SUPPLEMENTAL DATA

to

"*Building Prognostic Models for Breast Cancer Patients Using Clinical Variables and Hundreds of Gene Expression Signatures*"

by

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Supplementary Tables and Figures

Supplemental Table 1. Summary of the combined models built from expression and clinical variables in the different patient cohorts.

Supplemental Figure 1. Kaplan-Meier survival estimates of relapse-free survival among 550 patients, according to the data set evaluated.

Supplemental Figure 2a-c. Unsupervised hierarchical cluster analysis of 323 gene expression modules (rows) across the microarray data of 550 node-negative breast cancer patients (columns). Exact localization of modules is shown on the right side of figures 2a, 2b and 2c.

Supplemental Figure 3. Survival prediction analyses of the different models under evaluation from a total of 319 modules (which excludes the known modules that were trained on patient prognosis). (**A**) Models for all patients; (**B**) Models for ER-positive patients; (**C**) Models for ER-negative patients; (**D**) Models for HER2-positive patients. 1) Hazard ratio and p-value of the Cox proportional hazard model (Cox-model), for both the training and testing sets, respectively; 2)

Kaplan–Meier survival estimates of relapse-free survival among training set and testing set, according to each model. Patients were stratified into high-risk (red curve) and low-risk (blue curves) groups based on their respective risk score, which was defined as the natural logarithm of the hazard ratio. The chosen cut-off value for stratification into high and low-risk groups was zero. P-values were obtained from the log-rank test. + denotes observations that were censored owing to loss to follow-up or on the date of last contact.

Supplemental Figure 4. Significant prognostic combined models built for all patients (**A**) and ER-positive patients (**B**) from 319 gene expression modules (which excludes the known modules that were trained on patient prognosis). Modules in blue identify those modules and/or clinical variables that were evaluated in the combined model in Supplemental Figure 3. Colored squares identify the modules and/or clinical variables association with poor (red) or good (green) prognosis, respectively. Freq, frequency of selection of a particular module/clinical variable among 200 models; Ref, references of previously published modules.

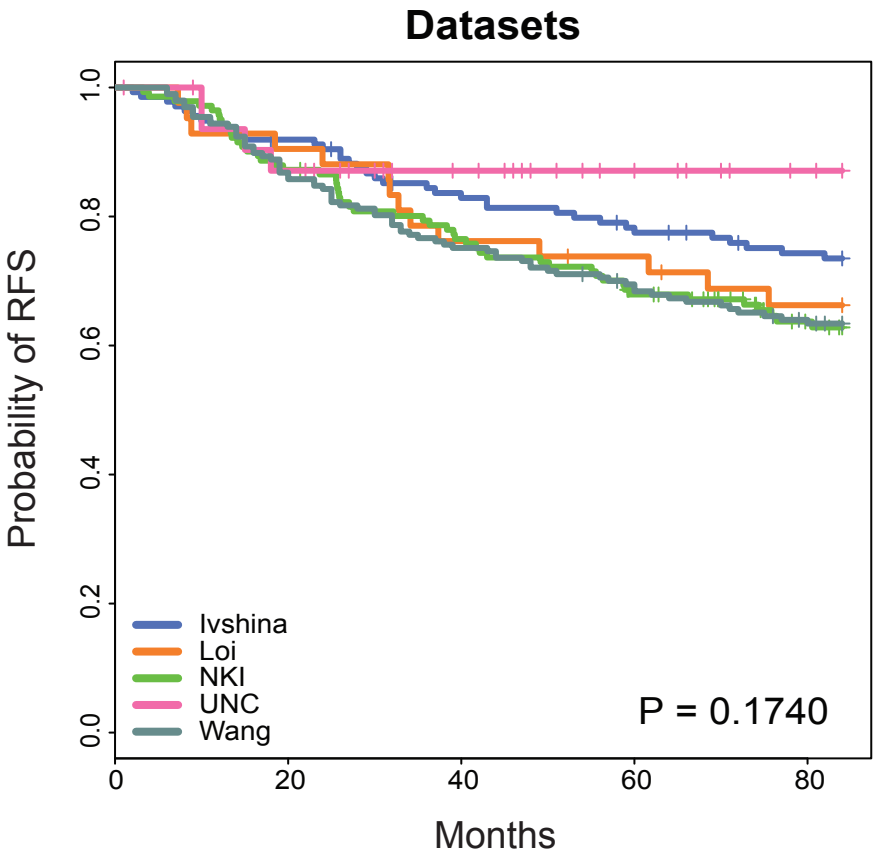
Supplemental Figure 5. Performance of the MDACC module for predicting pathological complete response (pCR) after anthracycline/taxane-based chemotherapy using Popovici et al. dataset (n=225).

Supplemental Table 1. Summary of the Combined Models Built from Expression and Clinical Variables in the Different Patient Cohorts.

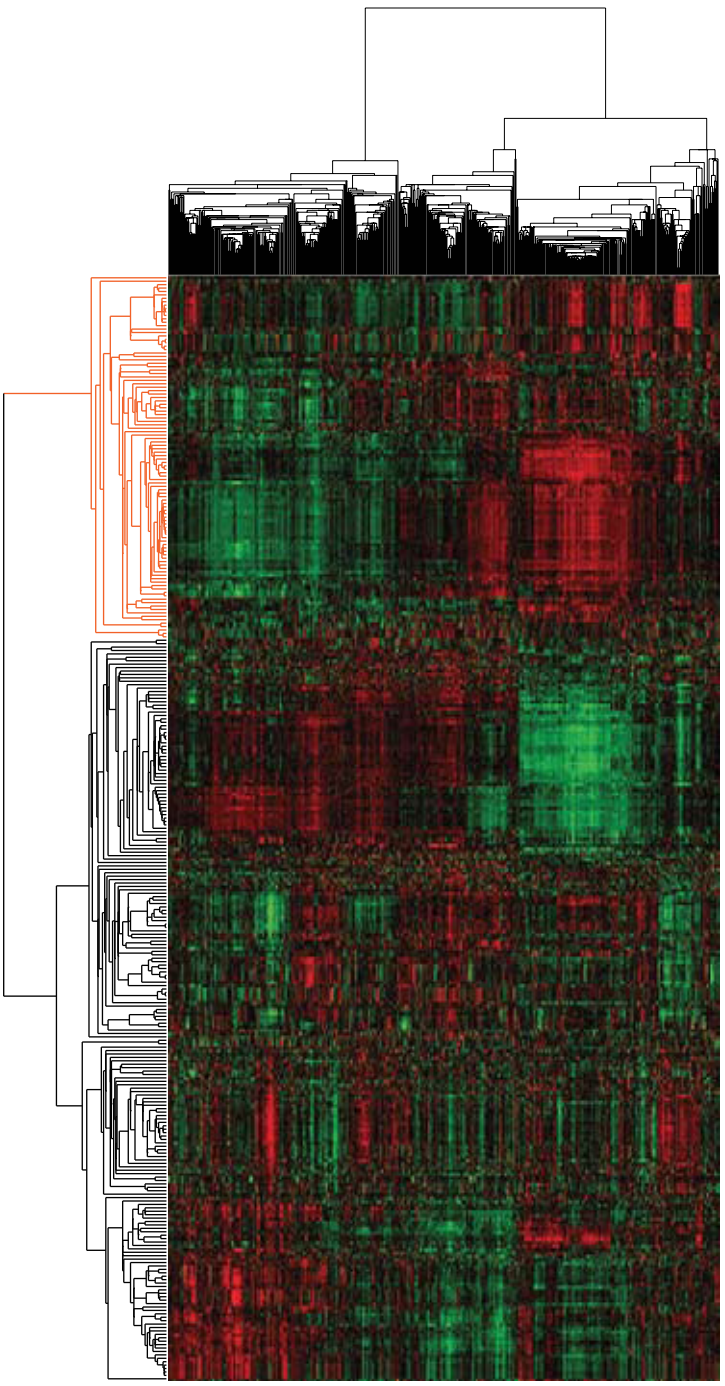
Patient Cohort	Train	Test	Train		Test	
			Cox HR*	P-value	Cox HR*	P-value
All	**359**	**191**	**5.99**	**<0.0001**	**3.71**	**<0.0001**
ER-positive (ER+)	**259**	**136**	**5.27**	**<0.0001**	**2.38**	**<0.001**
ER+/HER2-negative	**232**	**118**	**6.78**	**<0.0001**	**14.7**	**<0.001**
ER-negative	100	55	4.18	<0.0001	1.43	0.093
HER2-positive	73	37	7.03	<0.0001	0.801	0.670
Luminal	**183**	**104**	**4.67**	**<0.0001**	**2.33**	**<0.005**
Luminal A	98	58	7.06	<0.0001	0.996	0.99
Luminal B	85	46	11.4	<0.0001	7.93	0.08
Basal-like	72	34	20.4	<0.0001	2.26	0.59
HER2-enriched	56	27	NA	NA	NA	NA

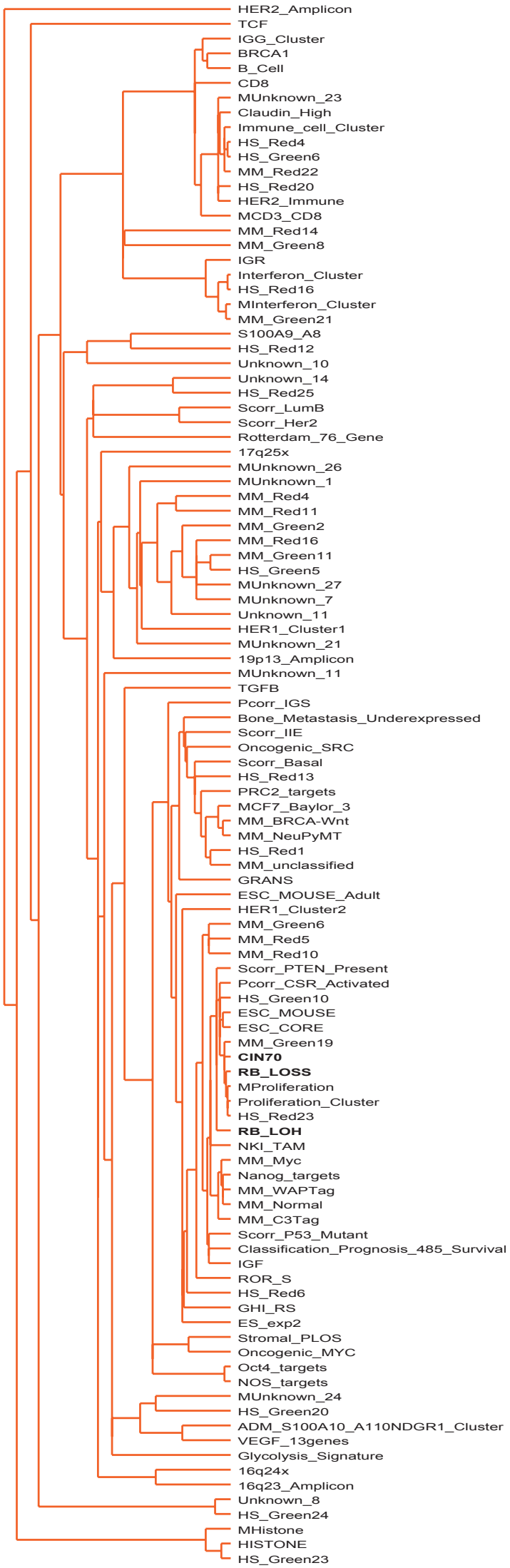
*Cox HR, hazard ratio for RFS. NA, a Cox proportional hazard model could not be built.

Supplemental Figure 1

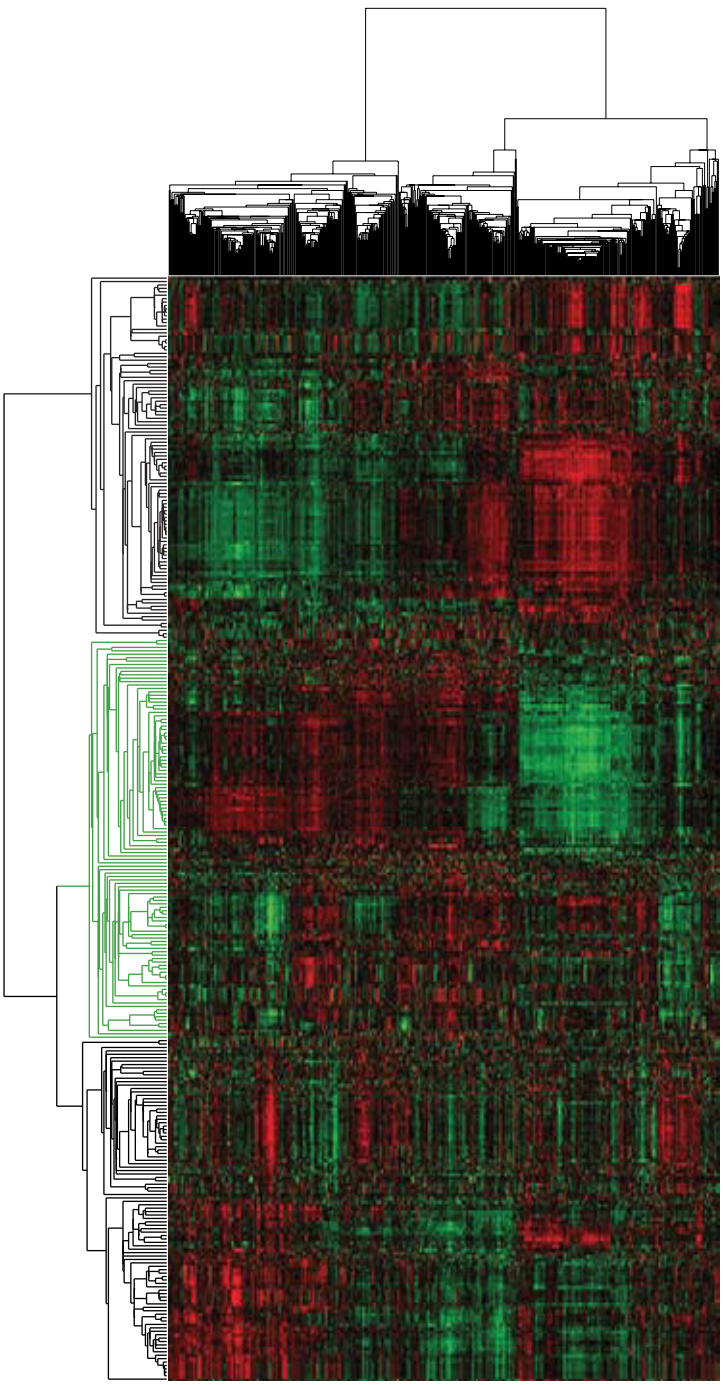


Supplemental Figure 2a





Supplemental Figure 2b

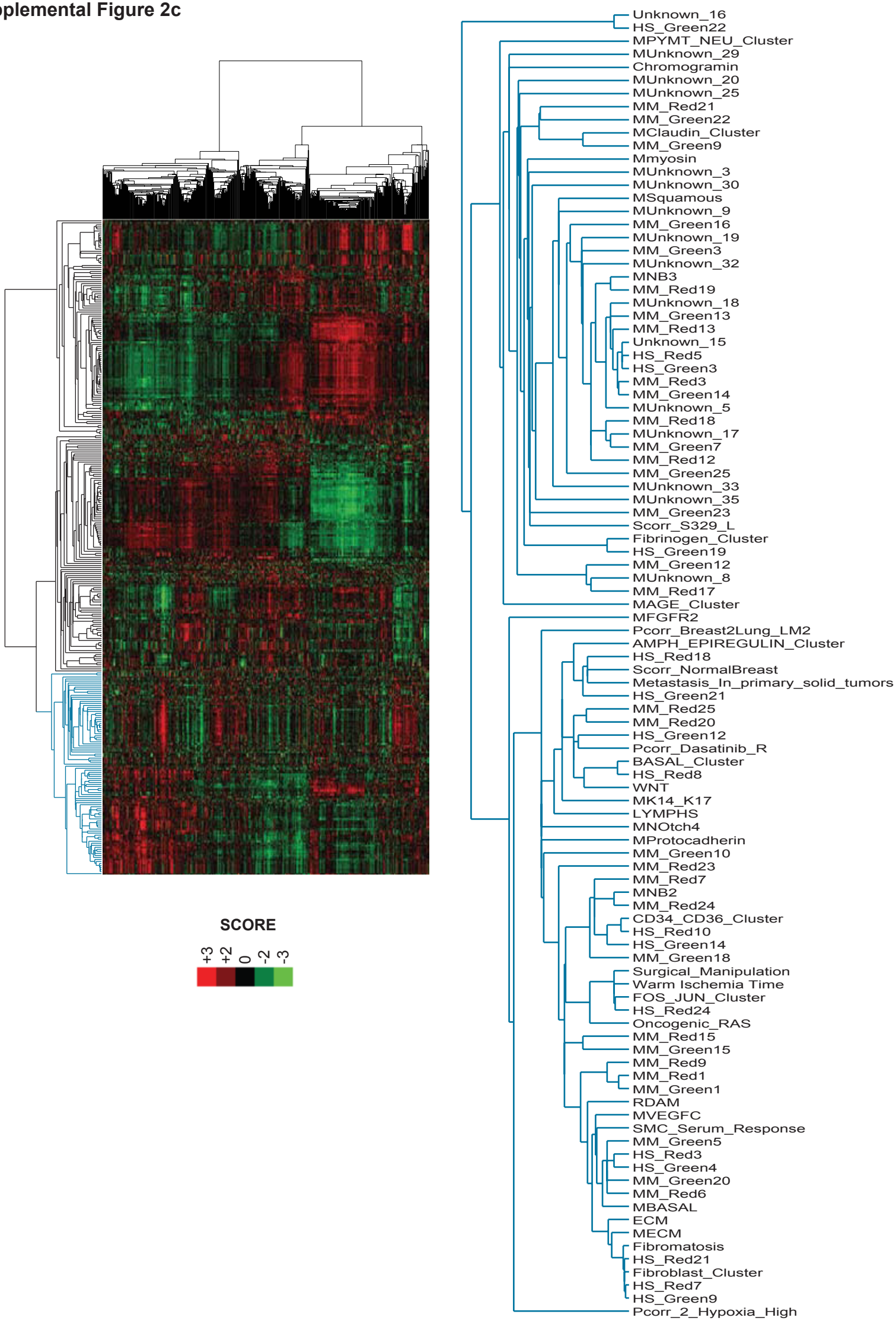


SCORE

+3 +2 0 -2 -3

MRibosomal
Ribosomal_Cluster
CD44+PROCR+-vs-CD24+-Upregulated
Pcorr_2_Hypoxia_Low
LKB1
VEGF_Hypoxia
MM_p53null
Secretoglobin
E2F1_Repressed_by_Serum
MUnknown_4
3p21Amplicon
MUnknown_2
16.13_Amplicon
CD44+PROCR+-vs-CD24+-Downregulated
MM_Red2
KRAS2
HS_Red9
Pcorr_Dasatinib_L
Claudin_Low
MM_DMBA-Wnt
MM_WapINT3
SDDP
Stromal_Predict_Outcome
LUMINAL_Cluster
HS_Red2
Classification_Prognosis_706
Immune_Response
Eed_targets
Suz12_targets
H3K27_bound
HS_Green1
Estrogen_Reg
MCF7_Baylor_4
MCF7_Baylor_1
GATA3
MCF7_Baylor_5
HS_Green8
HS_Green25
Oncogenic_E2F3
MCF7_Baylor_2
Response predictor MDACC
Pcorr_NKI70_Good
T_Cell
StemCell_11genes
E2F1_NOT_Repressed_by_Serum
Myc_targets1
WNT_Fibroblast
Scorr_LumA
Scorr_P53_Wt
Sox2_targets
Scorr_PTEN_Absent
Myc_targets2
ES_exp1
Genomic_Grade
ESC_HUMAN
Scorr_IE
HS_Green18
Bone_Metastasis_Overexpressed
Unknown_9
HS_Green13
HS_Red19
NOS_TFs
4p16_Amplicon
8p22_Amplicon
MUnknown_22
MUnknown_28
Unknown_13
Unknown_12
Pcorr_Breast2Lung_Parental
MUnknown_31
17PP13_Amplicon
MUnknown_14
13q14_Amplicon
12qMDM4
Scorr_S329_R
MUnknown_6
HER1_Cluster3
HS_Green2
MITO2
MM_Green4
HS_Red22
MUnknown_15
MNADH_CYTochrome
MUnknown_13
MUnknown_12
MITO1
MUnknown_16
MNB1
8p_Amplicon
HS_Red14
Claudin_Low_29
MKRAS_amplicon
KRAS_amplicon
HS_Red11
HS_Green7
MUnknown_10
MM_Green17
HS_Green16
Unknown_6
Unknown_4
MM_Green24
MM_Red8
HS_Green17
Unknown_7
Unknown_5
HS_Red15
15q25_Amplicon
11q13_Amplicon
Unknown_3
HS_Green11
Unknown_2
HS_Red17
Unknown_1
HS_Green15
MUnknown_34
1p36_Amplicon
Oncogenic_BCAT

Supplemental Figure 2c



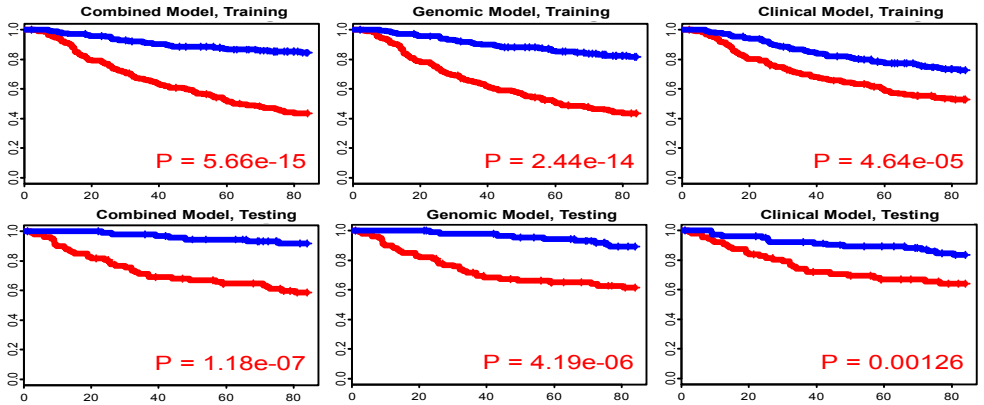
Supplemental Figure 3

A. All Patients (N = 550)

1)

		Combined model		Genomics model		Clinical model	
		Hazard Ratio	P-Value	Hazard Ratio	P-Value	Hazard Ratio	P-Value
Training	(N = 359)	6.28	<1.0e-22	6.7	<1.0e-22	3.34	3.4e-06
Testing	(N = 191)	3.47	9.3e-06	4.48	9.1e-06	4.34	0.001

2)

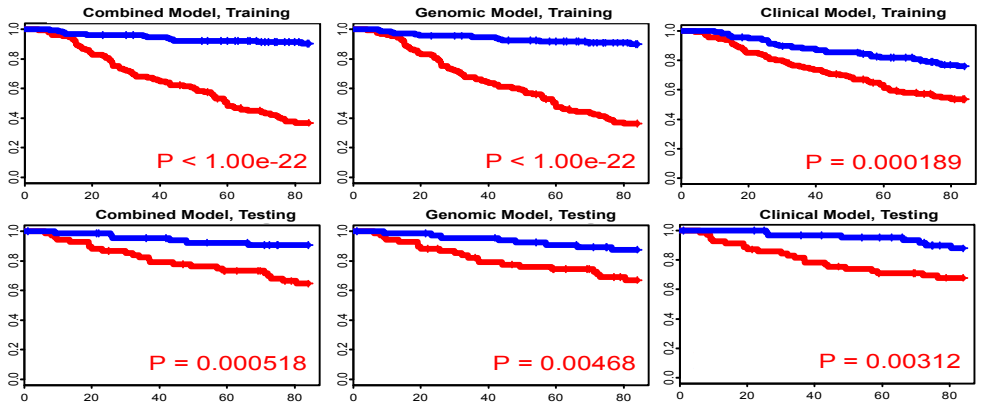


B. ER-positive Patients (N = 395)

1)

		Combined model		Genomics model		Clinical model	
		Hazard Ratio	P-Value	Hazard Ratio	P-Value	Hazard Ratio	P-Value
Training	(N = 259)	5.45	<1.0e-22	5.8	<1.0e-22	3.83	2.3e-05
Testing	(N = 136)	1.95	0.0097	2.15	0.011	5.16	0.0037

2)

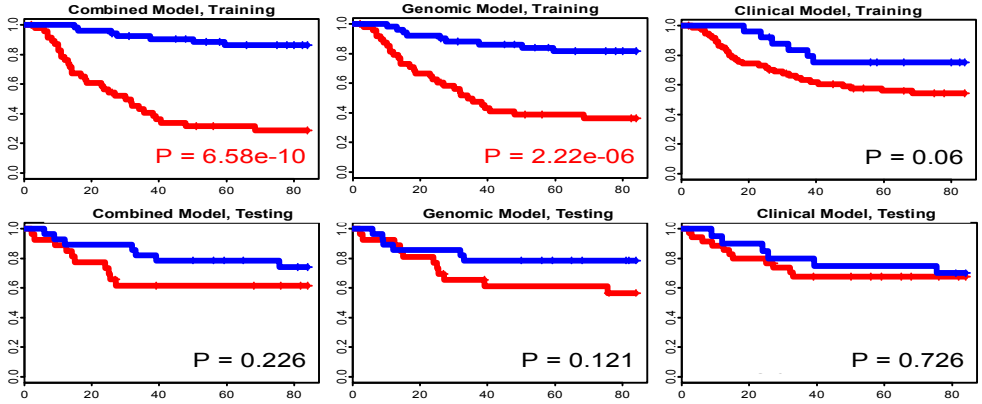


C. ER-negative Patients (N = 155)

1)

		Combined model		Genomics model		Clinical model	
		Hazard Ratio	P-Value	Hazard Ratio	P-Value	Hazard Ratio	P-Value
Training	(N = 100)	3.92	5.5e-9	3.52	5.5e-08	4.35	0.013
Testing	(N = 55)	1.51	0.073	1.47	0.096	1.29	0.73

2)

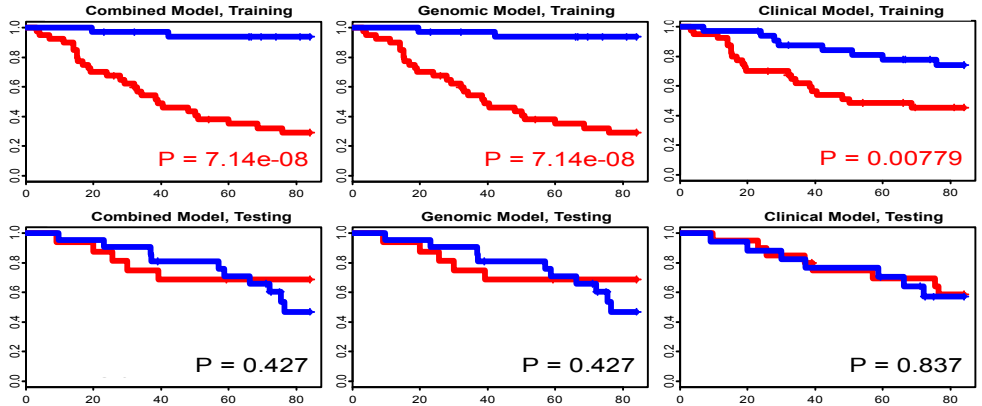


D. HER2-positive Patients (N = 110)

1)

		Combined model		Genomics model		Clinical model	
		Hazard Ratio	P-Value	Hazard Ratio	P-Value	Hazard Ratio	P-Value
Training	(N = 73)	7.54	7.6e-8	7.71	8.2e-08	2.85	0.011
Testing	(N = 37)	0.777	0.64	0.77	0.63	0.934	0.92

2)



Supplemental Figure 4

A. All Patients

	FREQ	REF
IGG_Cluster	99%	
E2F1_Repressed_by_Serum	86%	22
19p13_Amplicon	68%	
HS_Green19	62%	
MUnknown_28	58%	
E2F1_NOT_Repressed_by_Serum	49%	22
HS_Green22	47%	
MM_Red21	47%	
MKRAS_amplicon	46%	
MM_Green23	43%	
MNB1	25%	
8p22_Amplicon	21%	
MUnknown_20	21%	
MHistone	20%	
Scorr_LumA	19%	50
MM_Red18	19%	
Unknown_2	19%	
Oncogenic_MYC	18%	10
Scorr_P53_Wt	17%	11
MUnknown_15	17%	
ESC_CORE	8%	29
HS_Red25	13%	
Pcorr_IGS	16%	68
MM_p53null	20%	13
NKI_TAM	20%	20
MM_Red23	20%	
MUnknown_1	24%	
MUnknown_30	28%	
MNOtch4	30%	
Oncogenic_BCAT	31%	10
CD44+PROCR+-vs-CD24+-Downregulated	33%	12
HS_Red23	37%	
ADM_S100A10_A110NDGR1_Cluster	53%	
MM_Red10	55%	
HER2_Amplicon	59%	
VEGF_13genes	61%	26
Tumor Size	66%	
Scorr_Her2	88%	50
16q24x	97%	
Histological Grade	98%	

B. ER-positive Patients

	FREQ	REF
IGG_Cluster	90%	
Scorr_LumA	89%	50
Unknown_12	48%	
E2F1_NOT_Repressed_by_Serum	48%	22
MUnknown_28	39%	
MM_Red21	36%	
MNB1	30%	
HS_Red16	30%	
MHistone	28%	
HS_Green19	23%	
19p13_Amplicon	21%	
1p36_Amplicon	20%	
MM_Green23	16%	
Scorr_IE	16%	9
MKRAS_amplicon	16%	
HS_Green22	16%	
Oncogenic_MYC	13%	10
StemCell_11genes	12%	60
Fibrinogen_Cluster	11%	
Response predictor MDACC	7%	37
HER2_Amplicon	21%	
TGFB	23%	12
LKB1	23%	28
Scorr_Her2	24%	50
MM_p53null	24%	11
HS_Red25	26%	
CD44+PROCR+-vs-CD24+-Downregulated	28%	12
MUnknown_1	29%	
ADM_S100A10_A110NDGR1_Cluster	30%	
VEGF_13genes	32%	26
MNOtch4	34%	
MM_Red10	43%	
Glycolysis_Signature	44%	26
Tumor Size	47%	
Bone_Metastasis_Underexpressed	47%	58
HER1_Cluster2	55%	14
16q24x	61%	
HS_Red23	72%	
MUnknown_30	94%	
Histological Grade	99%	

Supplemental Figure 5