 samples using the HercepTest™ assay (immunohistochemistry) and another study of 568 samples using the PathVysion® assay (FISH). The standard deviation for the HER2 score is less than 0.6 units.[4]

References:

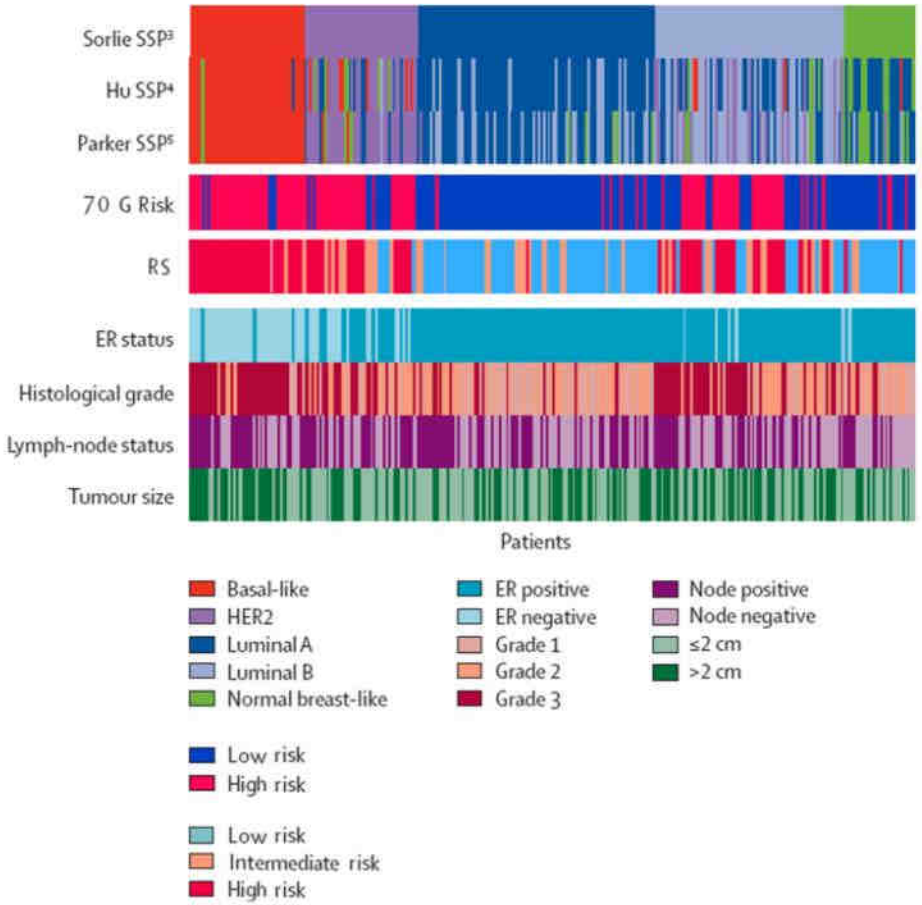
1. ER Score based on quantitative ESR1 expression (estrogen receptor); PR Score based on quantitative PGR expression (progesterone receptor); HER2 Score based on quantitative ERBB2 expression.
2. *ASCO Breast Cancer Symposium* 2007 Abstracts #67 by S.S. Badve et al., and #68 by F.L. Baehner et al.
3. *ASCO Annual Meeting* 2005 Abstract #510 by S. Paik et al.
4. *ASCO Breast Cancer Symposium* 2008 Abstracts #13 by F.L. Baehner et al., and #41 by F.L. Baehner et al.

Limitations of 1st generation of multigene predictors in breast cancer: ER and proliferation genes

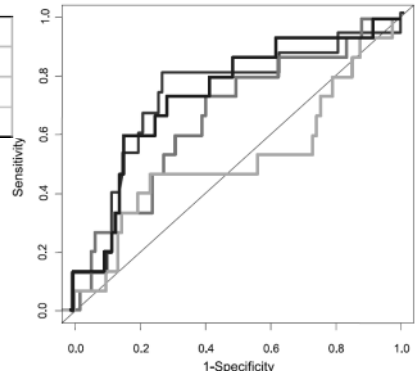


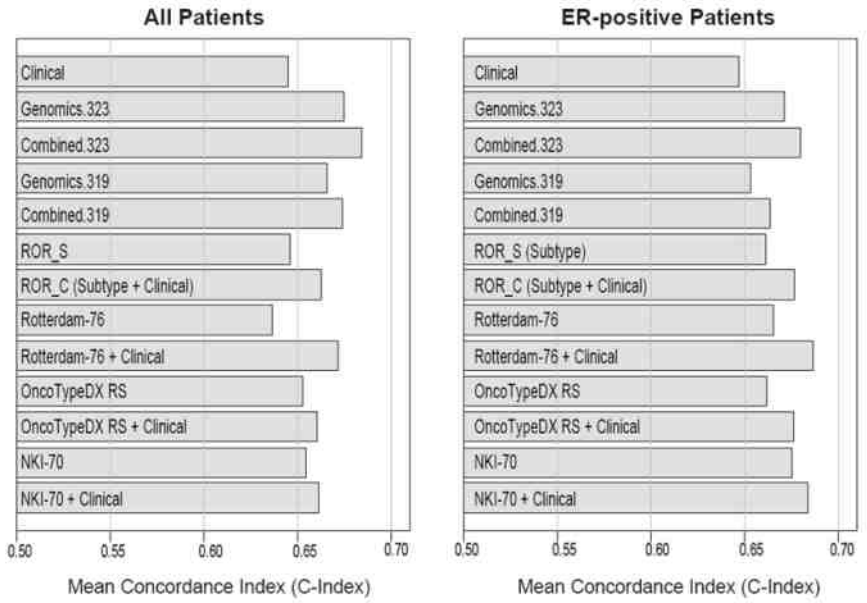
Reis-Filho, JS. AACR 2012
Weigelt, B. et al. Breast Can Res 2010
Lee, JK. et al. Clin Cancer Res 2010

Limitations of 1st generation of multigene predictors in breast cancer: Lack of concordance between platforms



Clinical nomogram score	0.73	0.65-0.80
DLDA30 score	0.73	0.66-0.80
in vivo-TFAC COXEN	0.67	0.60-0.74
in vitro-TFAC COXEN	0.5	0.41-0.59

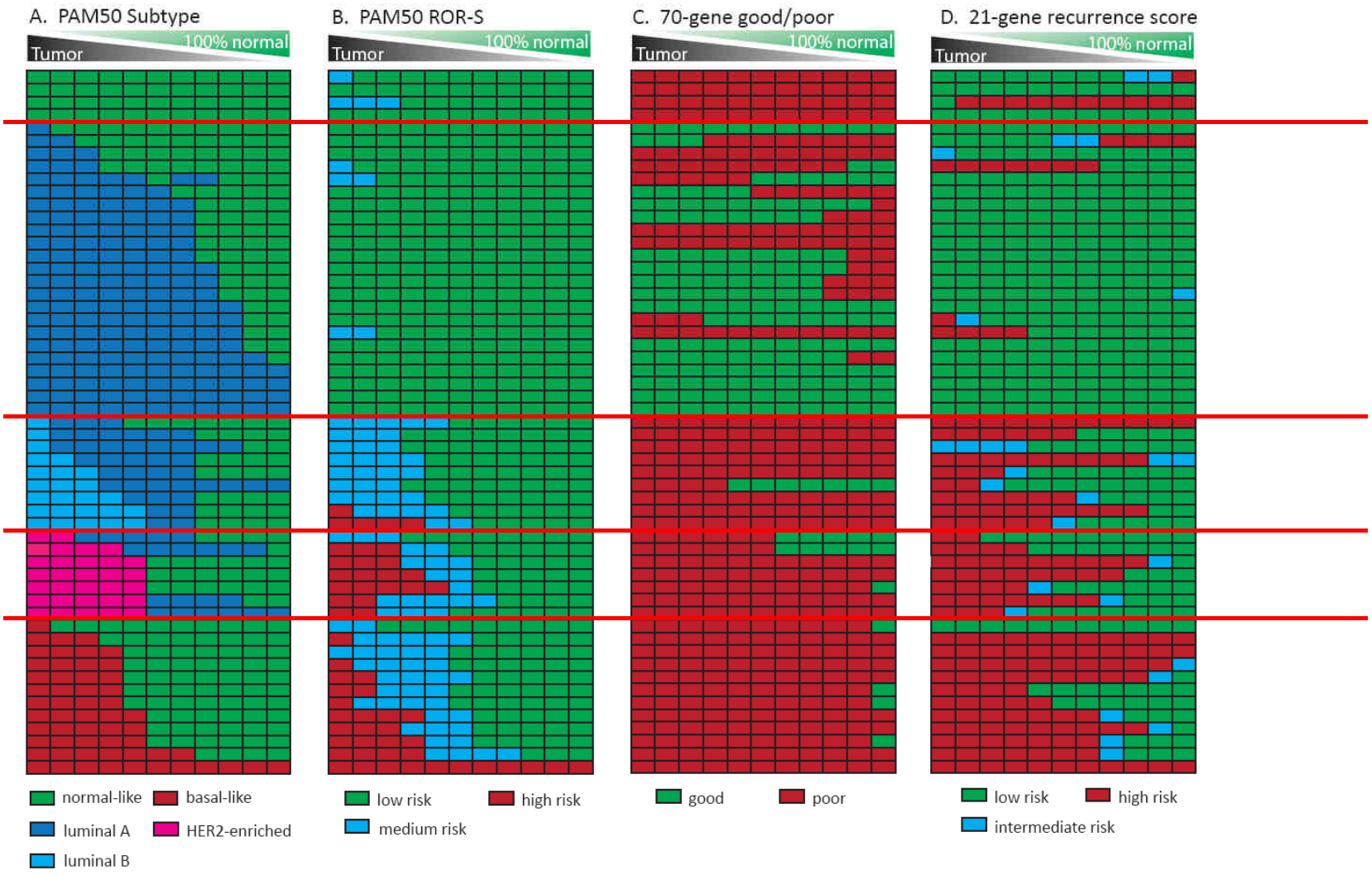




Reis-Filho, JS. AACR 2012
Haibe-Kains, B. et al. JNCI 2012

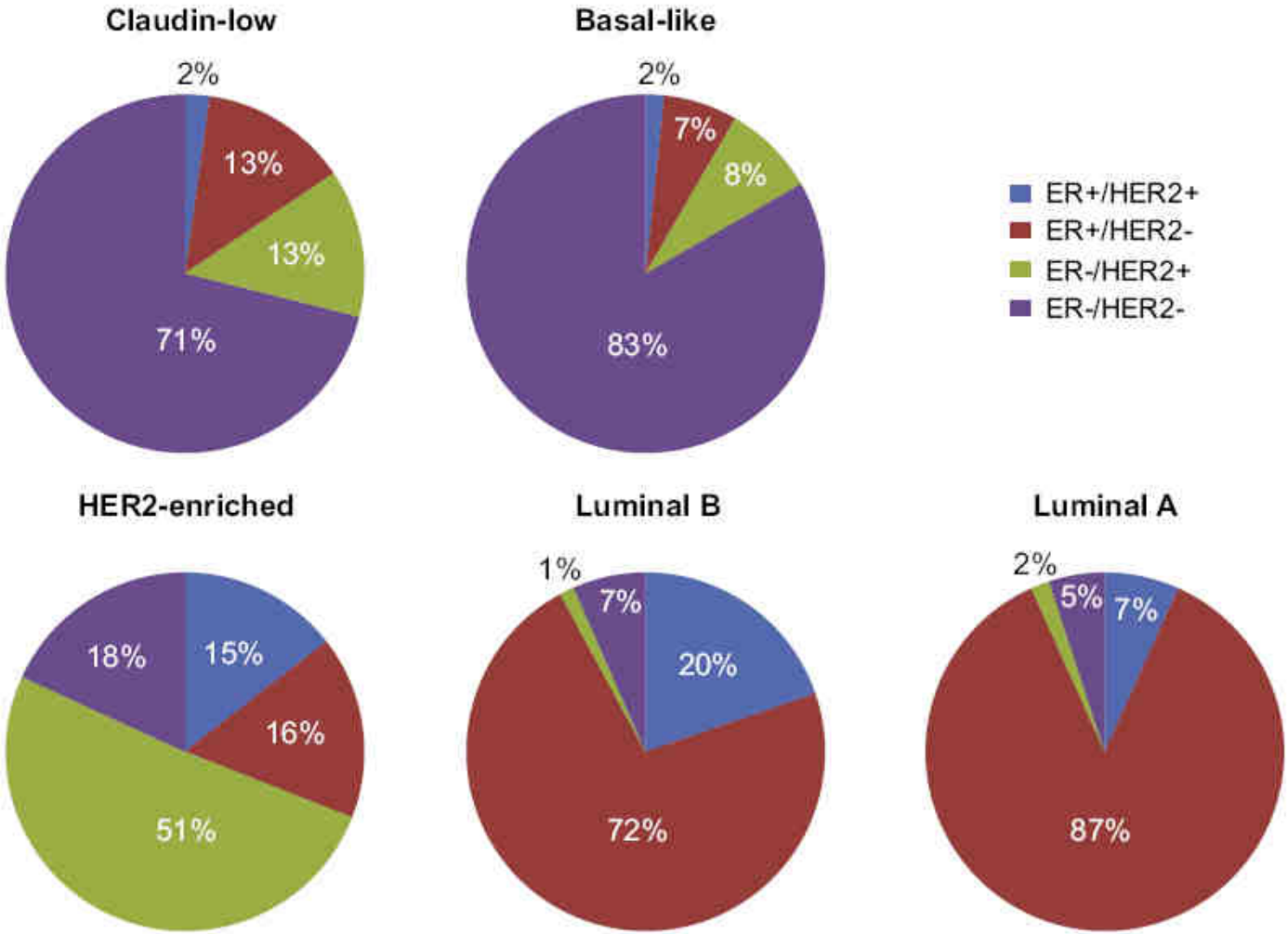
Fan, C. et al. BMC Med Genomics 2011
Weigelt, B. et al. Breast Can Res 2010

Systematic bias in genomic classification due to non-neoplastic cell proportion in breast cancer



Elloumi, F. et al. BMC Med Genomics 2011

Limitations of 1st generation of multigene predictors in breast cancer: Phenotype in breast intrinsic subtypes



Prat, A & Perou, CM. Mol Oncol 2011

Highlights of the St Gallen International Expert Consensus on early breast cancer 2011: Strategies for subtypes

definition of biological subtypes

The Panel strongly supported the clinicopathological determination of estrogen receptor, progesterone receptor, HER2, and Ki-67 as useful for defining subtypes, but did not support the incorporation of tests for cytokeratin 5/6 or epidermal growth factor receptor/HER1 for the determination of 'basal-like' tumors for clinical decision making. The endorsed clinicopathological criteria define a convenient alternative to formal subtyping and are likely to be refined in the future. The Panel did not require multigene array definition of tumor subtype, although there was acceptance of such assays for certain indications (see below). However, the Panel did recommend that the clinicopathological markers described above were generally sufficient to guide therapeutic choices.

Goldhirsch, A. et al. Ann Oncol 2011

Highlights of the St Gallen International Expert Consensus on early breast cancer 2011: Strategies for subtypes

Field or Treatment	Status of research/implications for patient care
Intrinsic breast cancer subtypes	Definition of intrinsic subtypes has proved efficient in defining prognosis for breast cancer patients [33]. Currently, there are no data from phase III trials on their role as predictive tools for chemotherapy benefit. Gene expression arrays are reproducible and quantitative, but cost considerations limit their wide availability. An approximation of gene expression array results is now possible using formalin-fixed paraffin-embedded material [7].
Gene-based testing	The commercial scores from assays such as Oncotype DX® [57] and Mamma Print® [58] have been used to determine prognosis. Oncotype DX® has been shown to predict chemotherapy benefit among patients with hormone receptor-positive disease.
	An interesting STEPP analysis [59] from the adjuvant trastuzumab NSABP B-31 trial examined the degree of HER2 mRNA expression and corresponding trastuzumab benefit separately for patients with estrogen receptor-positive and estrogen receptor-negative disease. The striking finding was that among patients with estrogen receptor-positive disease, trastuzumab benefit in terms of 8-year disease-free survival was entirely confined to those with the higher levels of HER2 mRNA expression. In contrast, patients with estrogen receptor-negative disease derived some benefit from trastuzumab at all levels of mRNA expression, though the quantitative benefit was greater among those with higher levels of HER2 [60].

Goldhirsch, A. et al. Ann Oncol 2011

Potential role for biomarker-based diagnostics