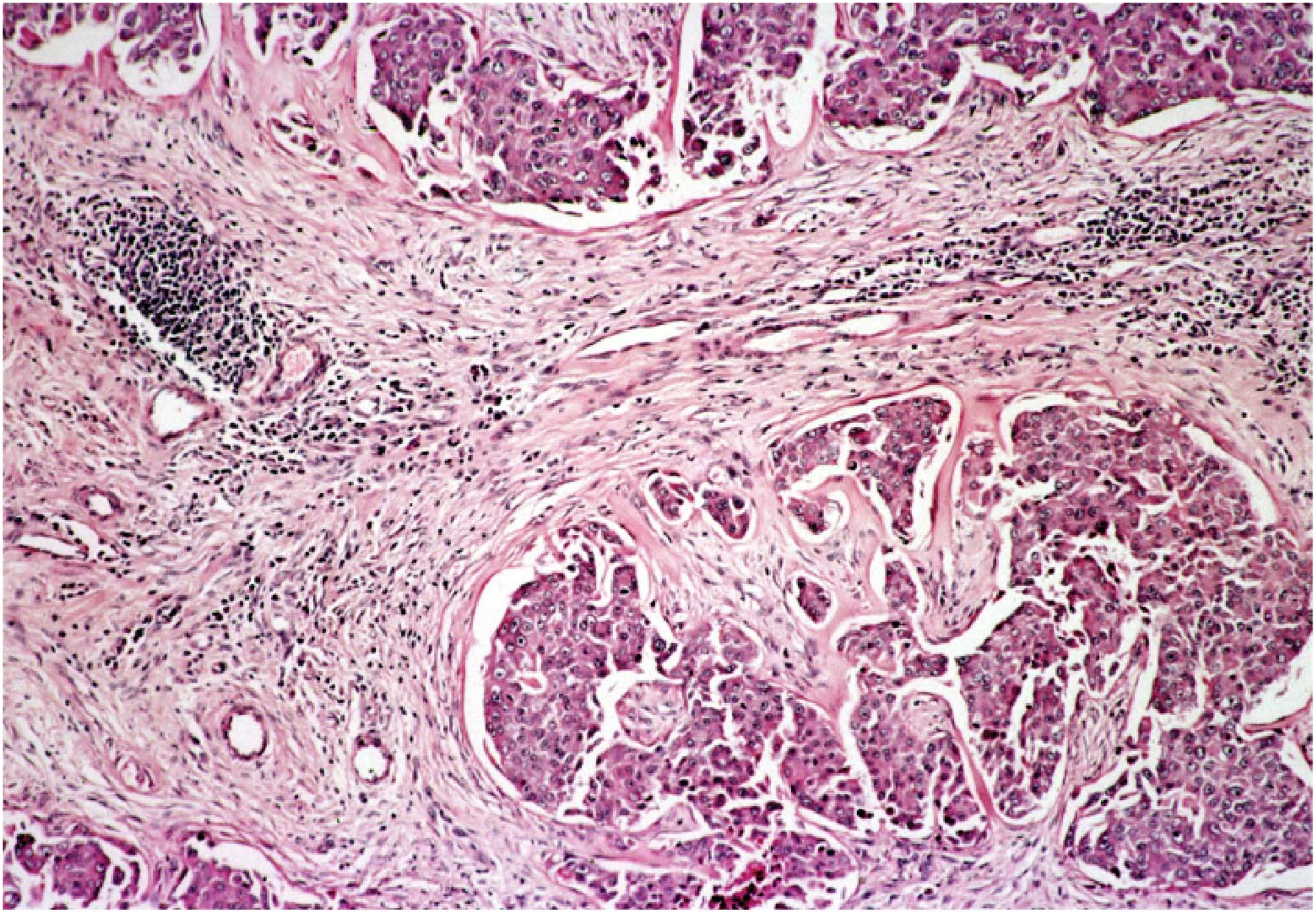
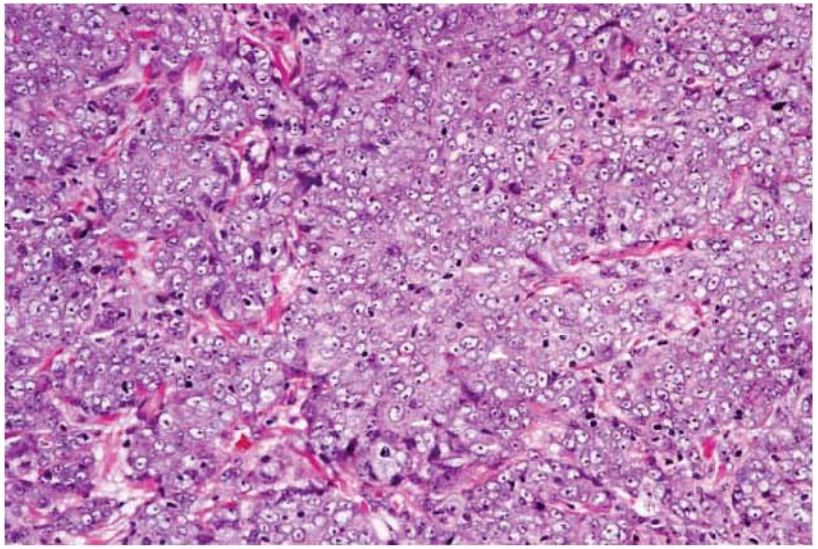
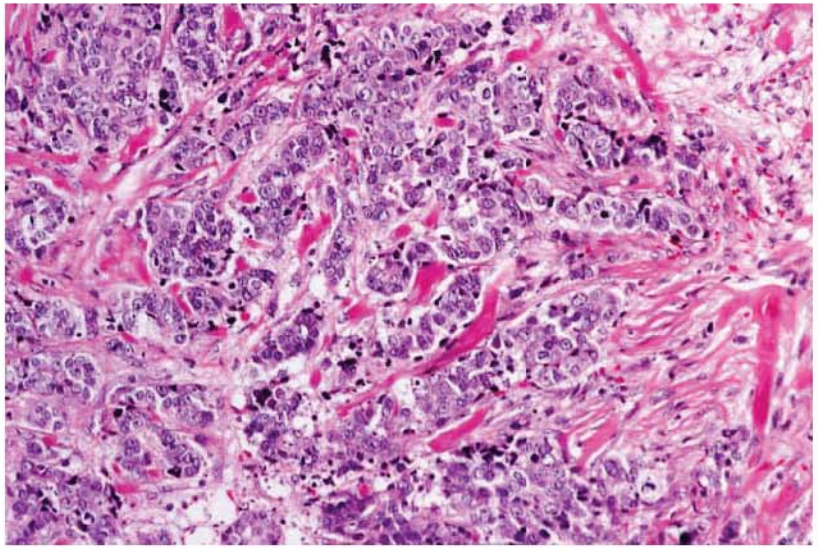
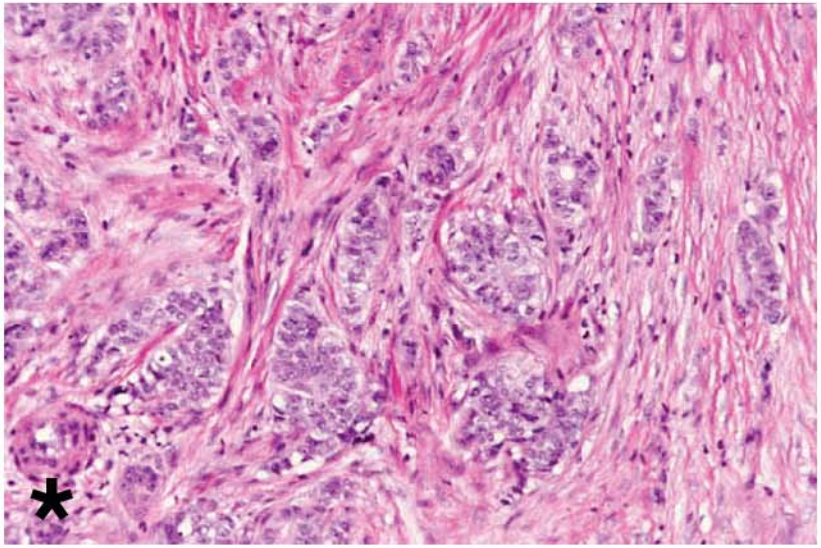
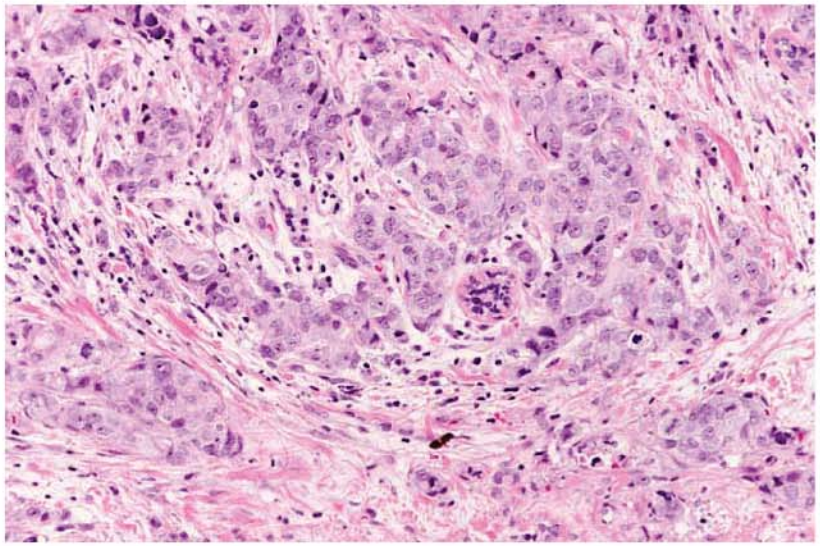


Grade III, Estrogen and Progesterone Receptor positive, ERBB2/HER2 negative
T3 tumors (diameter of > 5cm), 3/4 Node positive, all received Tamoxifen









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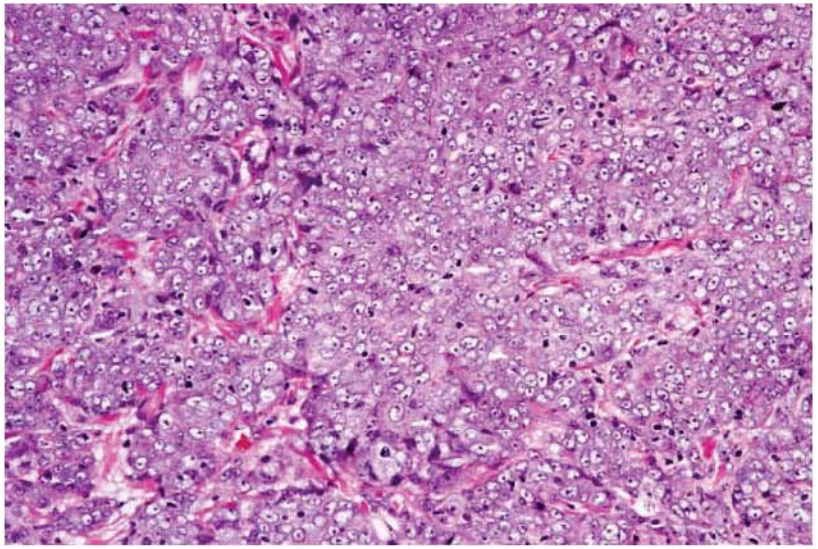
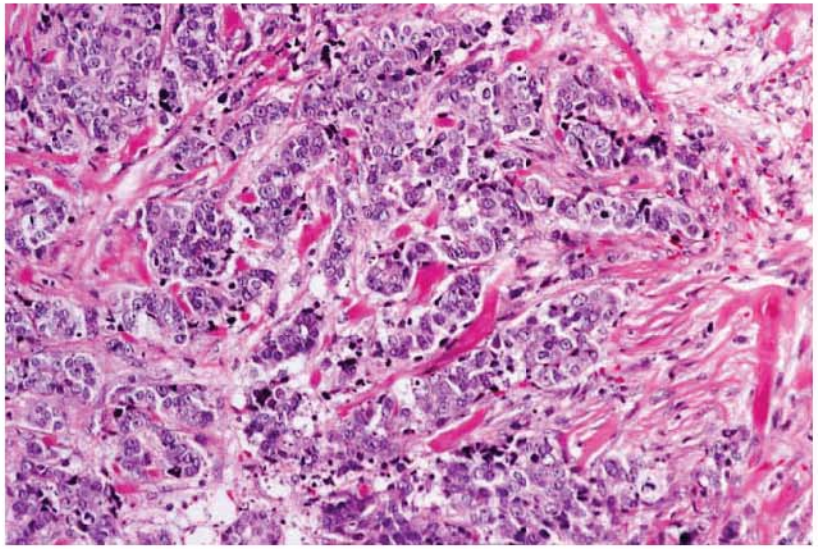
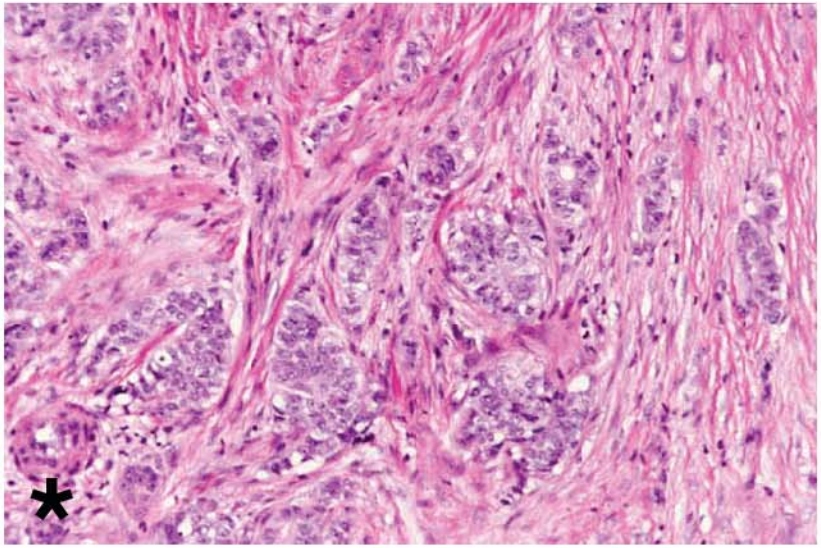


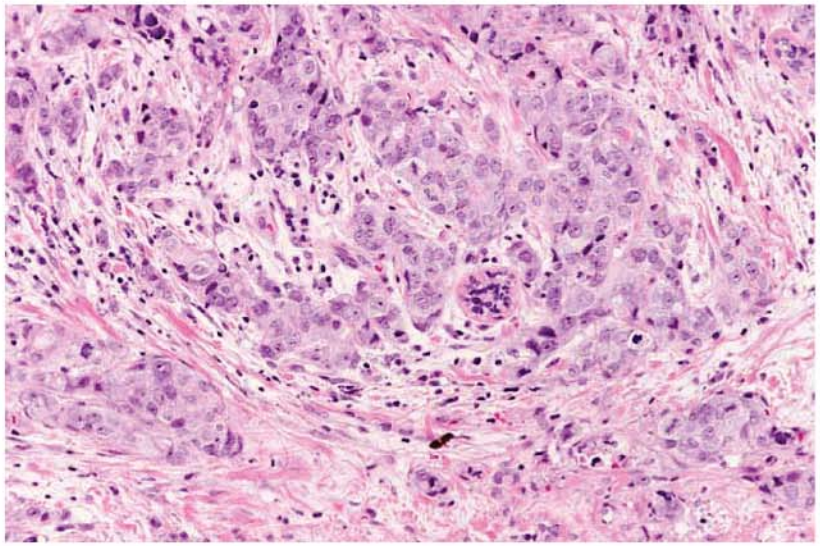
Died after 9 months



Alive and disease-free for 79 months

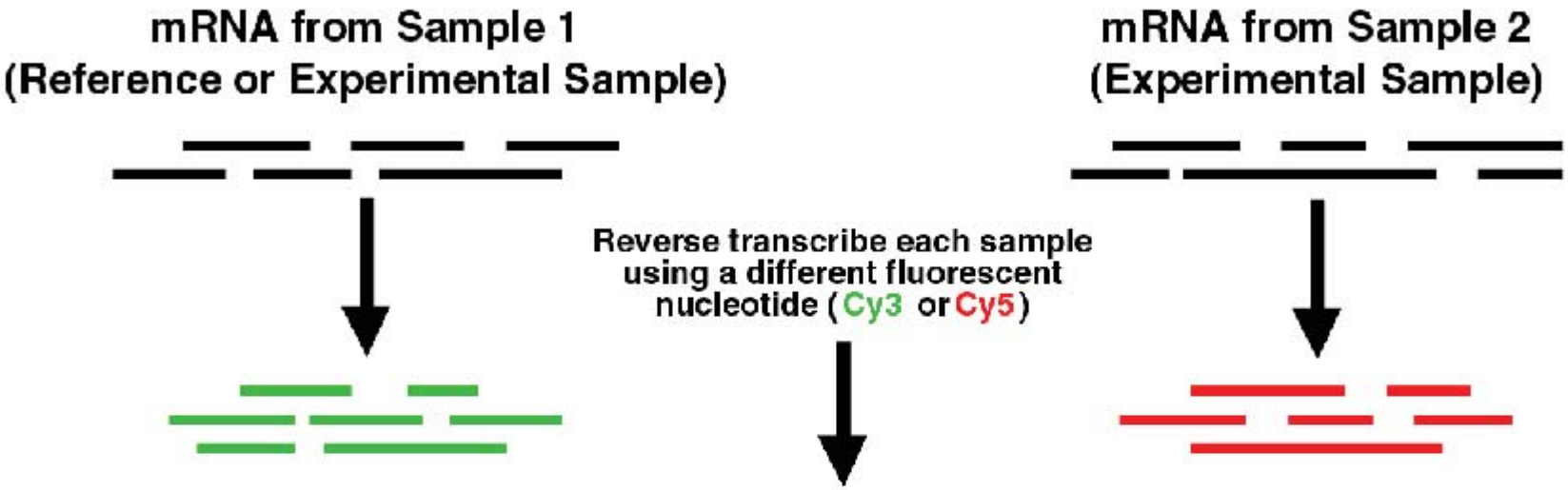


Died after 17 months

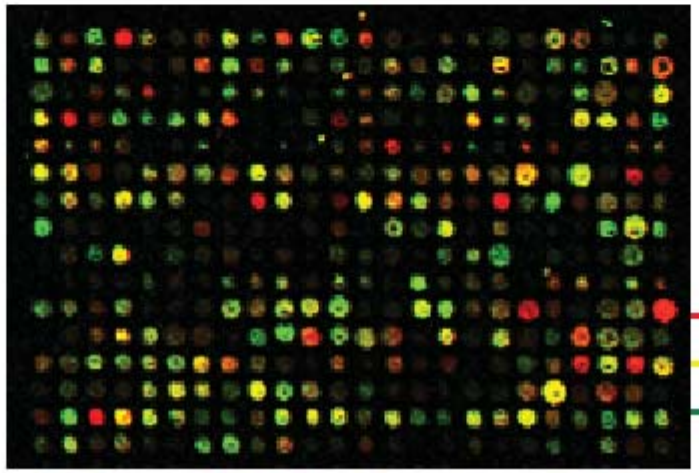


Alive for 95 months, with recurrance at 16 months

Two Color Fluorescent Hybridization for the Analysis of Gene Expression



Mix the complex probes together and hybridize overnight



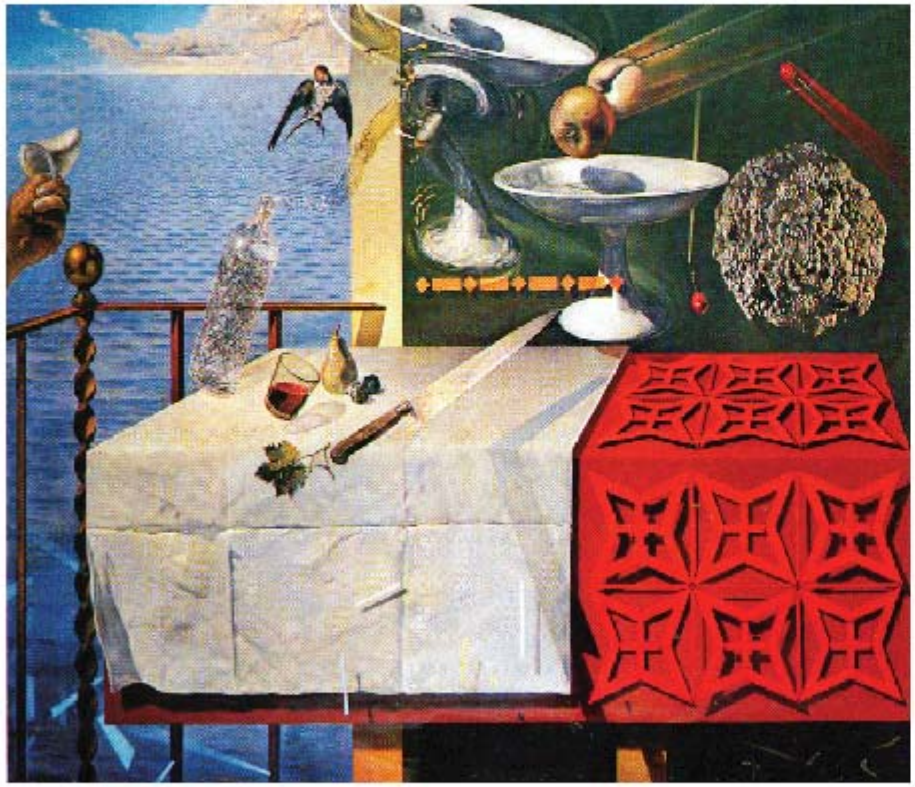
Cy3	Cy5	$\frac{Cy5}{Cy3}$	$\log_2\left(\frac{Cy5}{Cy3}\right)$
200	10000	50.00	5.64
4800	4800	1.00	0.00
9000	300	0.03	-4.91

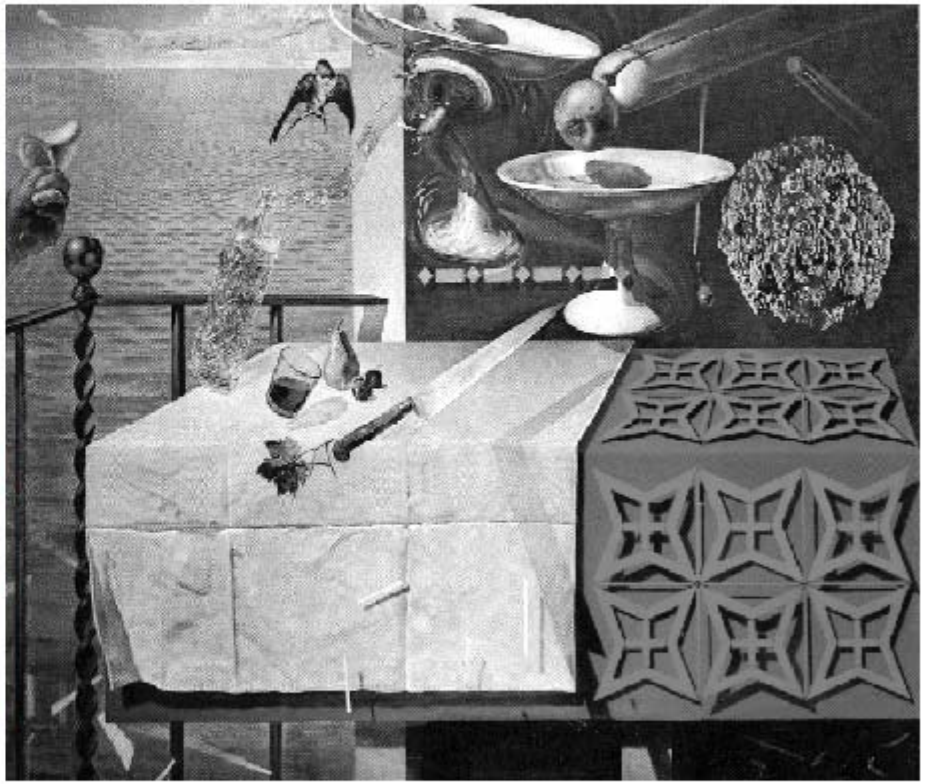
NAME	BC/FUM10	BC/FUM14	BC/FUM14	BC601B-A	BC601A-B	BC/FUM11	BC/FUM12	BC/FUM12	BC/FUM11	BC/FUM11	BC1028-B	BC/FUM12	BC/FUM13	BC/FUM13	BC/FUM11	BC/FUM11
adipose differentiation-related prote	0.242	1.21	-0.253	-0.841	-0.423	-0.363	-0.852	-1.383		-2.642	0.501	-0.25	-0.605	-0.636	0.229	-0.626
plasminogen activator, urokinase re	0.908	0.485	-0.397	-0.767	-0.886	-0.251	-0.683	0.057	-0.317	-1.2	0.125		-0.536	-0.248		-0.365
plasminogen activator, urokinase re	0.4635	0.3545	-0.8975	-1.23	-0.8335	0.0175	-1.002	0.1555	-0.4325	-1.008	-0.1785		-0.7445	-0.1485	0.0555	0.2055
coronin, actin binding protein, 1C A	0.551	0.151	-0.422	0.007	-0.638	0.087		-0.689	-0.91	-0.853	0.052	-0.492	-0.201	-0.152	-0.368	-0.741
** coatomer protein complex, subun	-1.061	-0.8655	-0.1235	-0.9895	0.3815	-0.4955	-0.2775	-0.1465	-1.109	-0.8635	0.2615	-0.0905	-0.3225	-0.6035	0.0195	-0.9345
coactosin-like protein R78490	-0.8835	-0.4545	0.2375	-1.177	0.2155	-0.2975	-0.9385	-0.2815	-1.494	-0.5985	0.4095	-0.3465	0.2185	-0.1345	-0.2895	-0.5525
folylpolyglutamate synthase R44864	0.686	1.583	1.313	0.048	-0.272	-0.143	-0.394	0.423	-0.445	-0.854	0.322	-0.03	-0.412	0.214	-1.098	-0.175
lysozyme (renal amyloidosis) N639	-0.18	1.155	1.575	-1.635	0.355	0.295	-0.805	0.135	-2.145	-0.955	0.575	0.735	-0.435	-0.855	-0.8	-1.705
chemokine (C-C motif) receptor 1 AA036881		0.524	1.233	-1.459	-0.095	-0.122	-0.196	0.101		-0.942	-0.2	-0.133	-0.549	-0.763		-0.059
interferon, gamma-inducible protein	-0.181	-0.062	0.37	0.064	0.418	-0.33	-0.098	-0.289	-1.042	-0.332	0.907	1.056	-0.8	-0.193	-0.789	-1.25
cystatin B (stefin B) H22919	-0.188	-0.489	-0.603	0.074	-0.212	-0.295	-0.54	-0.535	-0.453	-0.479	-0.021	0.291	-0.651	-0.536	-0.401	-0.511
cathepsin S AA236164	-0.791		0.334	-0.316	0.723	-0.46	0.39	-0.452		-0.413		1.063	-0.849	-1.088	-0.94	-1.291
small inducible cytokine A2 (monoc	0.2665	0.2955	0.5315	-0.1285	0.4255	-1.099	-0.7265	-0.6035	-1.052	-1.438	0.1355	0.0365	-0.4335	0.0875	-1.218	-0.7785
natural killer cell transcript 4 AA458	0.483	0.348	0.575	-0.685	0.971	-0.335	-0.222	-0.116	-1.644	-0.66	-0.322	0.885	-0.08	-0.02	-0.441	-0.51
superoxide dismutase 2, mitochond	0.431	0.301	-0.836	0.519		-0.492	-0.834	-0.86		0.781	0.005	-1.163	-1.283	-0.969		-0.586
superoxide dismutase 2, mitochondrial AA487		0.3185	-0.6835	0.4865	0.6925	-0.7895	-0.6005	-0.5815	0.4995	0.0165	0.3755	-0.1225	-1.129	-1.137		-0.6935
transforming growth factor, beta-ind	0.0235	0.6525	-0.3785	-0.5505	-0.3675	-0.4755	-0.1105	0.3435	0.0785	-0.4735	0.7925	1.532	-0.3355	-0.0885	0.2495	-0.1985
glycine dehydrogenase (decarboxy	-1.122	-1.412	-1.275	-1.764	-0.611	1.259	-1.25	-0.76	-2.159	-1.72	-1.017	-0.972	-0.715	-0.543	-0.658	-0.818
syndecan 2 (heparan sulfate proteo	-1.828	-1.7	-1.409	-1.964	-0.975	1.516	-1.24	-1.75	-2.219	-2.477	-1.08	0.29	-1.641	-2.045	-0.315	-1.356
glutathione S-transferase pi R3364	-1.726	-1.892	-1.568			1.528	-1.346	-2.157	-3.114	-3.146	-0.943	0.236	-1.349	-1.674	-0.416	-1.557
chitinase 3-like 2 AA668821				-0.771	-1.436	-1.454	-0.813	-1.578	0.312	-0.167	0	-0.469	0.129	-0.566		-0.489
nuclear factor I/B W87528	0.464	-1.314	-0.187	-1.429	-0.189	0.551	-1.94	-1.372		-2.152	-1.825		-0.441	-0.928	0.316	-1.188
ras homolog gene family, member	-1.382	-0.471	-0.421	0.304	-0.448	-0.805	-0.945	-0.737	-1.222	-0.915	-0.713	-0.167	0.09	1.074		-0.393
ras homolog gene family, member	-1.311	-0.763	-0.61	0.198		-0.764	-0.391	-0.867	-1.469	-1.106	-0.486	-0.778	-0.579	0.812	0.348	-0.222
** zinc finger, DHHC domain containing 5 AA4		-0.965	-0.571	-0.304	-0.328	-0.417	-0.518	-0.473	-0.973	-0.94	-0.926	-1.153	-0.462	-0.683	0.828	0.347
keratin 5 (epidermolysis bullosa sim	-0.309	-0.485	-0.748	-0.909	-0.403	-0.127	-0.371	-0.778	-1.596	-1.787	-0.782	0.242	-0.559	-0.804	0.79	0.374
keratin 5 (epidermolysis bullosa simplex, Dowl		-0.655	-2.421	0.301	0.689	-0.38	-0.131	-1.647		-1.396	0.248	-1.118	-0.389	-1.423	1.963	-0.068
keratin 17 AA026100		-0.593	-2.294	0.181	-0.45	0.457	-1.132	-0.754		-2.708	-0.641	-0.148	-0.201	0.161	2.264	1.758
tripartite motif-containing 29 AA055	-0.523	-0.763		-0.726	-0.155	-0.401		-1.8	-1.591	-1.789	-1.076	-0.929	-1.132	-1.051		-0.24
pleiomorphic adenoma gene-like 1 AA463204	-0.7035	-0.5595	-0.7765	-0.2835			-0.1885		-1.466	-2.035	-0.1475	-0.7075	-0.4025	-1.054	0.3535	-0.5835
secreted frizzled-related protein 1 AA002080	-1.951	-2.022	-1.982	0.069	-0.117	-1.543	-2.996			-2.657	-0.275	-1.187	-0.262	-0.688	3.135	0.295
Homo sapiens cDNA FLJ11796 is, clone HEM	-1.425		-0.74	-0.798	0.243	-0.225	-0.061			-0.957	-0.001		-0.491	-0.28	0.595	-0.721
ESTs AA074677		-0.411	-0.412	-0.879	-0.78	-0.401	-0.135	-0.508		-2.237	0.077		-0.72	-1.057		-1.301
pellino homolog 1 (Drosophila) W8	-0.3805	-1.159	-0.6945	-0.3935	-0.1785	-0.3665	-0.3835	-0.2825	0.1245	0.3185	0.2735	-1.329	-0.9455	-1.313		-0.4235
matrix metalloproteinase 7 (matrilys	-0.887			-2.32	0.16	-1.65		-1.54		-1.065	1.453		-1.55	-2.859		-0.04
moesin R22977	0.452	-0.759	-0.433	-0.691	0.148	-0.538	-0.28	-0.478	-0.477	0.019	0.062		-0.001	0.259	-0.24	-0.314
prion protein (p27-30) (Creutzfeld-	-0.8095	-1.302	-0.5695	-1.843	-0.8365	-0.3325	-0.7305	0.2015	-0.3825	-0.2335	-0.4605	-1.181	-0.6875	-0.3315	0.2825	-0.0605
chitinase 3-like 1 (cartilage glycoprotein-39) A		1.474	1.071	0.678	0.987	-1.357		-2.185		-1.619	3.517	-0.465	-1.549	-1.699		-1.262
annexin A8 AA235002		-0.55		-0.832	0.209	0	-0.576	-0.199		-1.046	-0.454	-0.221	0.134	-0.015	0.619	0.519
hypothetical protein FLJ20481 N32	-0.078	-0.939	-1.002	0.058	-0.058	-0.158	-1.65	-0.794		-1.612	0.17	1.318	0.404	-0.312		-0.039
ADP-ribosylation factor-like 7 N353	-0.9415	-0.0585	-0.3685	-0.9365	-0.2155	0.0715	-0.2825	-0.5505		-1.107	-0.5855	0.2285	-0.2475	0.1635		-0.1405
cystatin A (stefin A) W72207		-0.532	-0.941	0.909	1.783	0.164	-0.106	-0.577		-1.496	0.588	3.351	-0.73			-0.855
inhibitor of DNA binding 3, dominan	-0.46	-0.587	-0.421	-0.358	0.326		0.638		-0.642		-0.224	-0.143	-0.445	-0.58	0.377	
complement component 1, r subcor	0.116		0.475	-1.506	0.089	-0.624	0.876	-1.115		-1.773	-0.505	-0.276	-0.204	-1.308	0.584	-0.431
nicotinamide N-methyltransferase T	0.675	-0.083	0.035	-0.244	0.053	-0.021	-0.365	-1.174	-1.235	-1.789	-0.688	0.972	-0.261	-0.532	0.606	0
myosin IE AA029956	-0.6075		-0.5465	-0.8195	-0.3755	-0.3535	-0.5545	-0.6505		-1.089	0.0005	-0.0205	0.1535	-0.1775		-0.0005
major histocompatibility complex, cl	-0.494	-0.582	-1.091	-0.32	0.305	-0.098	-0.085	0.262	-1.668	-1.457	-0.039	-0.362	-0.218	-0.838	-0.197	-0.537
fatty acid binding protein 7, brain W72051			-1.595	-2.086	-1.717	-0.387	-2.433	-0.184			-1.441		-0.603	0.446		0.728
kynureninase (L-kynurenine hydrolase) H87 47	-0.342	-0.591	1.233	0.358	-0.954	-1.687	-1.194	-1.515		-2.291	-0.158	0.075	-0.657	-1.675	-0.58	-1.138
cytochrome P450, subfamily I (diox	1.065	-0.579	0	-0.767	0.392	-0.386	-0.479	-0.752	-0.401	-0.549	0.165	0.11	-0.605	-0.779	0.499	-0.131
cytochrome P450, subfamily I (diox	2.202	-0.047	-0.231	-0.604	-0.234	-0.713	-0.836	-1.99	-1.558	-1.474	0.425	0.622	-0.872	-1.706		-0.579
S100 calcium binding protein A8 (c	-1.641	0.014	-1.05	4.29	-0.162	-0.899	-1.625	-1.818		-2.268	-1.165	-1.2	-1.797	-1.329		-1.087
signal transducer and activator of transcription	-0.2855	-0.6135	2.59	-0.0565	-0.4895	-0.3215	-1.224	-1.718		-1.387	-0.4765	-0.7565	-1.143	-0.8755		-0.9545
gamma-aminobutyric acid (GABA) A receptor	3.044		-1.498	0.076	0.153	-0.766	-0.789			-1.485	-0.69		-0.823	-0.104		-0.235
Eph B6 AA609284			0.6365	-1.062	-0.5295	-0.1345		-0.6965				-0.0415	-0.0885	0.0535		-0.3235
secretory leukocyte protease inhibi	-2.088	-1.806	-1.596	0.434	-1.378	-1.269	-0.849	-1.961	-2.645	-3.187	-1.637		-0.996	-1.568	0.538	-1.344
aldo-keto reductase family 1, member C1 (dih	0.83	0.835	-0.435	1.743	1.173	-0.558	-1.21			-1.547		-0.834	0.712	0.104		-0.296
latrophilin W74533	-1.28	0.216	-0.322	-0.467	-0.563	0.111	0.383	-0.648	-0.95	-1.333	-0.903		0.469	0		0.274
echinoderm microtubule associated	-0.0045	-0.1755	-0.1055	0.1595	-0.2585	-0.5155	-1.05	-0.3895	-0.1395	-0.8335	-0.0445	-0.4845	0.0045	-0.7135	0.1435	-0.2125
epidermal growth factor receptor (erythroblast	-0.676	-1.527	-0.203	-1.07	-1.157	-0.979	-1.085			-2.181	-1.547	-0.782	-0.768			0.432
ERO1-like (S. cerevisiae) AA186800	0.3395	0.4075	-0.6115	-0.3415		-0.4095	-0.8285	-0.4075	-0.4405	-0.4075	-1.335	-0.2325	-0.7075	-0.7125		-0.3035
** hypothetical protein FLJ20624 R5	-0.232	-0.341		-0.153	-0.446	0.838	-1.658	0.466	-0.553	-0.909	-0.159	-0.662	-0.334	0.371	-0.029	0.617
forkhead box D1 AA069132	-1.192	-0.07	-0.666	-0.596	0.02	0.388	-0.54	0.11		-1.016	-1.28	-1.077	-0.051	-0.477	-0.561	0.796
met proto-oncogene (hepatocyte growth factor receptor) AA410591				-1.151	-0.373	0.228		0.322		-0.654	-0.23	0.176	0.74	0.446		0.177
ESTs, Weakly similar to TRHY_HUMAN TRICH		-0.137	-0.378	-0.339	0.263	0.618	0.02	0.518		-1.656	1.242	0.885	0.19	0.389		-0.164
ESTs AA149250				1.847	-0.295	0.293		-0.215		-1.641	-0.868	-0.33	-0.395	0.21		-0.185
Homo sapiens mRNA; cDNA DKFZp564O2364	3.135	0.0215	0.3145	0.7915	-0.2245	1.343	-0.0505			-0.1155	1.125		-0.1125	-0.5255		-0.3445
hypothetical protein FLJ10337 AA1	-0.6325	0.8375	0.2155	-0.7935	-0.1815	-0.3315	-0.4795	-0.6435	-0.6095	-0.4435	0.2225	0.0585	-0.3355	0.2375		0.1205
integral membrane protein 3 AA034	-0.998	-0.313	0.52	-1.106	-0.005	-0.618	-0.901	-0.847	-2.533	-2.828	-1.247	-0.647	-1.005	-1.651	-0.119	-0.465

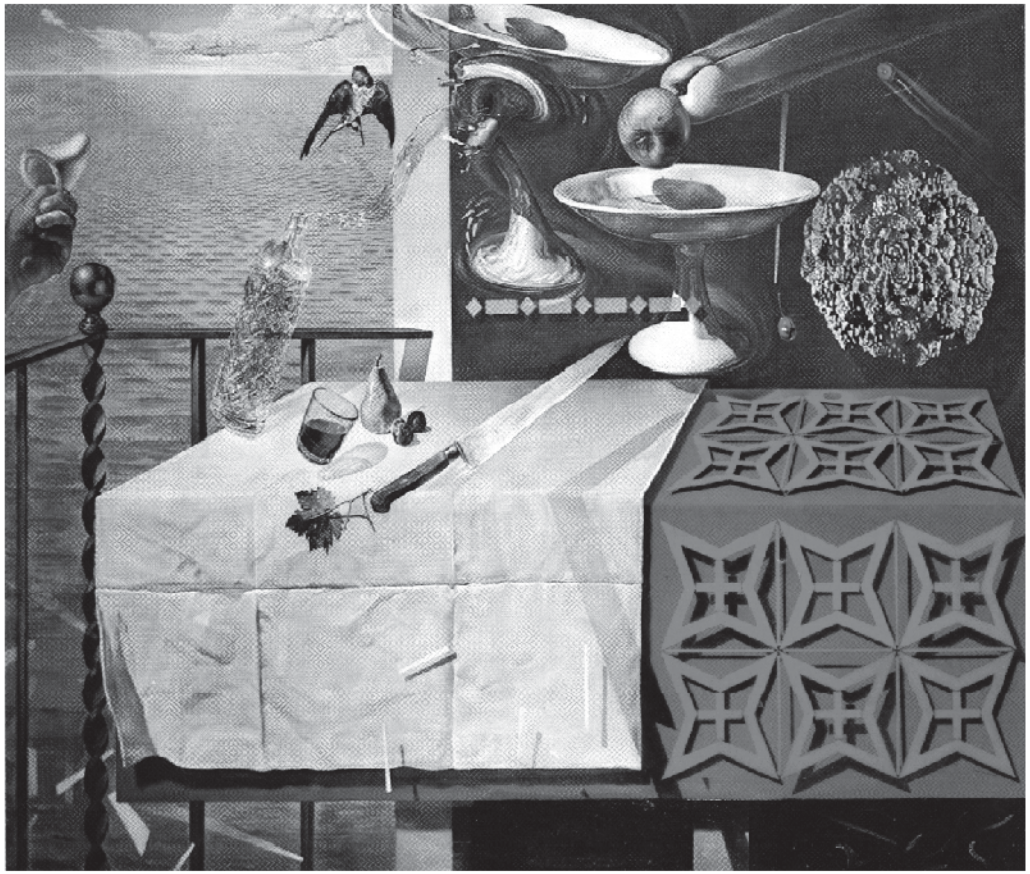
Cluster analysis and display of genome-wide expression patterns

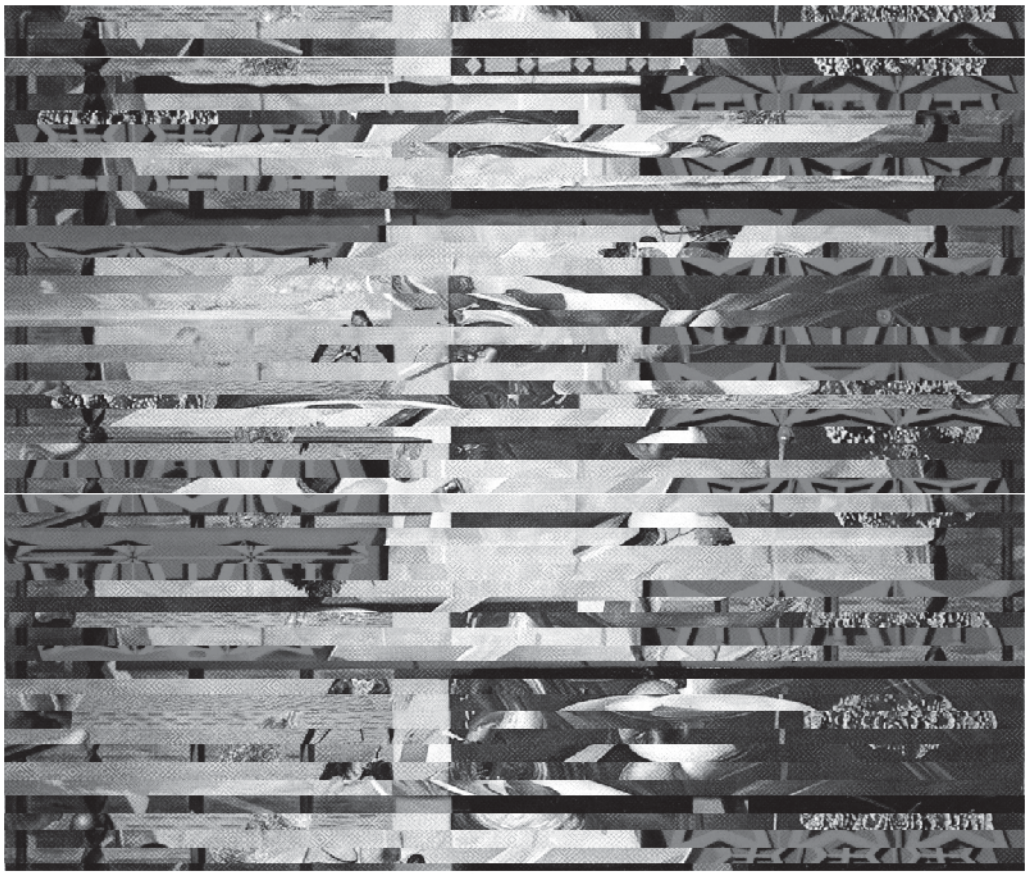
MICHAEL B. EISEN, PAUL T. SPELLMAN, PATRICK O. BROWN, AND DAVID BOTSTEIN

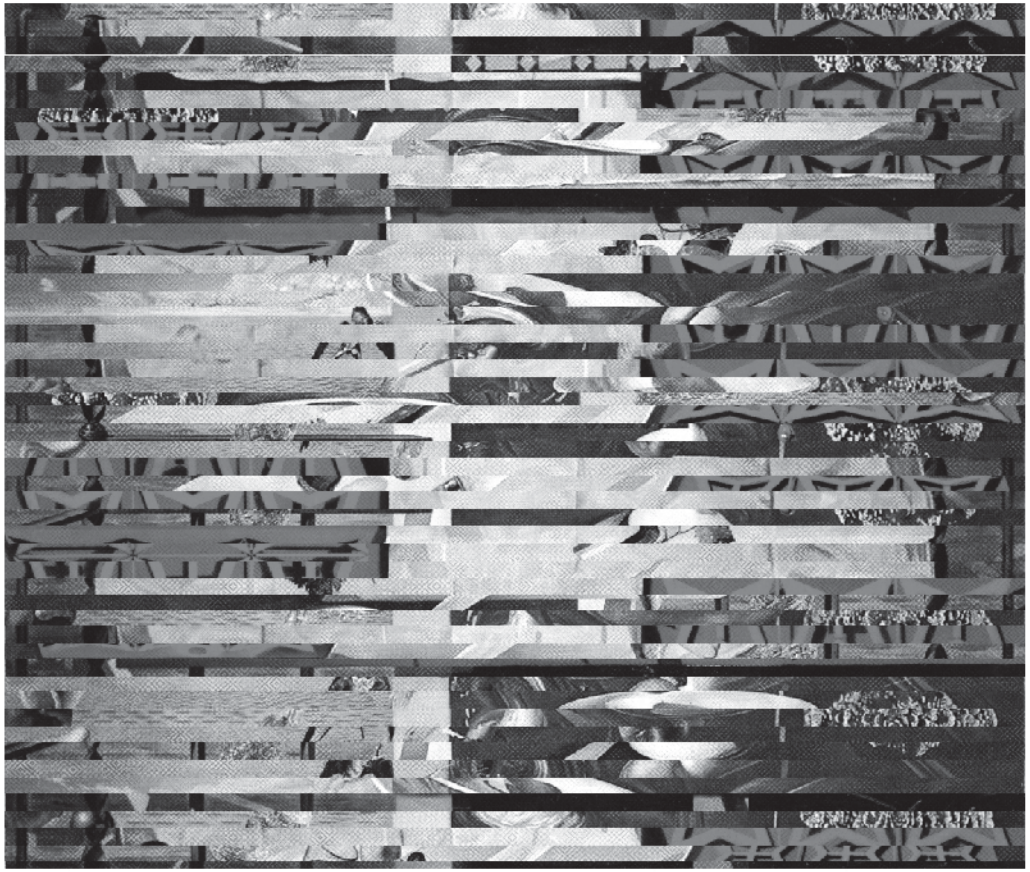
Proc.Natl. Acad.Sci.USA Vol. 95, pp. 14863-14868, December 1998

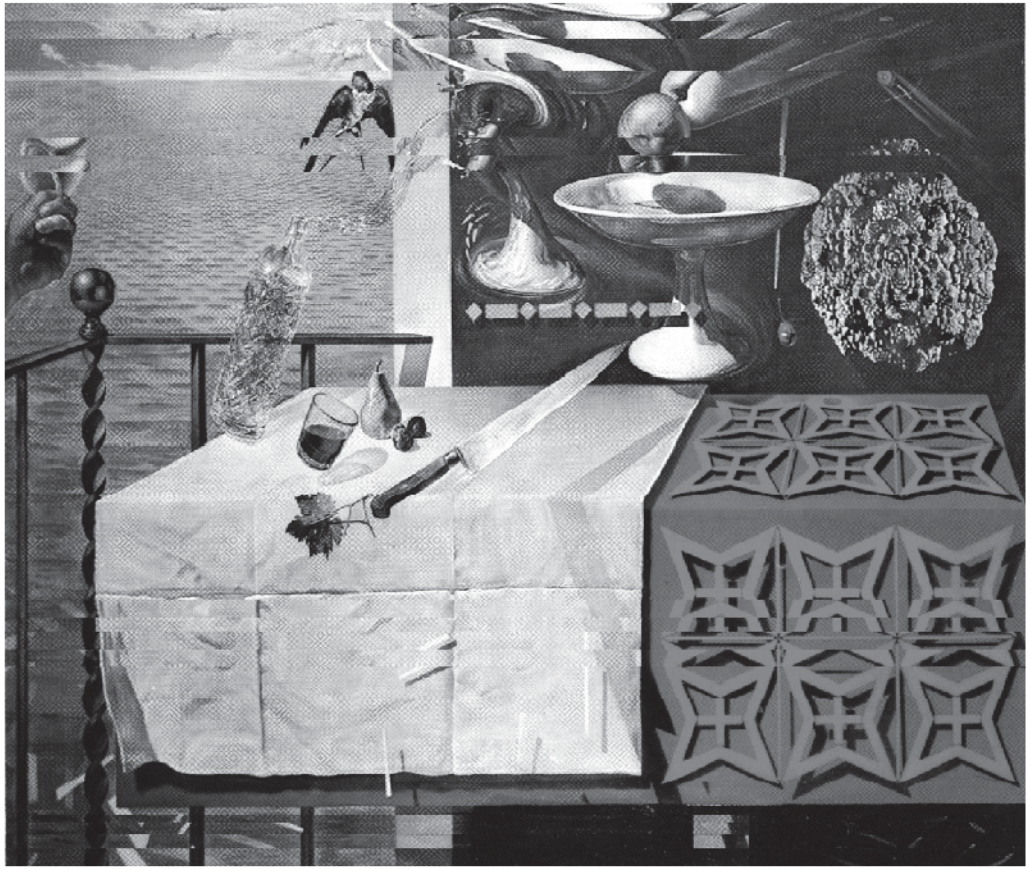








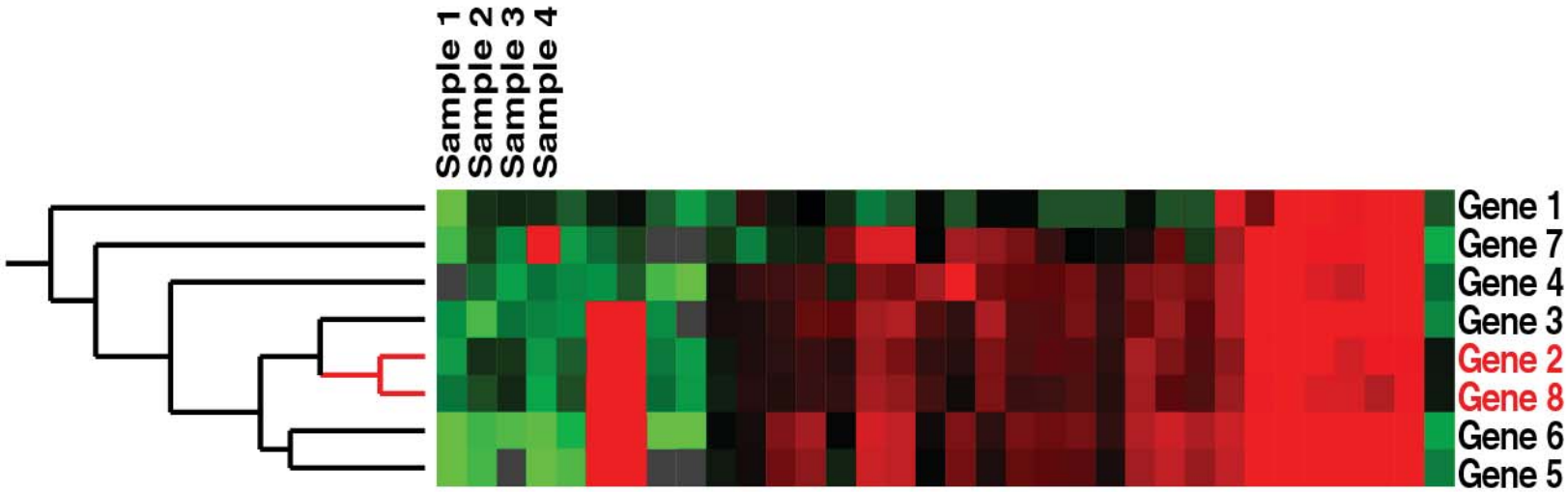




Cluster analysis and display of genome-wide expression patterns

MICHAEL B. EISEN, PAUL T. SPELLMAN, PATRICK O. BROWN, AND DAVID BOTSTEIN

Proc. Natl. Acad. Sci. USA Vol. 95, pp. 14863-14868, December 1998



= above average

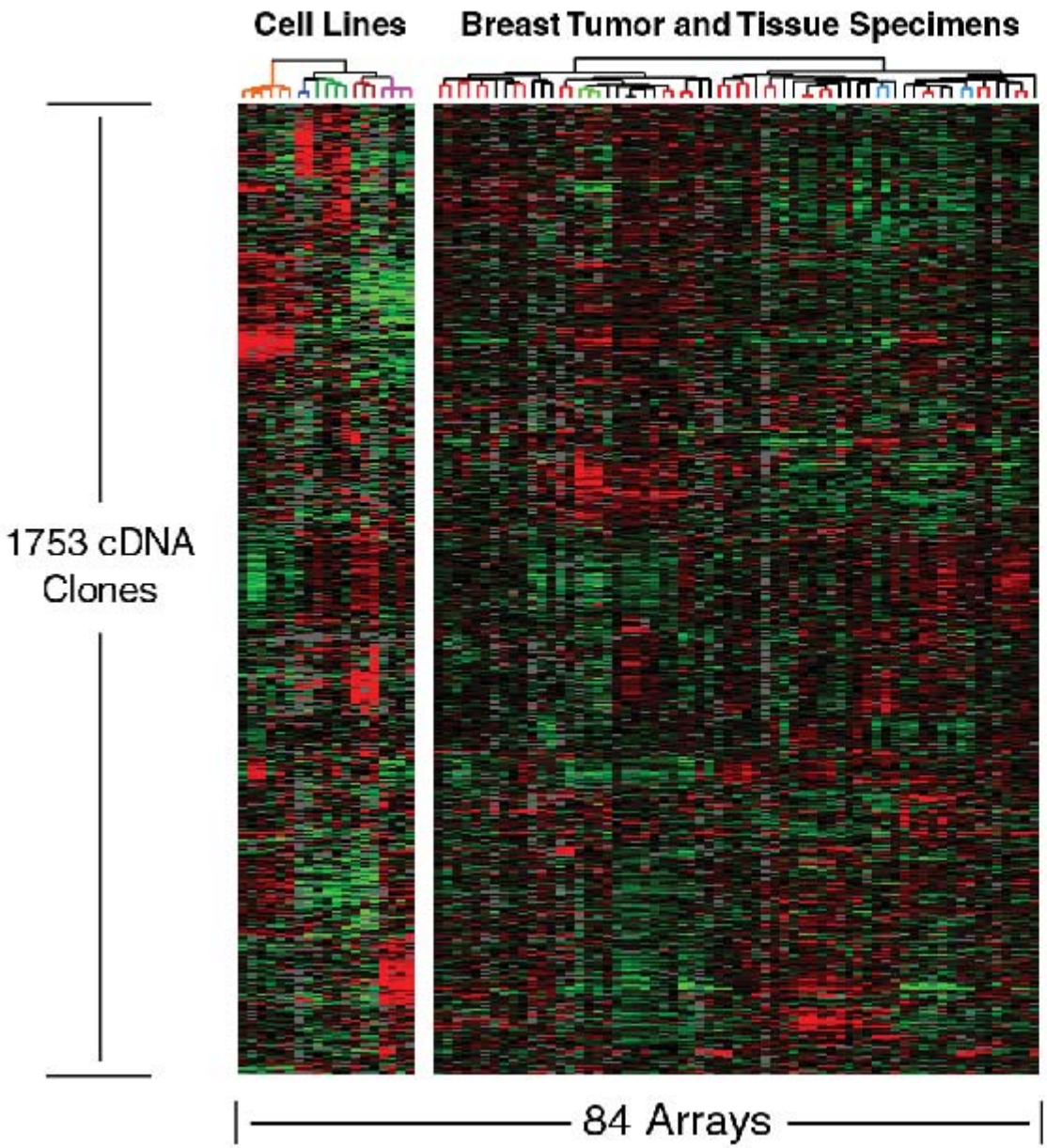
= average

= below average

= not determined

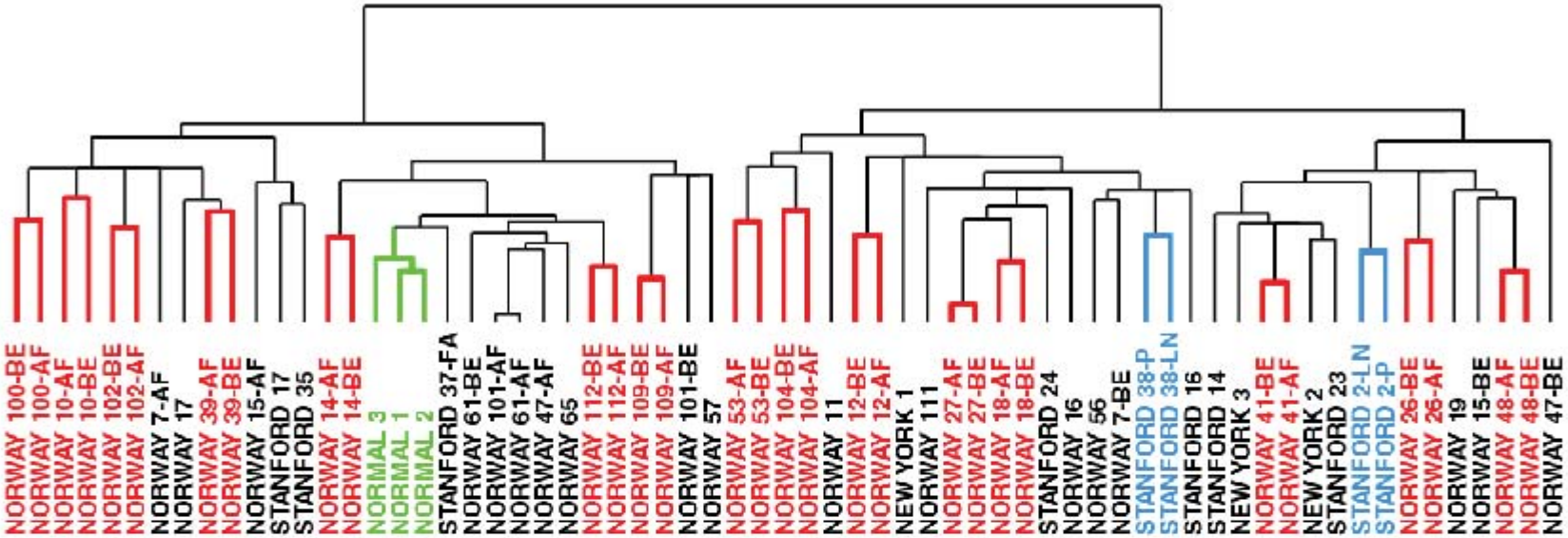
"Molecular Portraits of Human Breast Tumors"

Perou et al. Nature, vol 406, 747-52 (2000).



40 tumors total

- 18 single specimens
- 2 tumor/lymph node metastasis pairs
- 20 "before" and "after" doxorubicin pairs
- 3 normal breast samples
- 1 fibroadenoma
- 17 different cell lines



22 tumor pairs tested (20 "before and after" doxorubicin pairs)

A. 15/20 "before and after" pairs were on the same terminal dendrogram branch

B. 2/2 tumor/lymph node metastasis pairs were on the same dendrogram branch

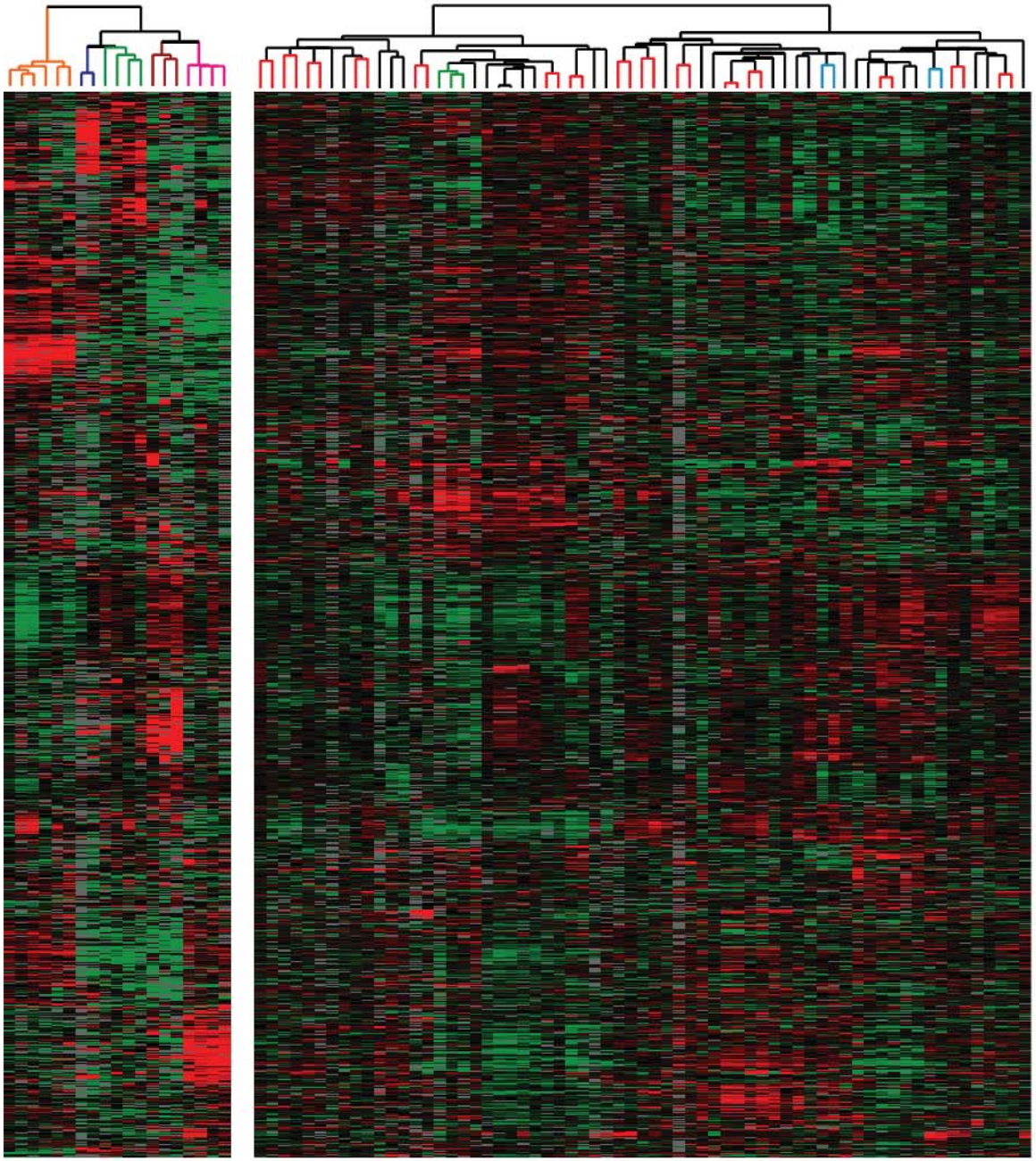
C. 3/20 "before and after" pairs had the "after" sample in the normal breast branch

D. 2/20 "before and after" pairs were not grouped together

E. 3/3 normal breast samples were on the same dendrogram branch

44 "before and after" pairs now completed, with 33 paired using 1753 clone list

Before and after clinical studies done by Per Eystein Lønning, Haukeland University Hospital (Bergen, Norway)

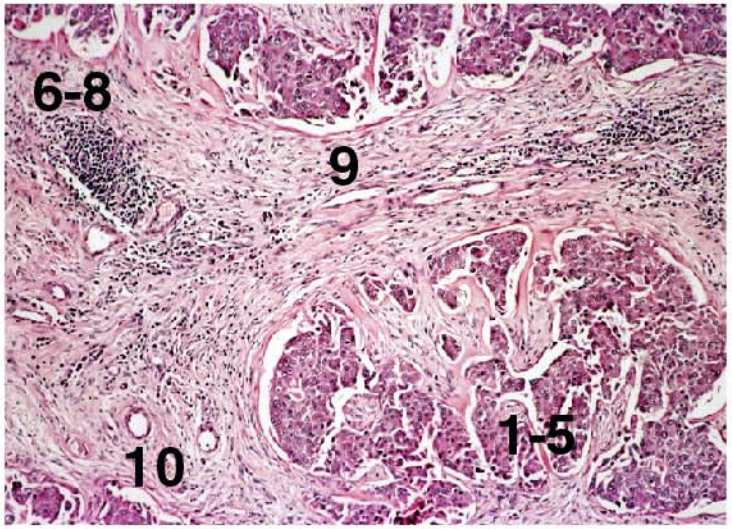


Epithelial Cell Clusters

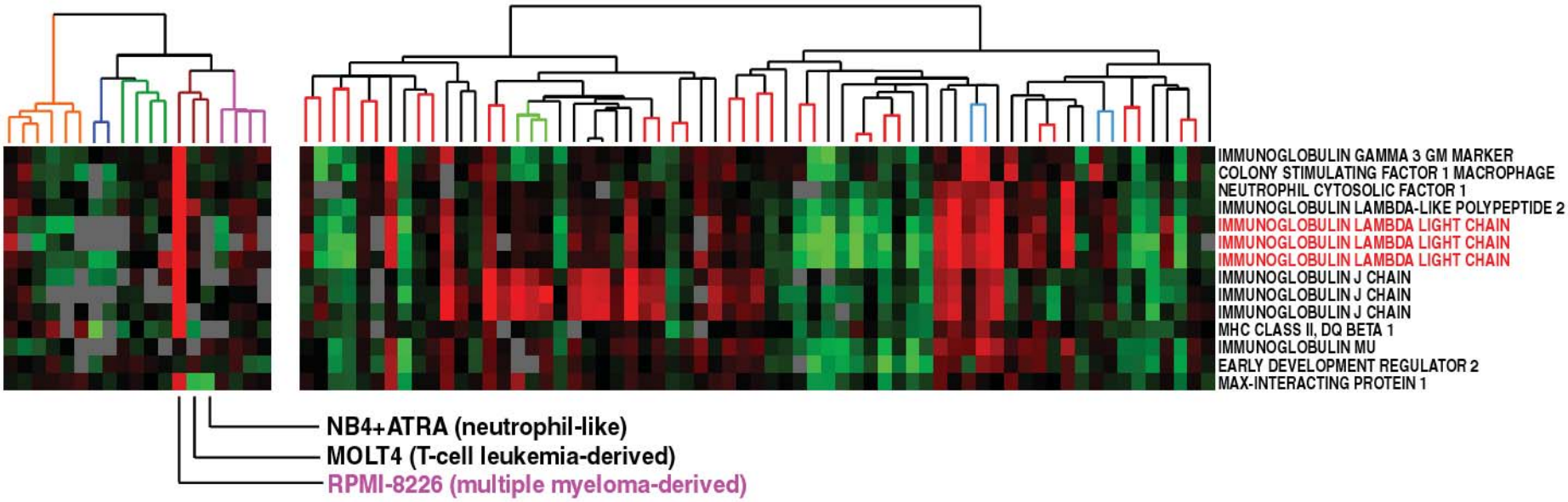
1. Basal Epithelial
2. Luminal Epithelial
3. Proliferation
4. HER2/ERBB2
5. Interferon/STAT1

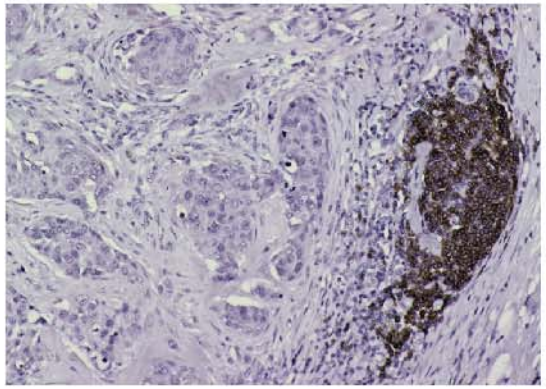
Other Cell Types

6. B-cell
7. T-cell
8. Macrophage
9. Fibroblast
10. Endothelial
11. Adipose

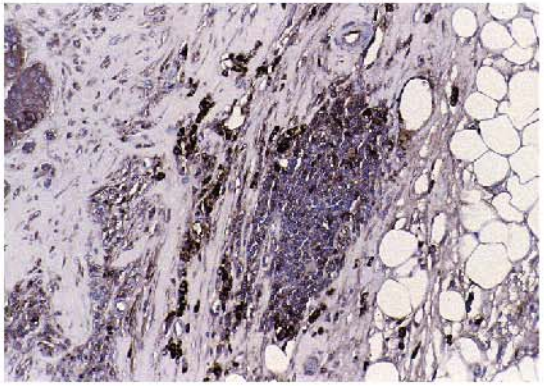


B-cells



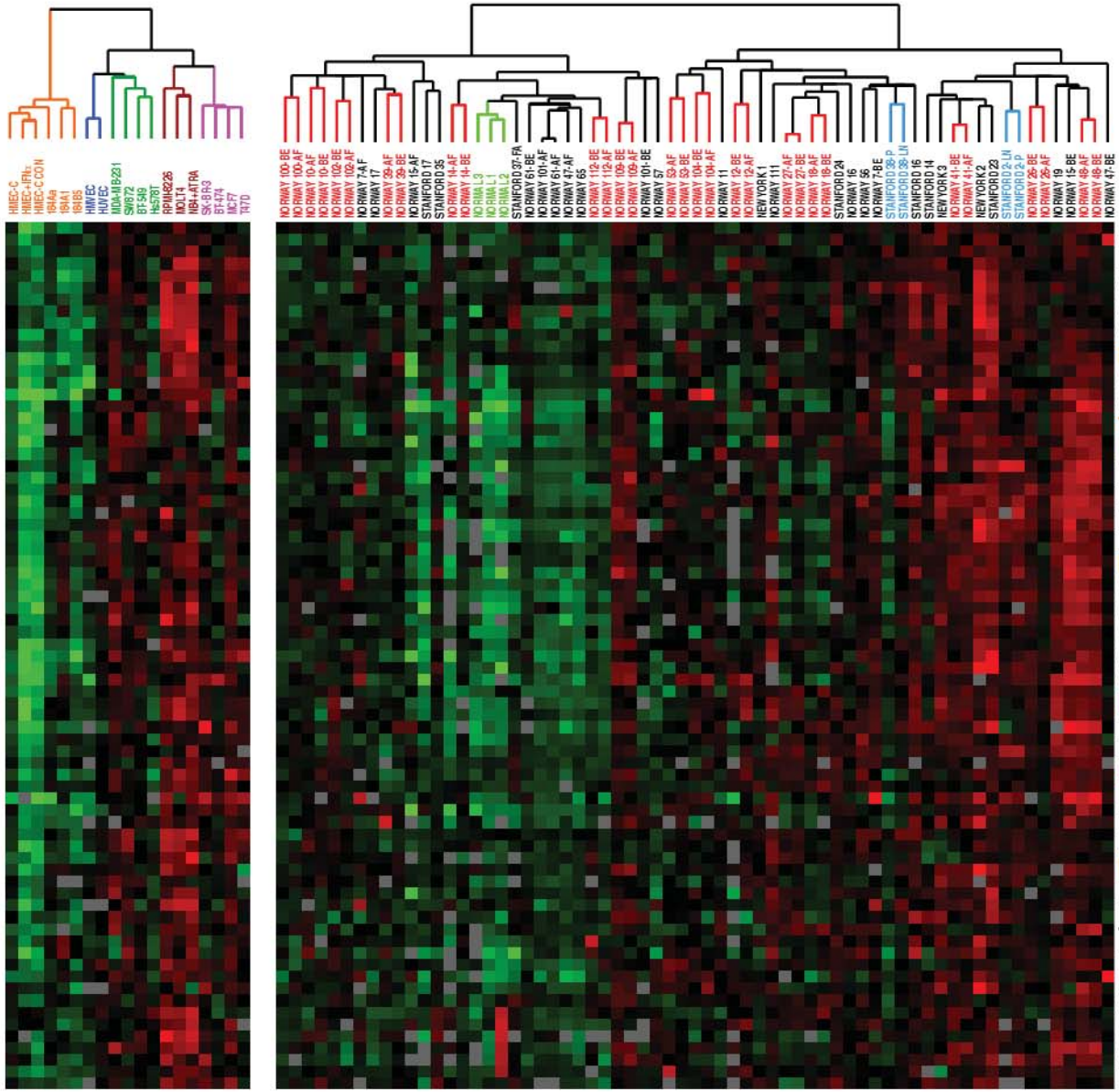


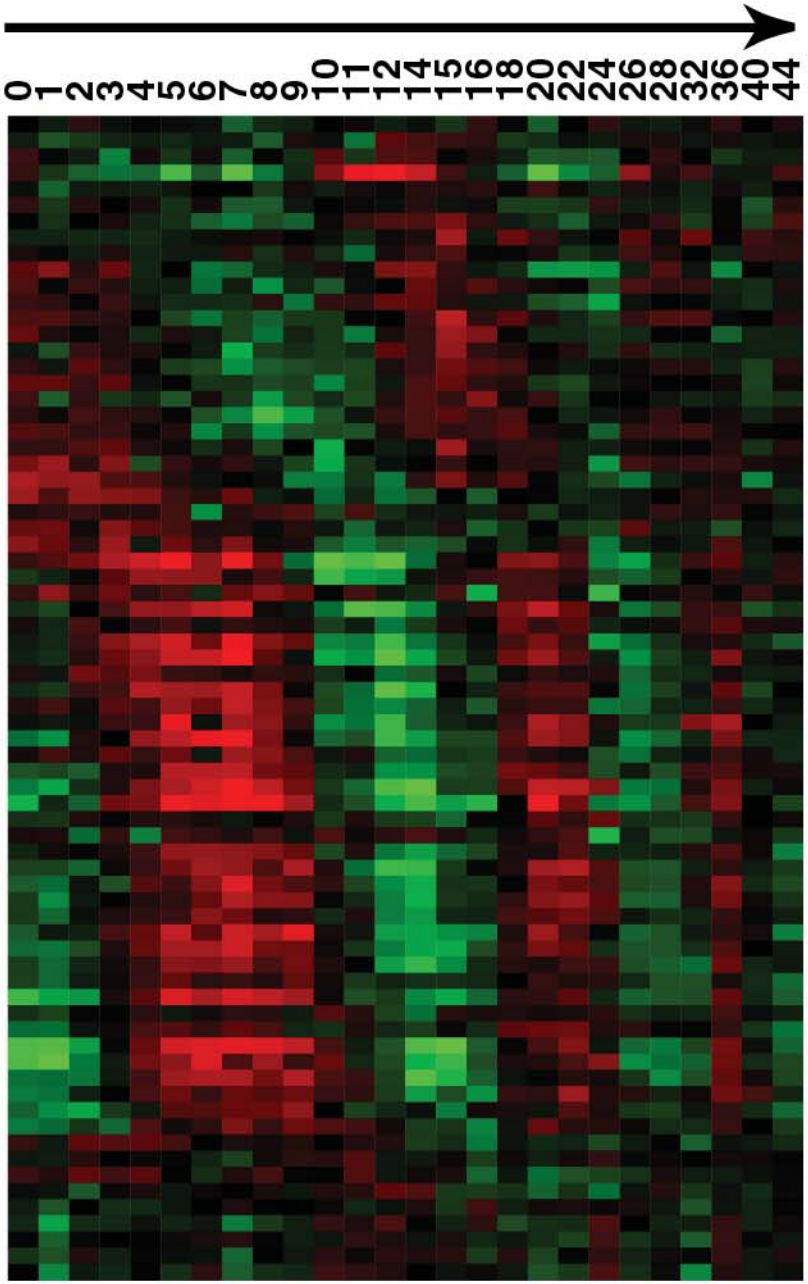
Stanford 2 with CD20



Stanford 2 with lambda light chain

Proliferation Cluster





S-Phase Genes

CCNE1 cyclin E1
MCM6 minichromosome maintenance deficient 6
E2F1 E2F transcription factor 1
MCM3 minichromosome maintenance deficient 3
PCNA proliferating cell nuclear antigen
POLE polymerase DNA directed, epsilon
RFC4 replication factor C activator 1 4

G2-M Genes

CDC2 cell division cycle 2
KNSL2 kinesin-like 2
TOP2A topoisomerase DNA II alpha
MAD2L1 MAD2 mitotic arrest deficient
KNSL5 mitotic kinesin-like protein 5
CCNA2 cyclin A2
FOXM1 forkhead box M1
CENPE centromere protein E
STK15 serine/threonine kinase 15
CHEK1 CHK1 checkpoint
CDC25B cell division cycle 25B
CKS2 CDC28 protein kinase 2
BUB1 budding uninhibited by benzimidazoles 1
CENPF centromere protein F
PLK polo Drosophia-like kinase
CDC20 cell division cycle 20

Hela cell cycle time course using the breast tumor proliferation cluster genes

M. Whitfield et al. Molecular Biology of the Cell, In Press

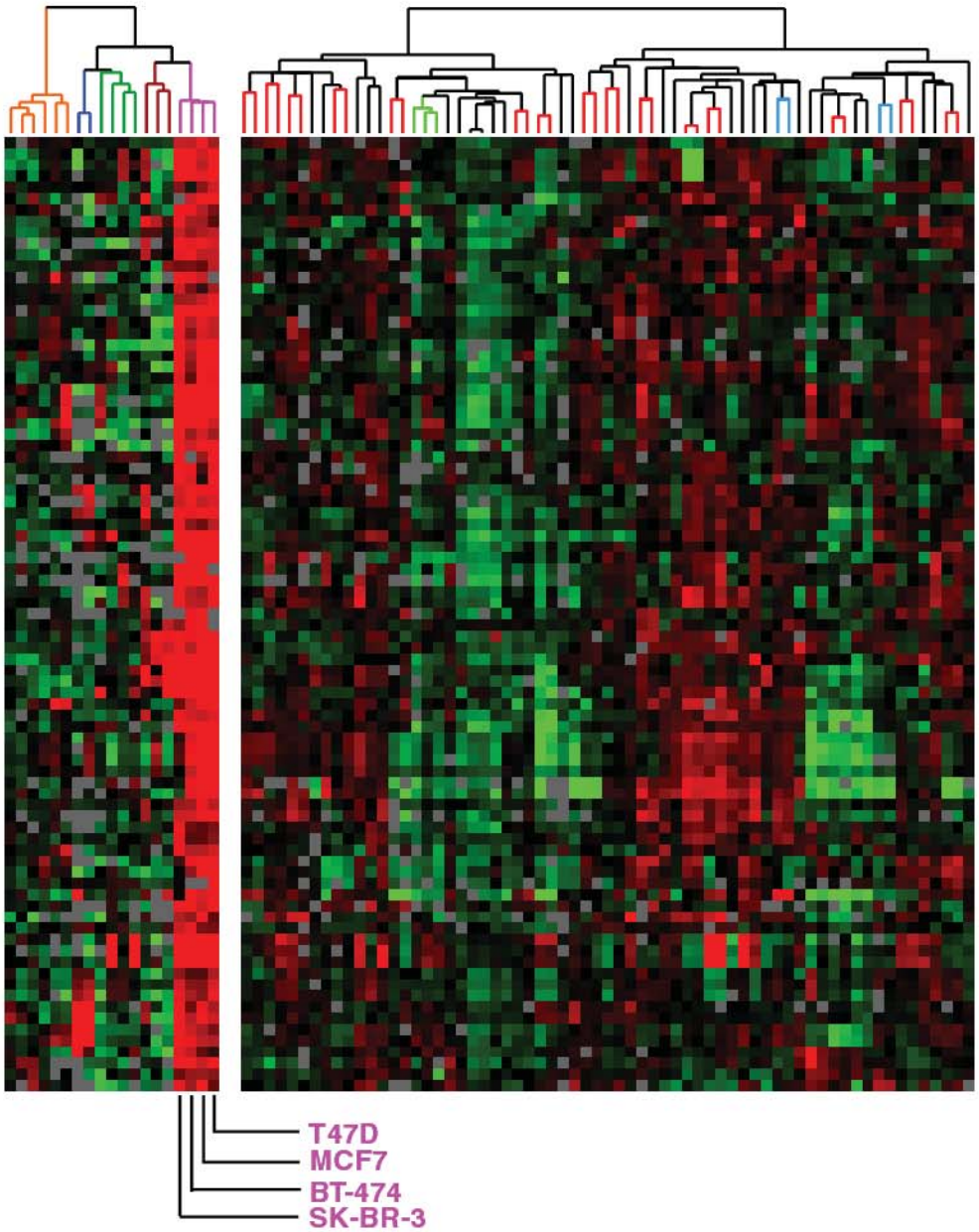
Keratin Immunostaining Profiles of Normal Breast

Basal

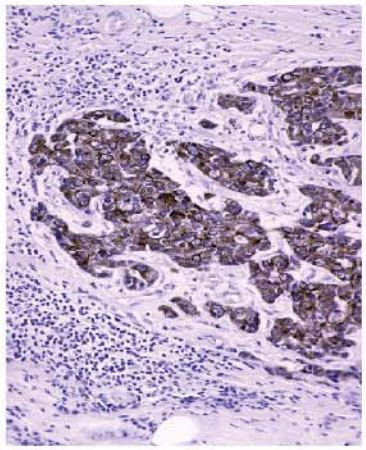
Keratin 5

Luminal

Keratin 8/18



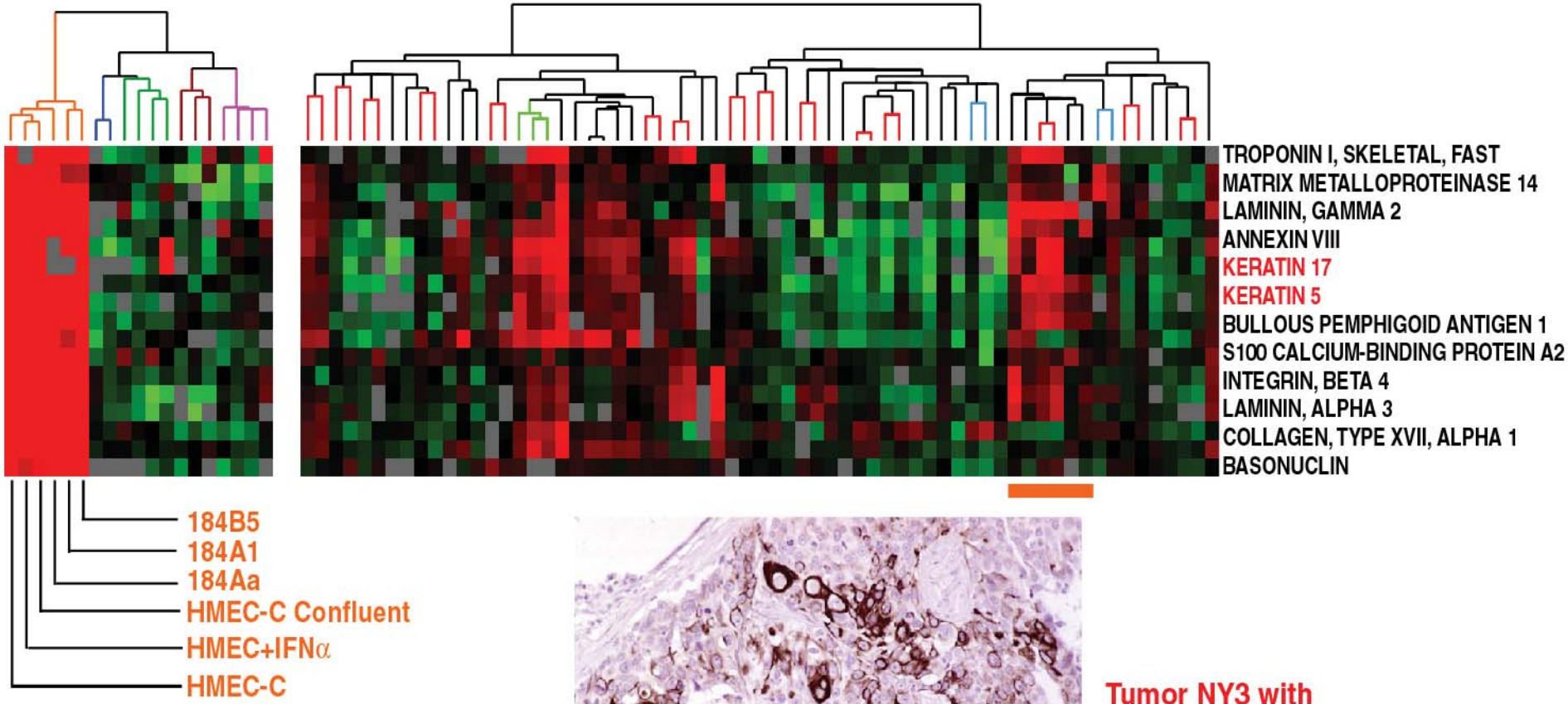
Tumor 16 with
Keratin 8/18

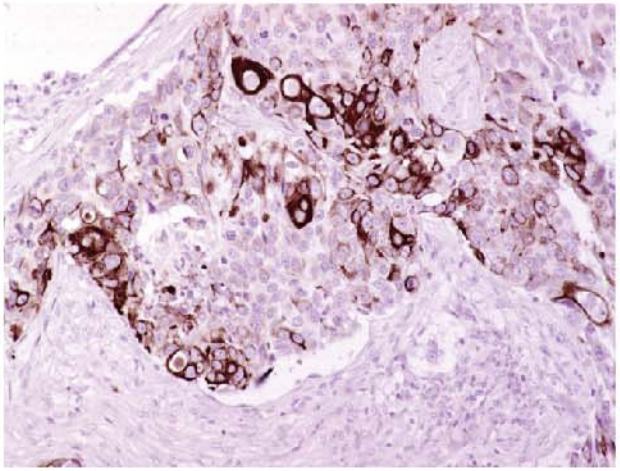


XMP
EPITHELIAL MEMBRANE PROTEIN 2
KERATIN 8
KERATIN 18
EPITHELIAL-SPECIFIC TRANSCRIPTION FACTOR ESE-1B
TRANSFORMING GROWTH FACTOR BETA 3
PROLACTIN RECEPTOR
X-BOX BINDING PROTEIN 1
HEPATOCYTE NUCLEAR FACTOR 3, ALPHA
GATA-BINDING PROTEIN 3
ESTROGEN RECEPTOR 1
ANNEXIN XXXI
CELLULAR RETINOIC ACID-BINDING PROTEIN 2
IGFBP5
RAS HOMOLOG GENE FAMILY, MEMBER B
CYTOCHROME P450, SUBFAMILY IIJ

Luminal Epithelial Cells

Basal Epithelial Cells





Tumor NY3 with Keratin 5

"Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications"

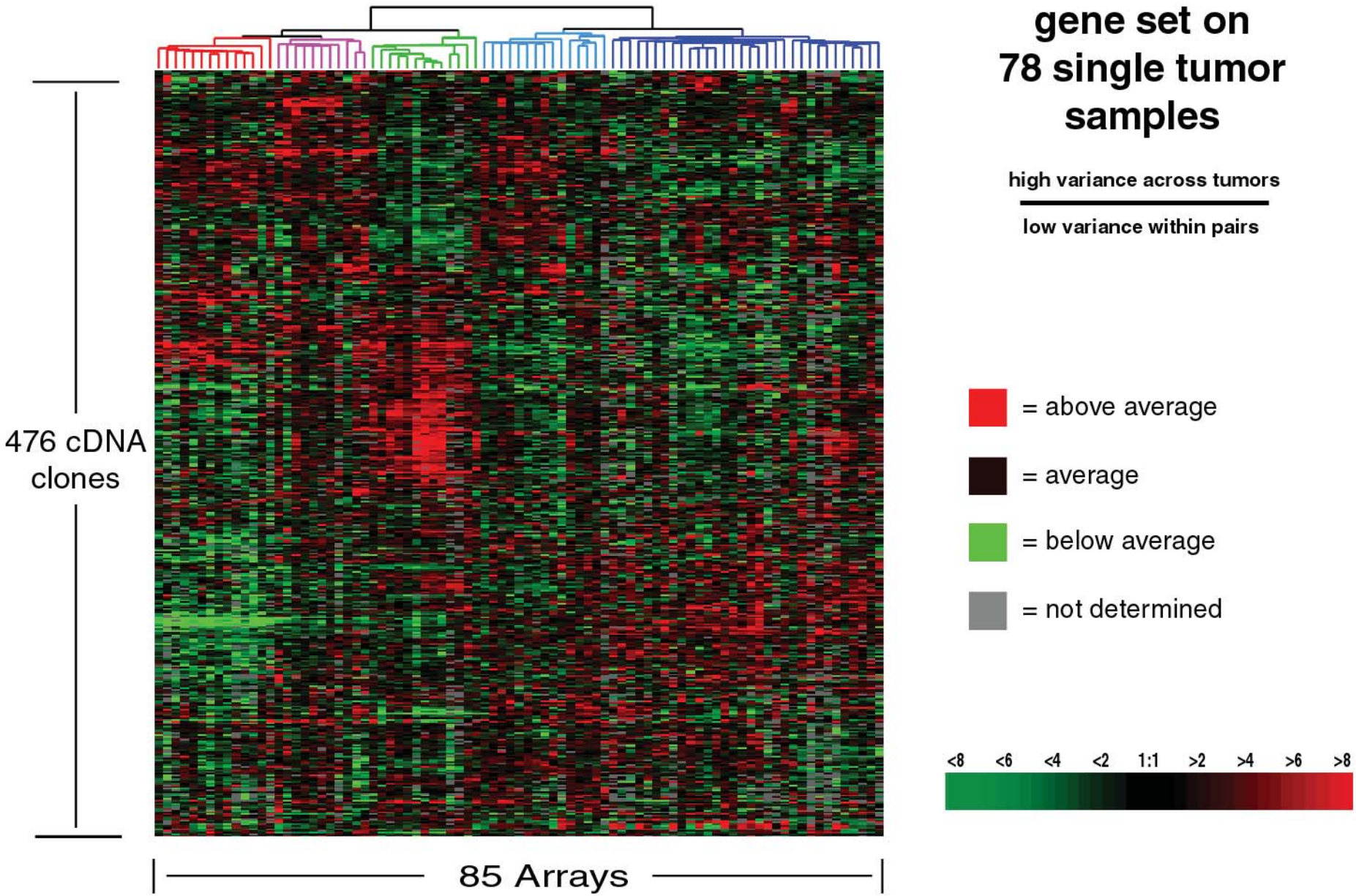
Sørlie et al., Proc. Natl. Acad. Sci. 19, 10869-10874 (2001)

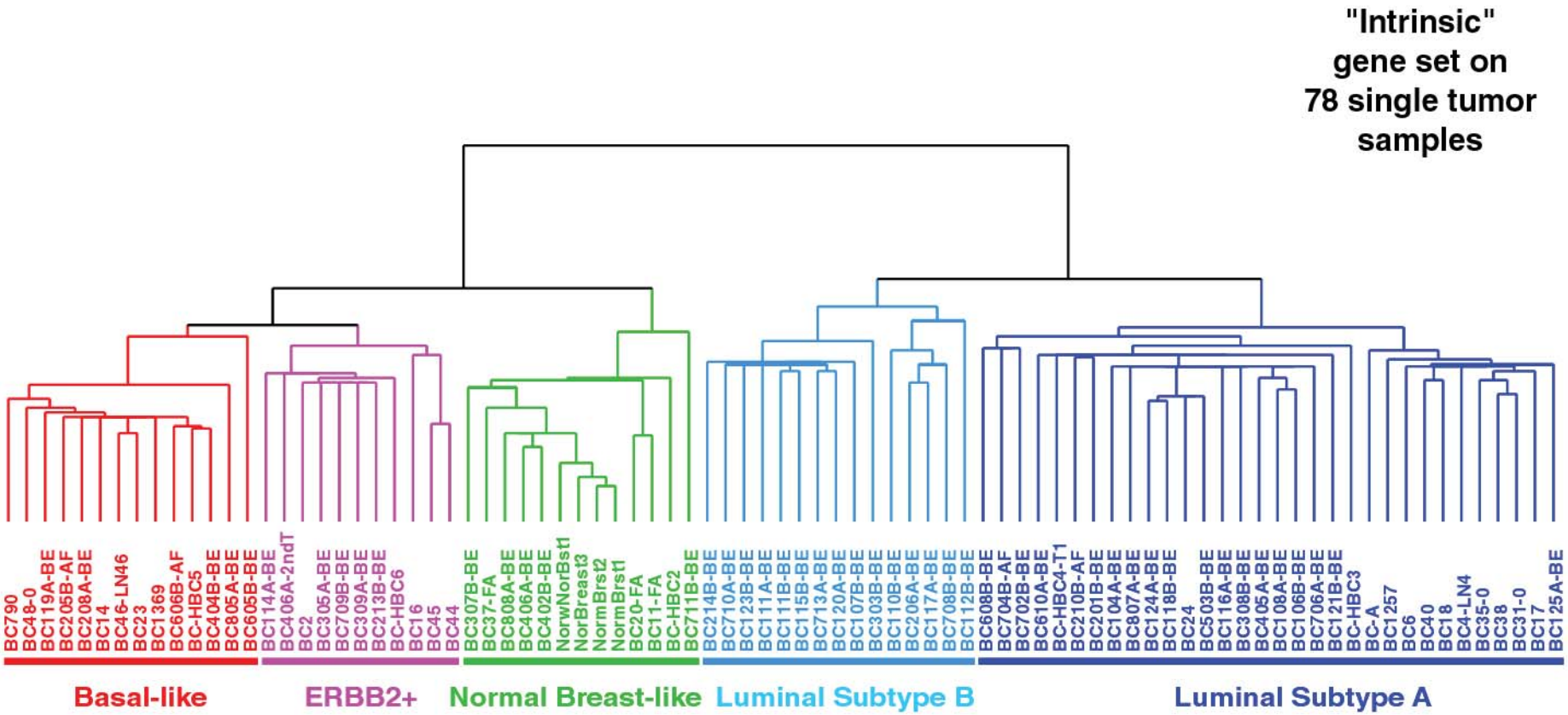
A. 78 Individual Breast Tumors Tested

1. 22 single breast tumor specimens (norway and stanford)
2. 2 primary tumor/lymph node metastasis pairs
3. 54 "before" doxorubicin samples (all T3 or T4)

87% infiltrating ductal carcinoma, 6.5% lobular, 6.5% others
57% T3, 20% T4, 15% T2, 8% T1
44% Grade III, 44% Grade II, 12% Grade I
57 from Norwary and 21 from Stanford

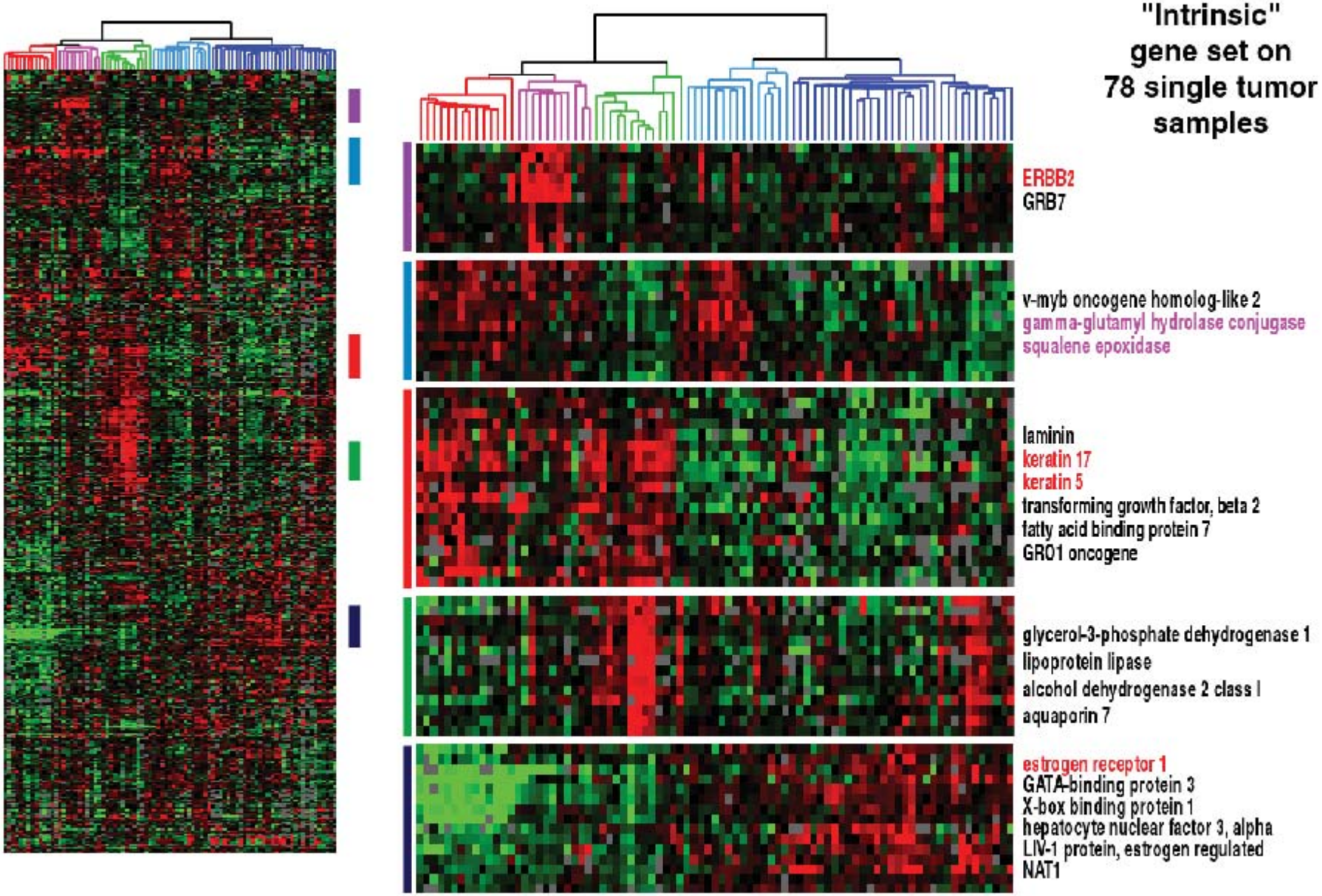
B. 4 normal breast specimens
C. 3 fibroadenomas
D. TGIF - thank god its frozen


"Intrinsic" gene set on 78 single tumor samples
high variance across tumors
low variance within pairs
476 cDNA clones
85 Arrays
= above average
= average
= below average
= not determined
<8
<6
<4
<2
1:1
>2
>4
>6
>8



78 tumor specimens / 3 fibroadenomas / 4 normal breast samples

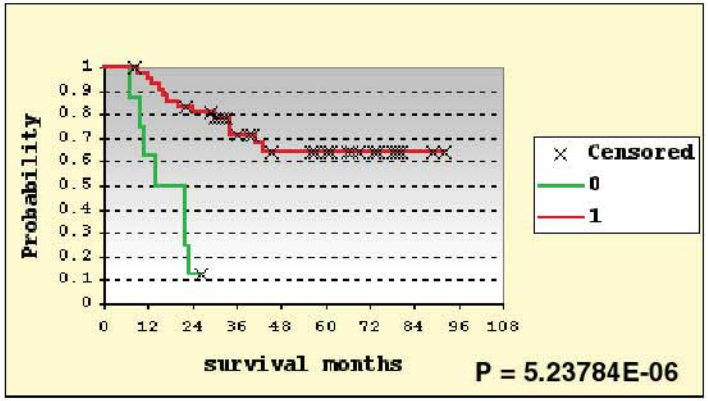
(if we use all samples, then 30/35 "before and after" doxorubicin sample pairs were paired, and 2/2 primary tumor/lymph node metastasis pairs were paired)


"Intrinsic" gene set on 78 single tumor samples
ERBB2
GRB7
v-myb oncogene homolog-like 2
gamma-glutamyl hydrolase conjugase
squalene epoxidase
laminin
keratin 17
keratin 5
transforming growth factor, beta 2
fatty acid binding protein 7
GRO1 oncogene
glycerol-3-phosphate dehydrogenase 1
lipoprotein lipase
alcohol dehydrogenase 2 class I
aquaporin 7
estrogen receptor 1
GATA-binding protein 3
X-box binding protein 1
hepatocyte nuclear factor 3, alpha
LIV-1 protein, estrogen regulated
NAT1

Three Standard Clinical Parameters

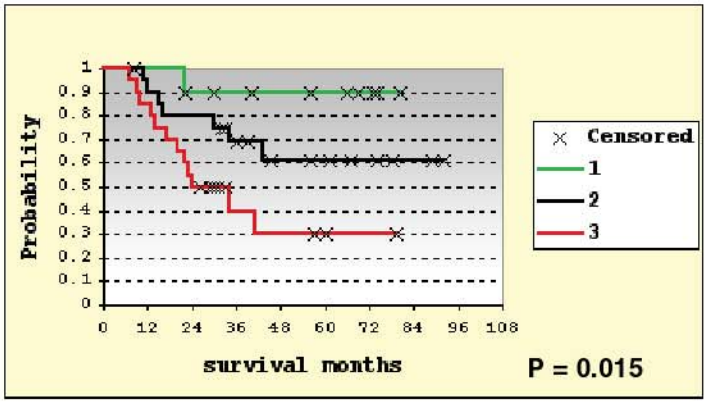
tested on the 51 patients/tumors specimens from the prospective doxorubicin "before and after" study (before samples only)

Estrogen Receptor Status



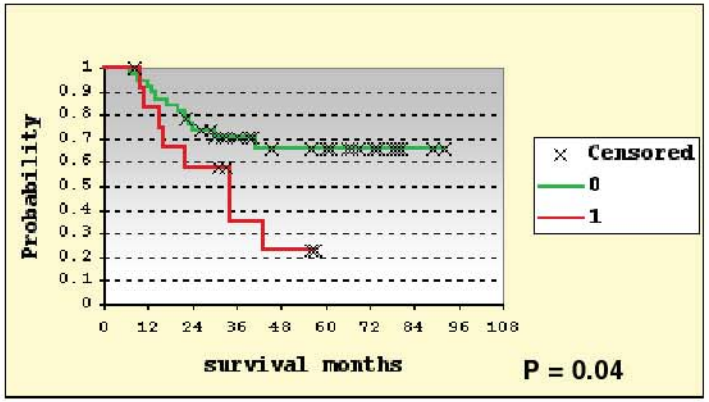
0 = ER negative
1 = ER positive

Bloom-Richardson Grade

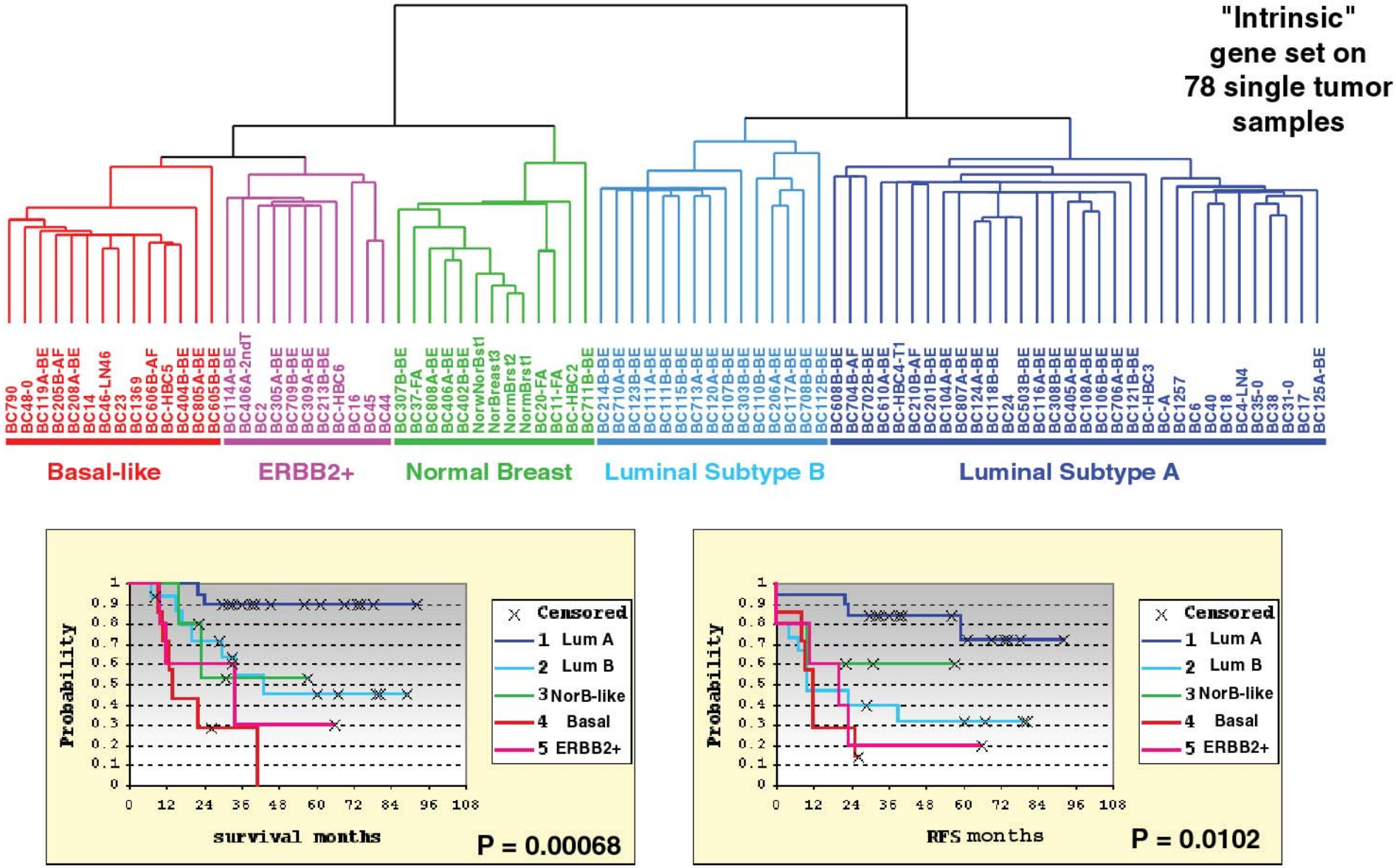


1 = Grade 1
2 = Grade 2
3 = Grade 3

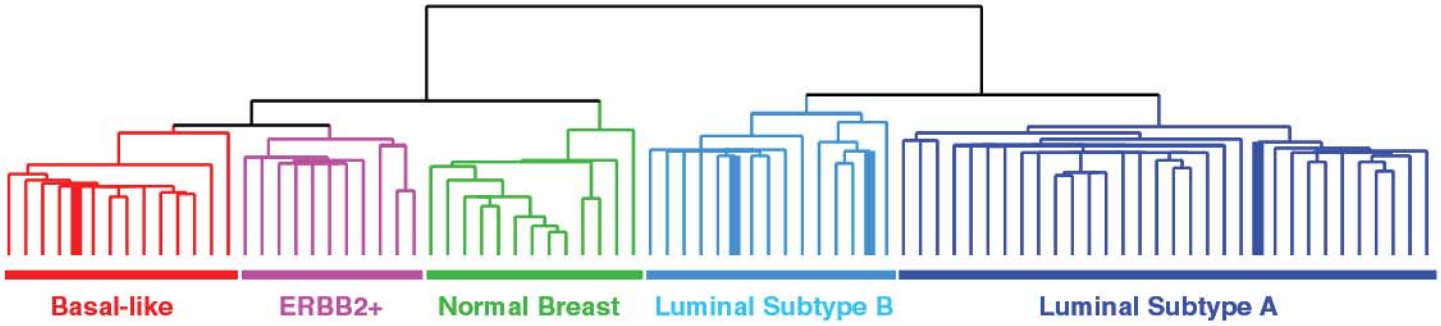
HER2/ERBB2 Status

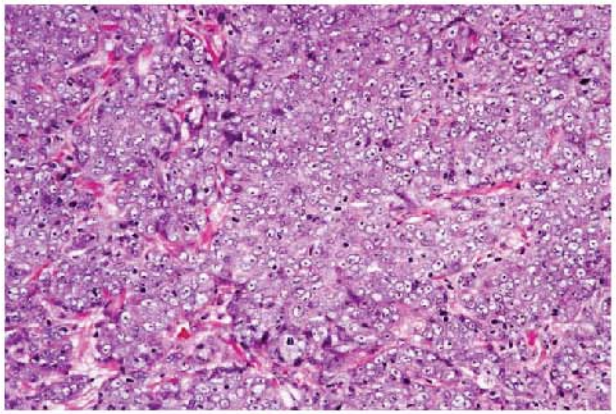


0 = ERBB2 negative
1 = ERBB2 positive

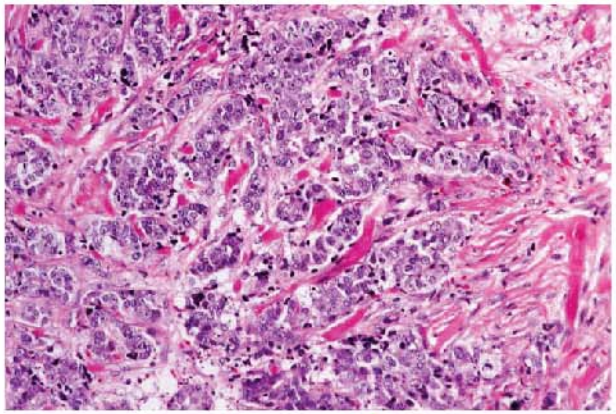


survival analysis was done on the set of 51 doxorubicin treated patients only
(if all 76 patients are used, then the "basal" and "ERBB2+" groups are significant predictors in a multivariate analysis versus ER, grade, tumor size and node status)

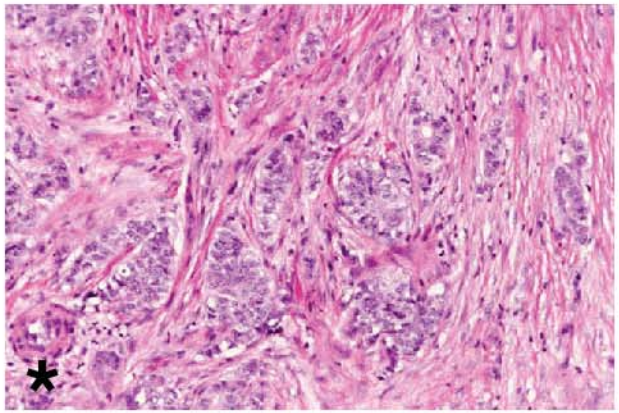




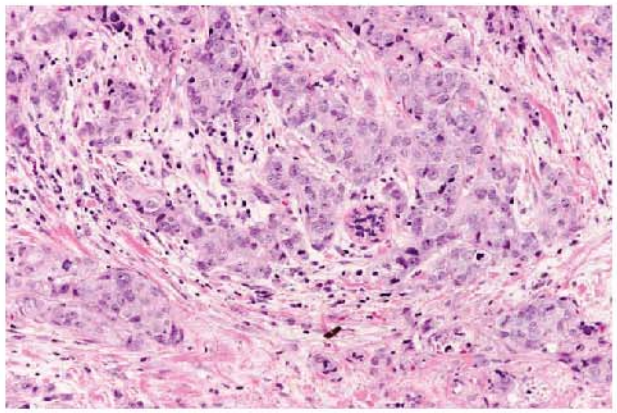
Basal



Luminal B



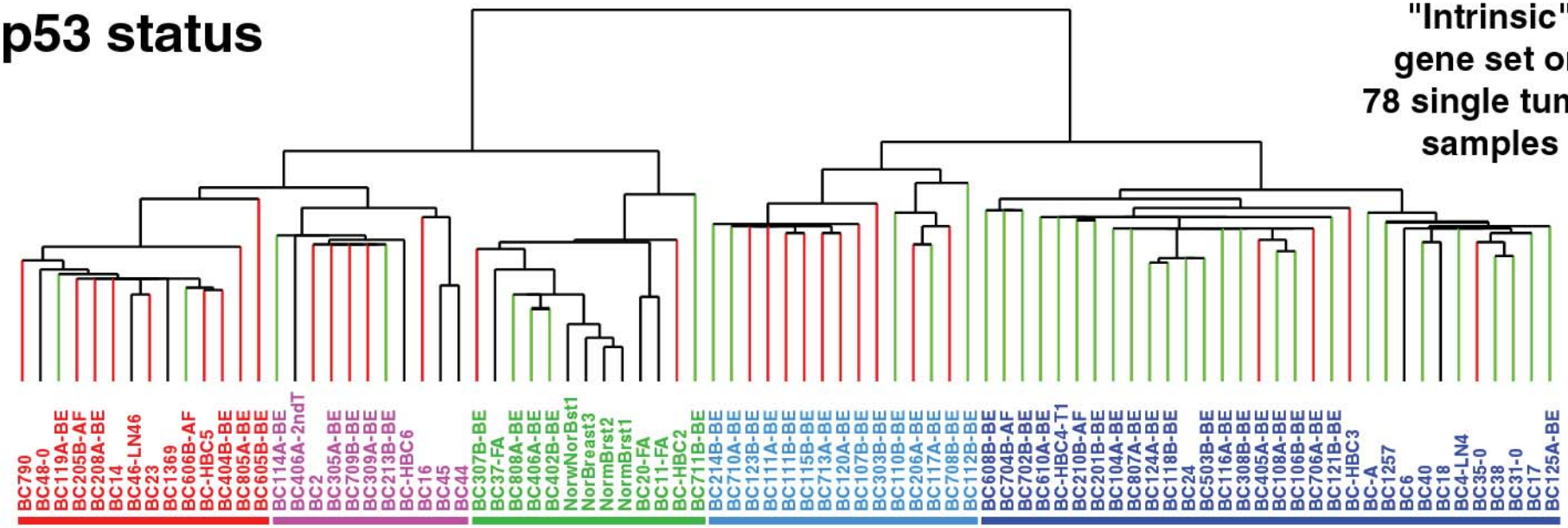
Luminal B

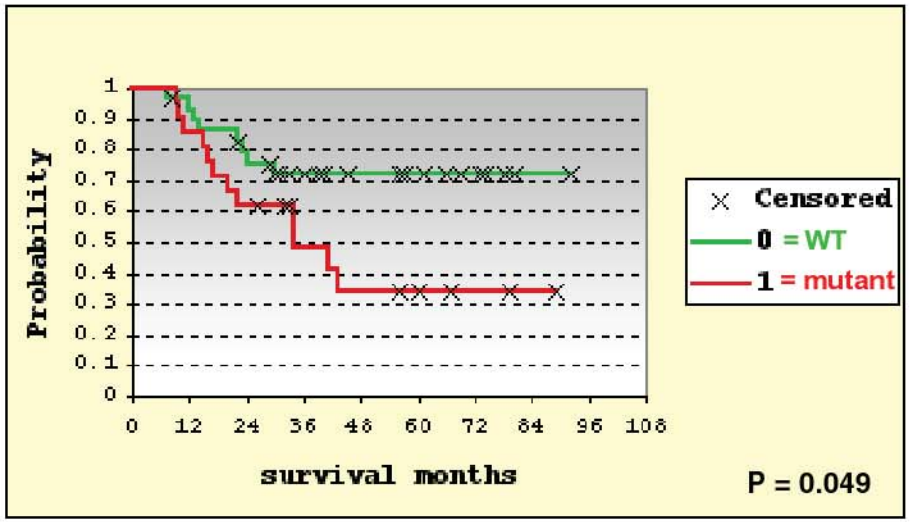


Luminal A

p53 status

"Intrinsic" gene set on 78 single tumor samples

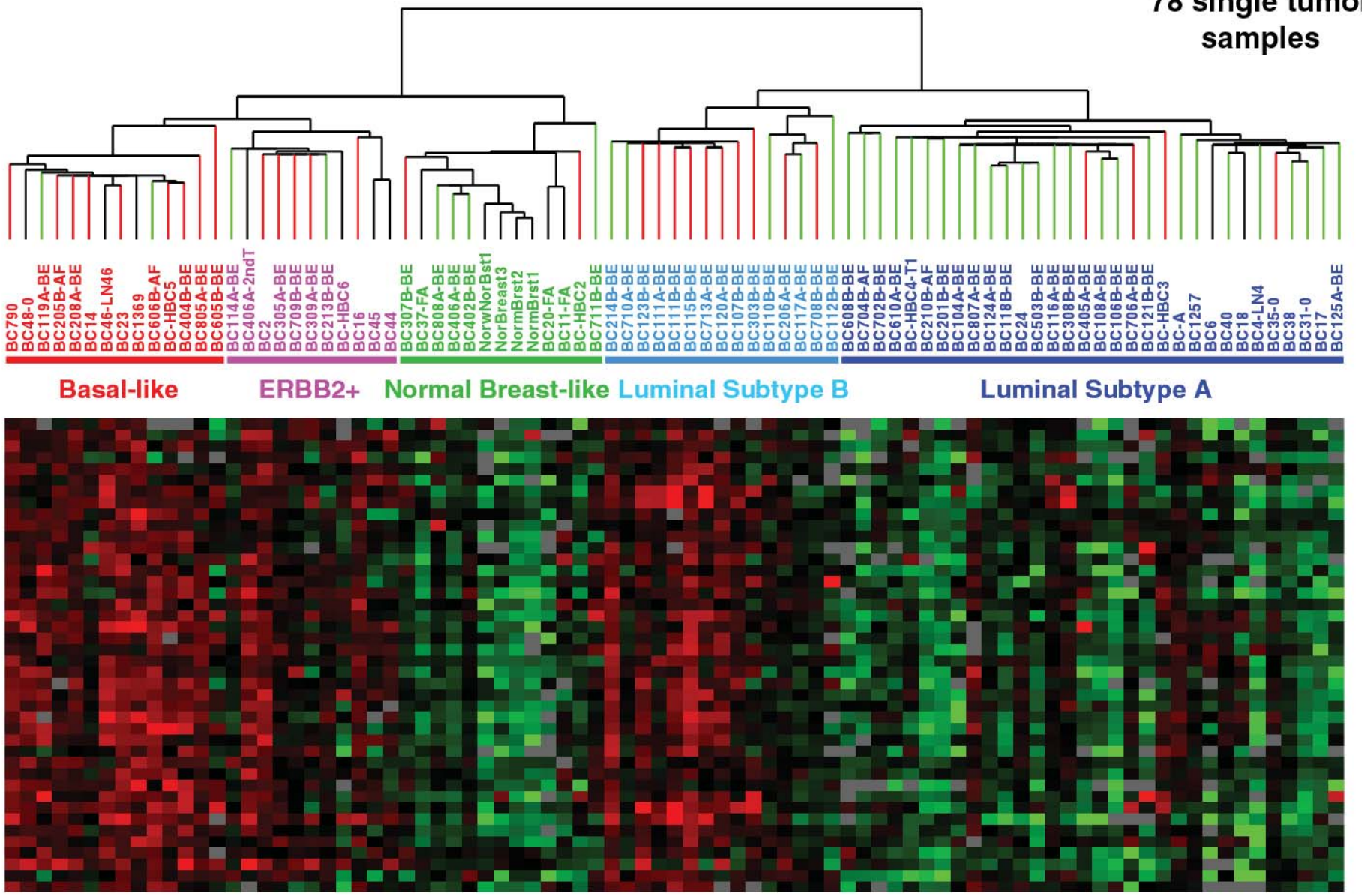




p53 status:
WT = GREEN
p53 mutation = RED
not tested = BLACK

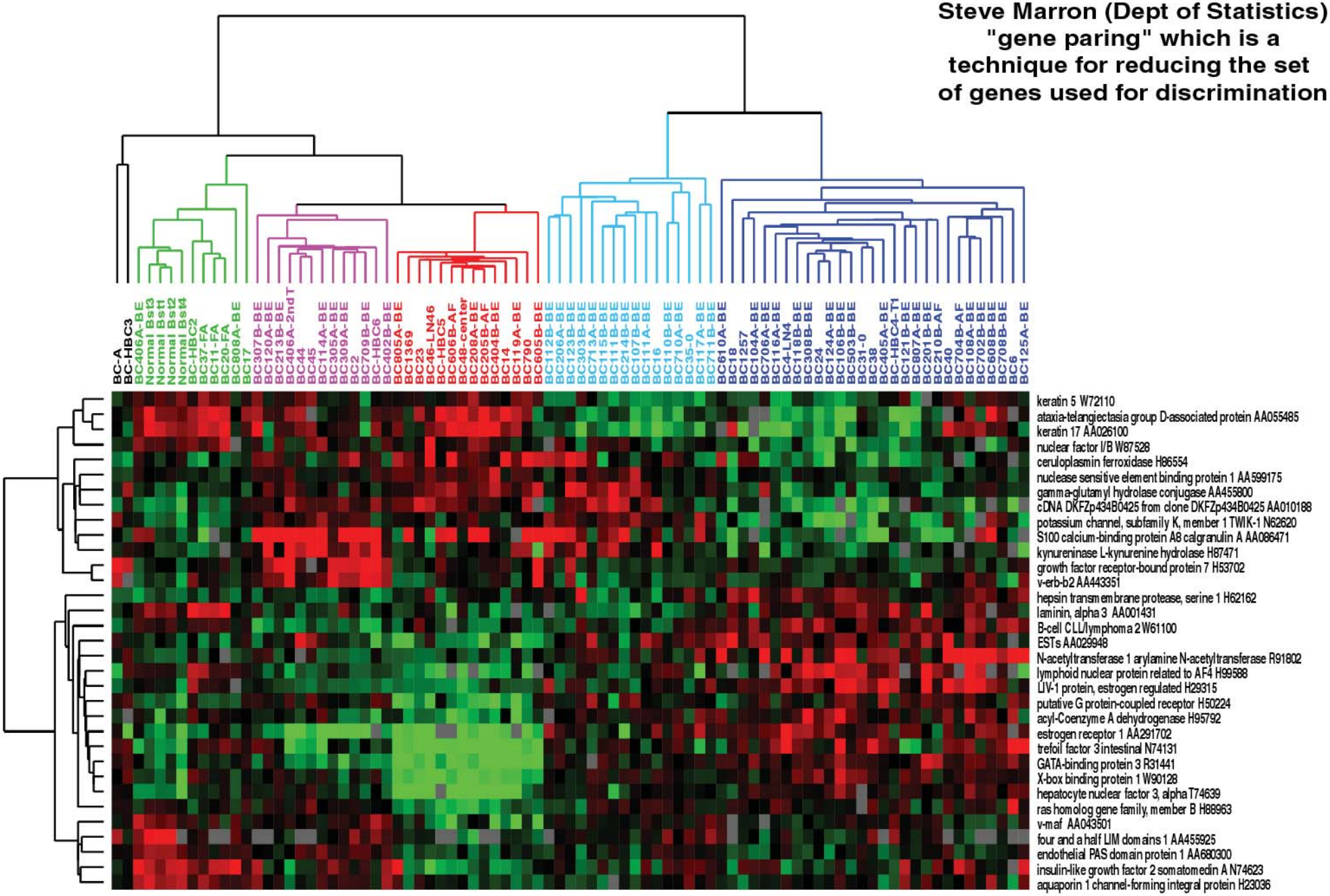
Proliferation genes

"Intrinsic" gene set on 78 single tumor samples

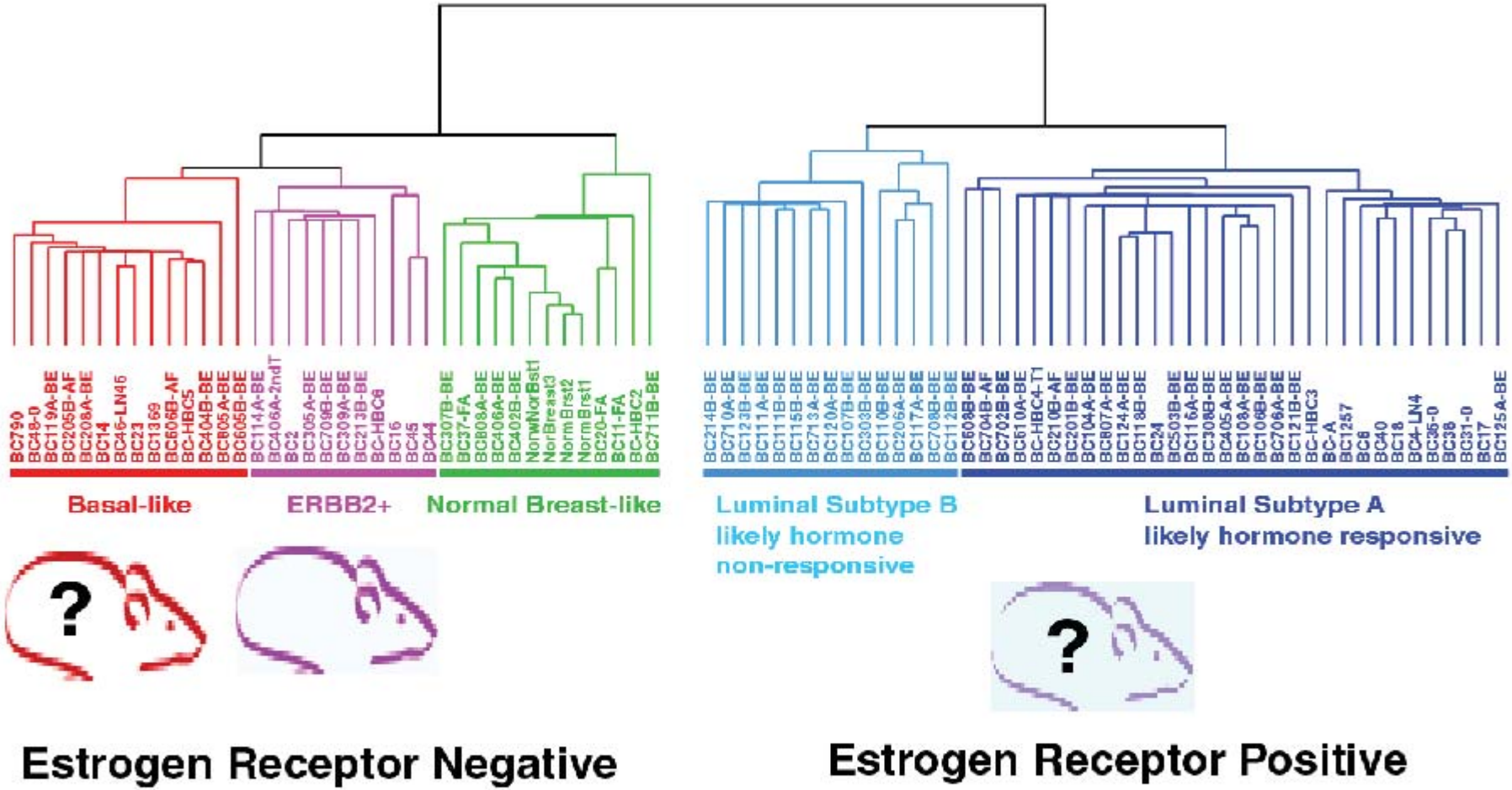


33 gene based tumor classification

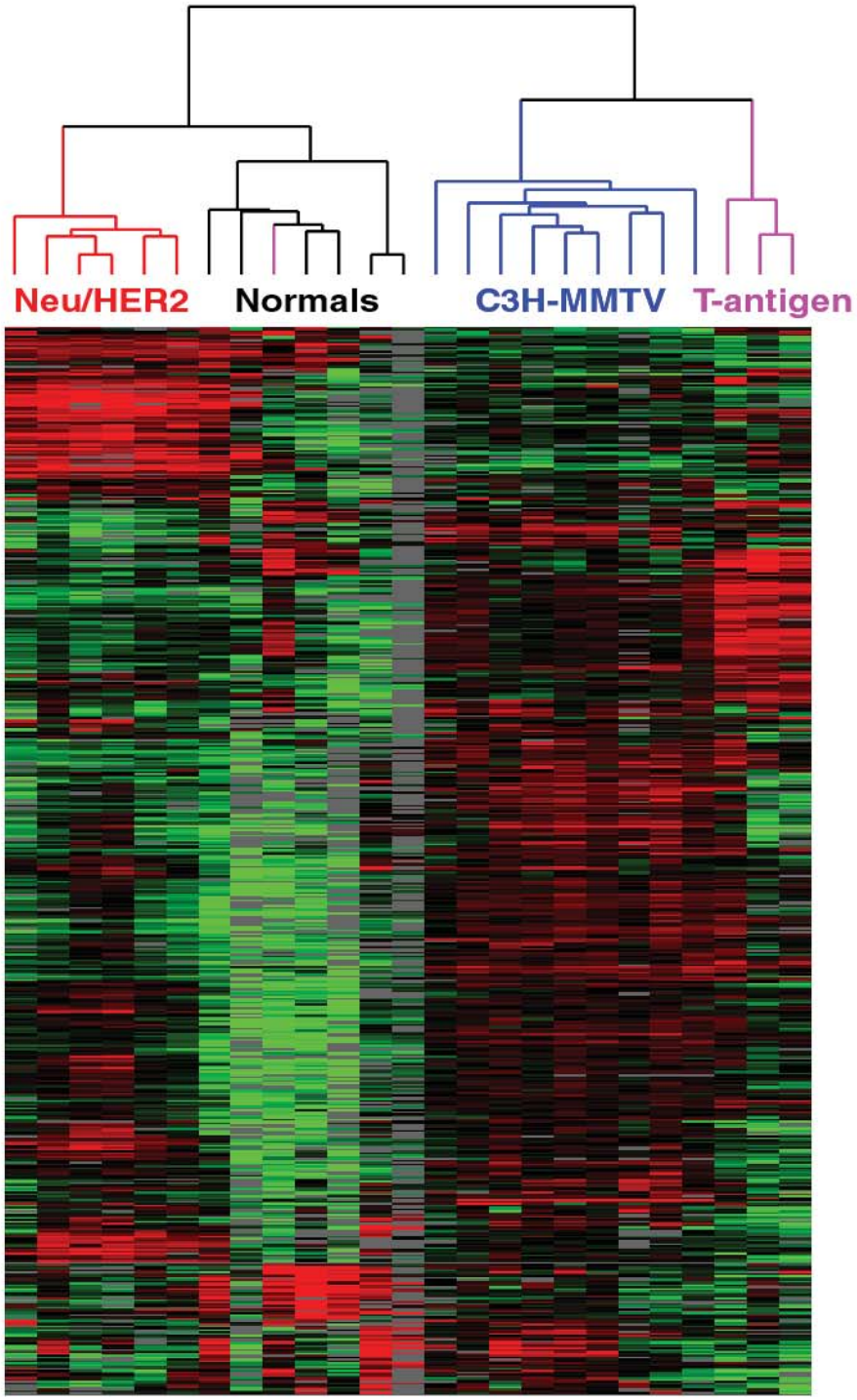
Steve Marron (Dept of Statistics) "gene paring" which is a technique for reducing the set of genes used for discrimination



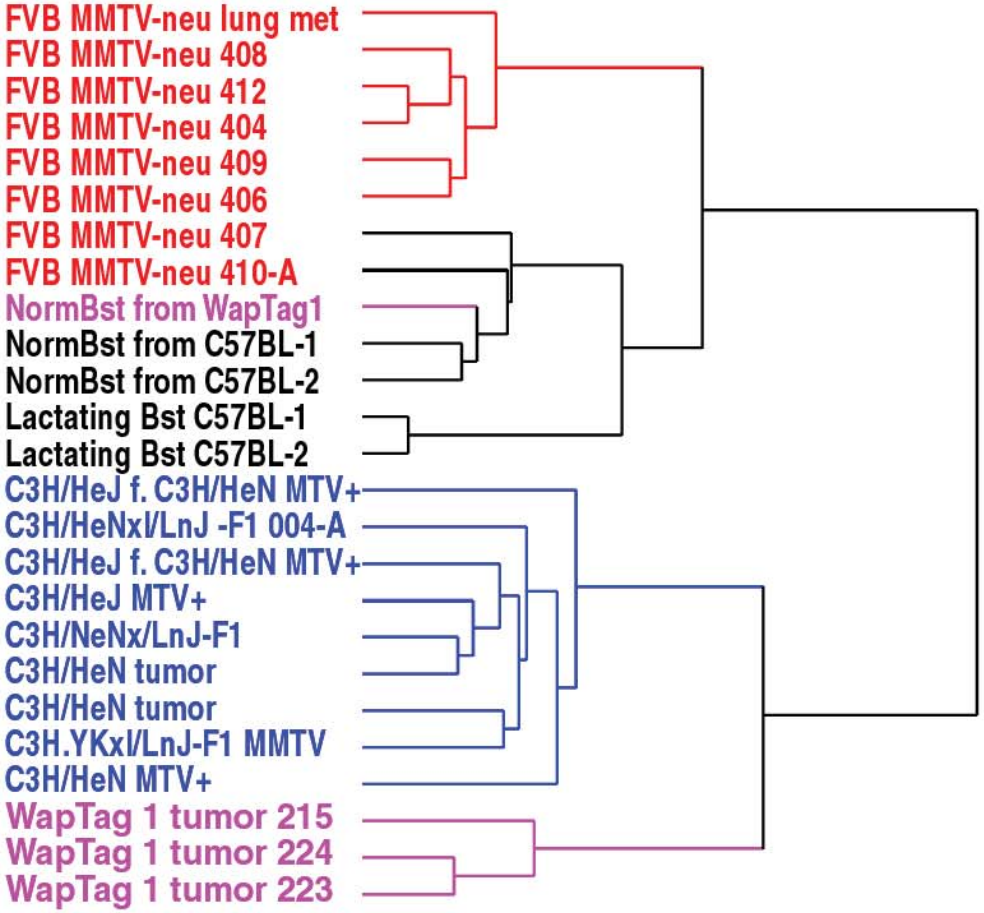
Mouse Models of Human Cancer Consortium



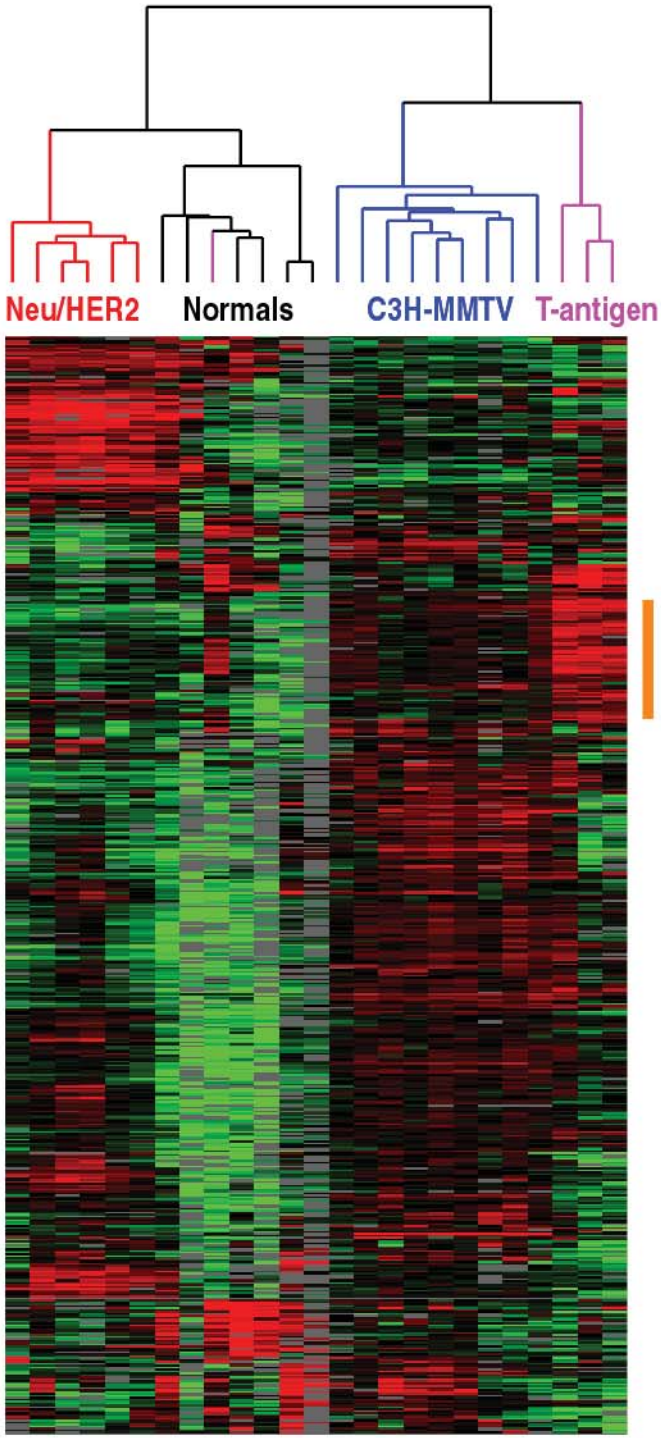
Jeff Green, M.D.
Laboratory of Cell Regulation and Carcinogenesis
National Cancer Institute

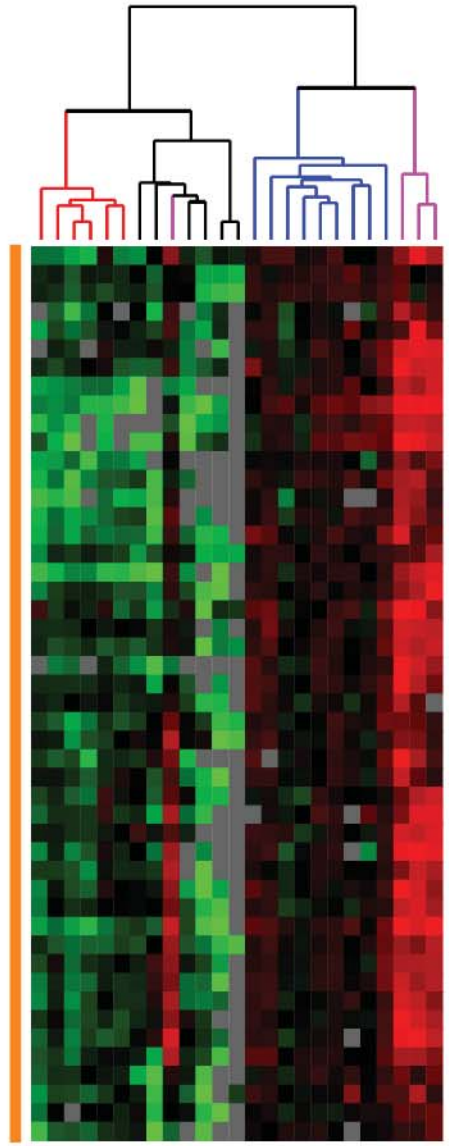


Mouse Mammary Tumor Profiling Project. a collaboration with Gary Churchill, Karen Rasmussen and others at the JAX

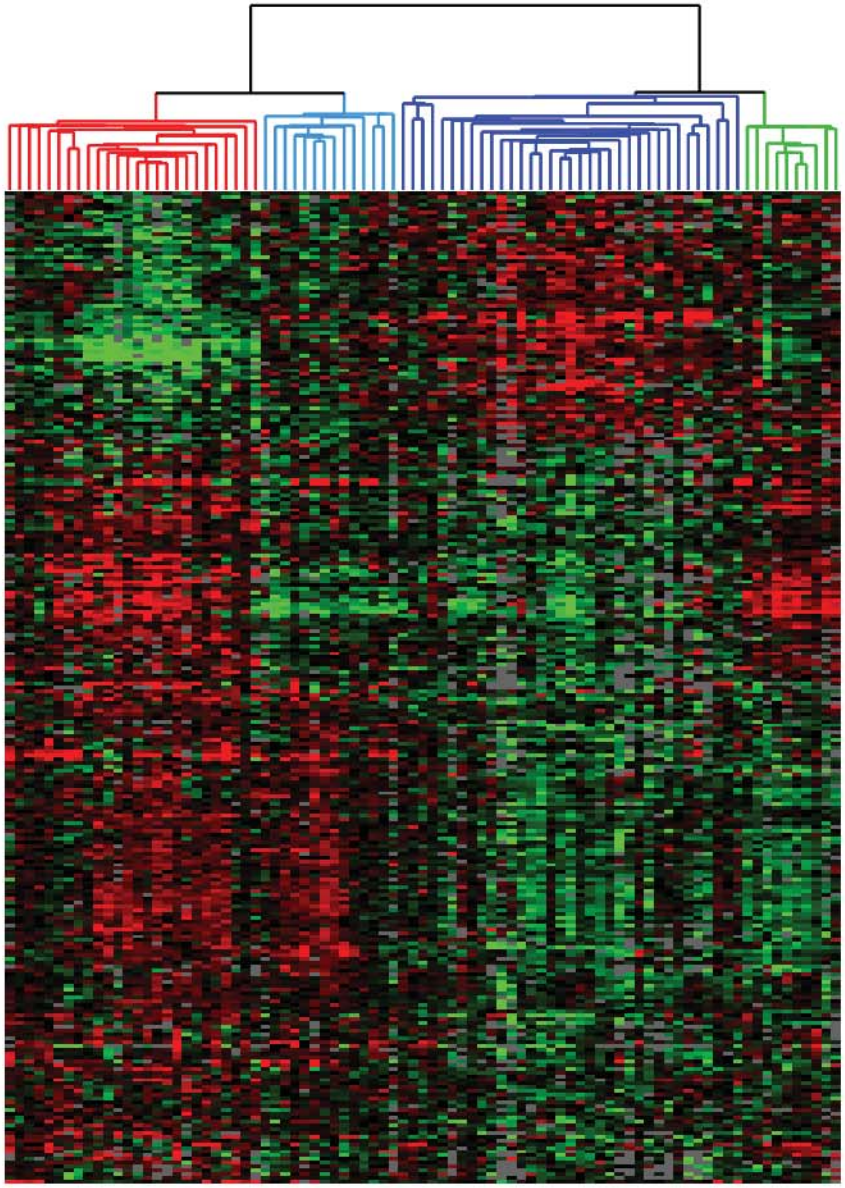


Mouse Proliferation cluster





H2A histone family, member Y AF171080
cell division cycle 71 homolog S. cerevisiae-like 1 NM_009863
DNA primase, p58 subunit NM_008922
serine/threonine kinase 6 U69106
cyclin A2 NM_009828
mini chromosome maintenance deficient 2 S. cerevisiae NM_008564
H2A histone family, member X NM_010436
activator of S phase kinase NM_013726
mutS homolog 6 E. coli NM_010830
mini chromosome maintenance deficient 5 S. cerevisiae NM_008566
ligase I, DNA, ATP-dependent NM_010715
mini chromosome maintenance deficient S. cerevisiae X62154
cyclin B1, related sequence 1 NM_007629
DNA polymerase epsilon NM_011132
antigen identified by monoclonal antibody Ki 67 X82786
DNA primase, p49 subunit NM_008921
DNA polymerase alpha 1, 180 kDa NM_008892
mini chromosome maintenance deficient 4 homolog S. cerevisiae NM_008565



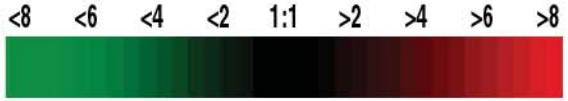
"Significance Analysis of Microarrays"
to identify genes that correlate
with patient survival
(254 genes/264 cDNA clones)

81 gene overlap with Intrinsic List

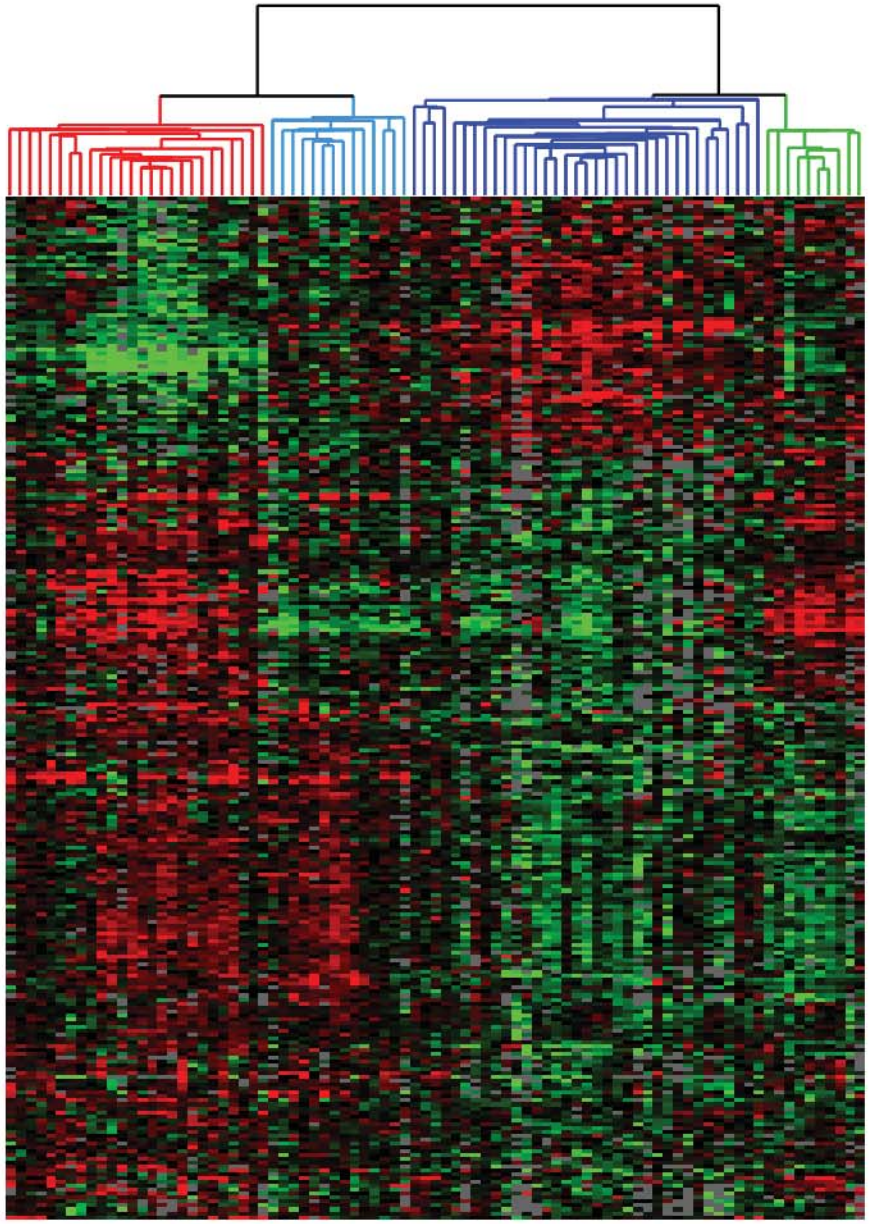
Luminal Epithelial

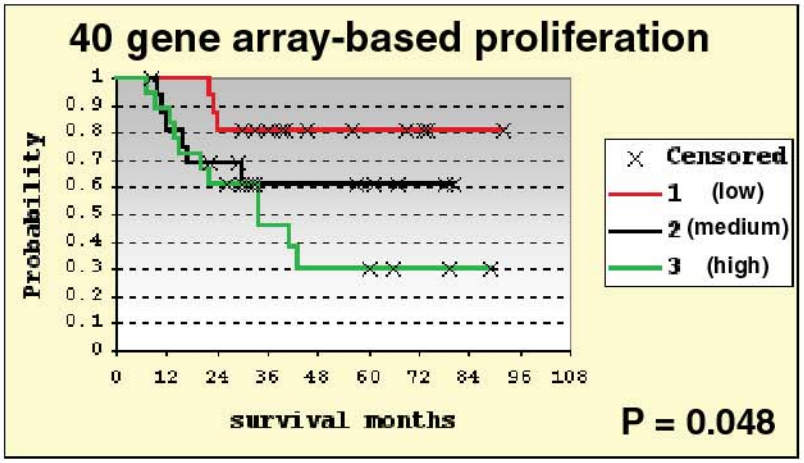
Basal Epithelial

Proliferation



"Significance Analysis of Microarrays"
SAM264 survival set

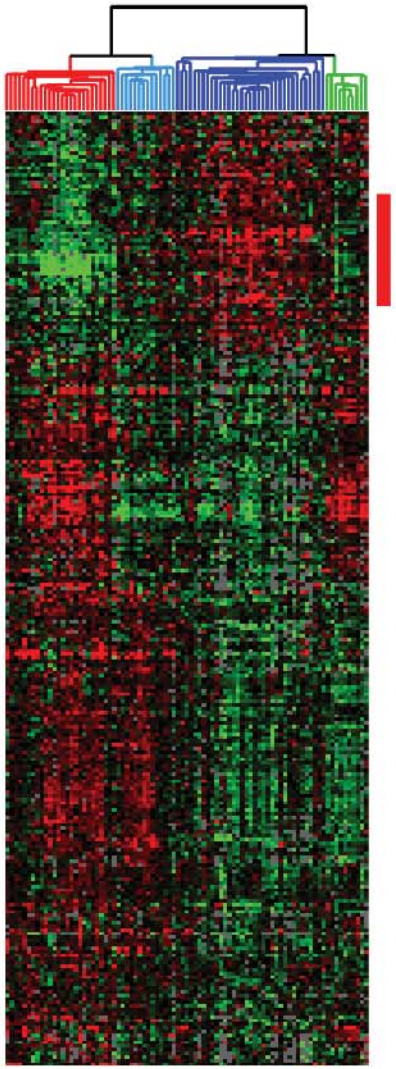




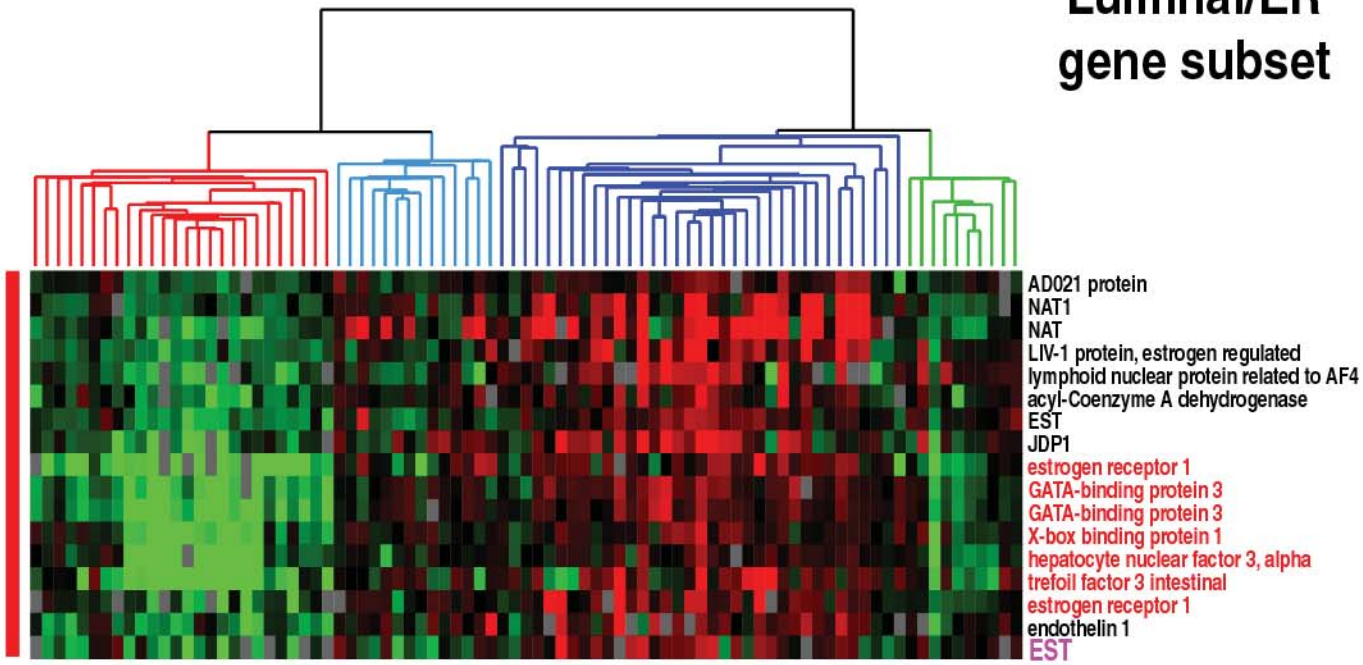
1 = lowest proliferation rates
2 = middle proliferation rates
3 = highest proliferation rates

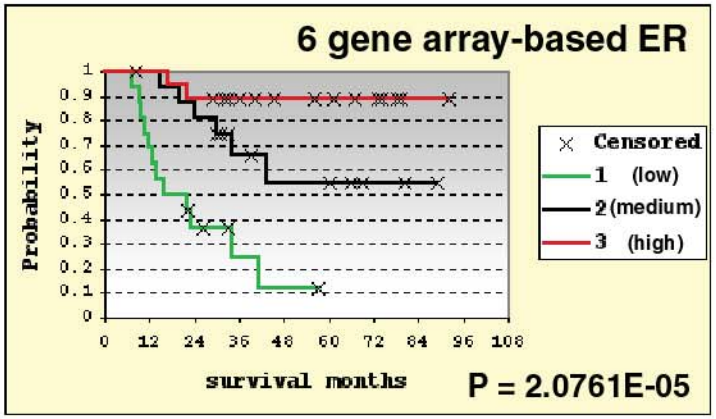
→ Proliferation

"Significance Analysis of Microarrays"
SAM264 survival set



Luminal/ER gene subset





Gene expression profiling predicts clinical outomce of breast cancer
L. J. van 't Veer et al.
Nature 415, 530-536 (2002).

Sporadic breast tumours
patients <55 years
tumour size <5 cm
lymph node negative (LN0)
No chemotherapy given

5,000 genes differentially expressed across 78 tumors

↓

supervised correlation analysis to identify genes that correlated with Bad versus Good prognosis
(230 genes)

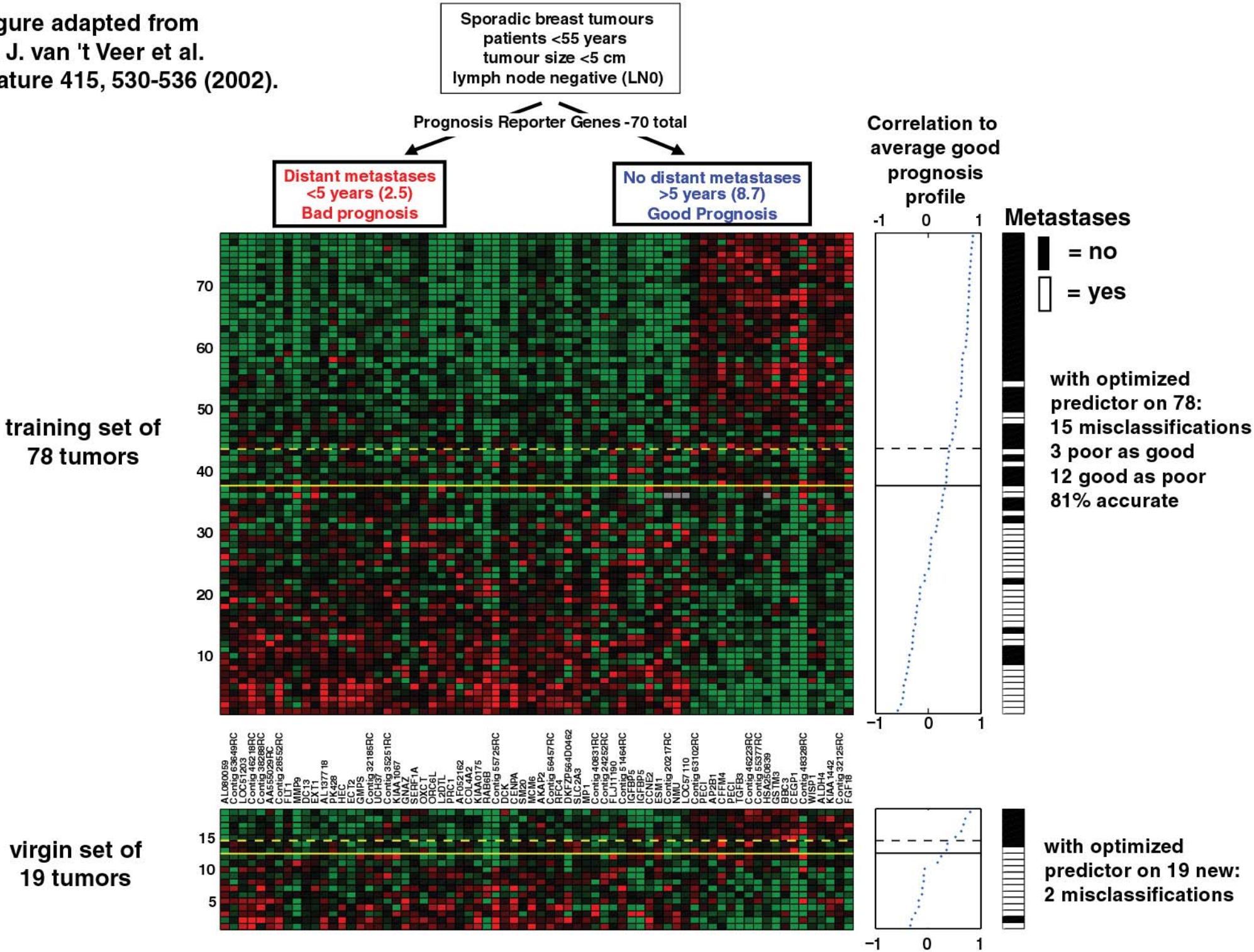
Distant metastases
<5 years (2.5)
Bad prognosis

No distant metastases
>5 years (8.7)
Good Prognosis

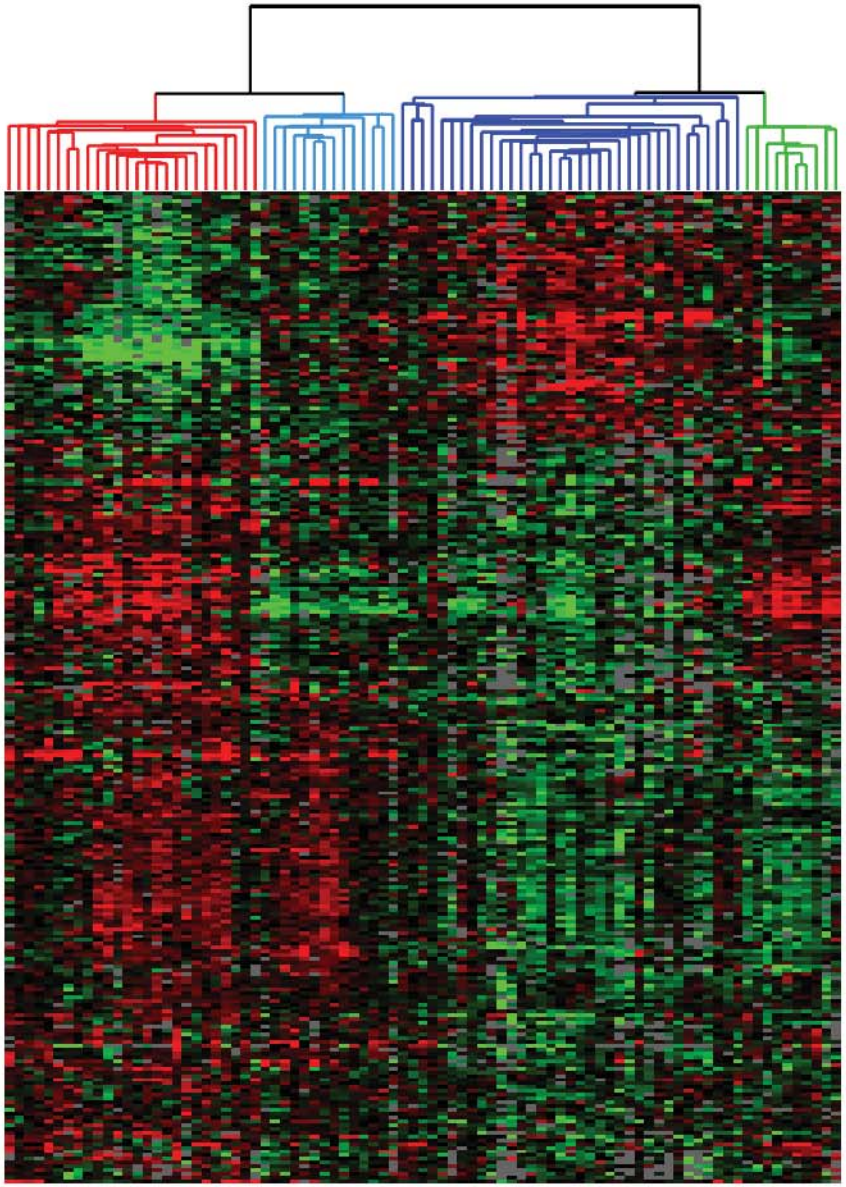
↓

Prognosis reporter genes set and predictions optimized to identify pateints that might not require chemotherapy versus those that do require therapy

figure adapted from
L. J. van 't Veer et al.
Nature 415, 530-536 (2002).



"SAM264" survival list and the metastasis predictor list overlap by approximately 21 genes and make similar predictions

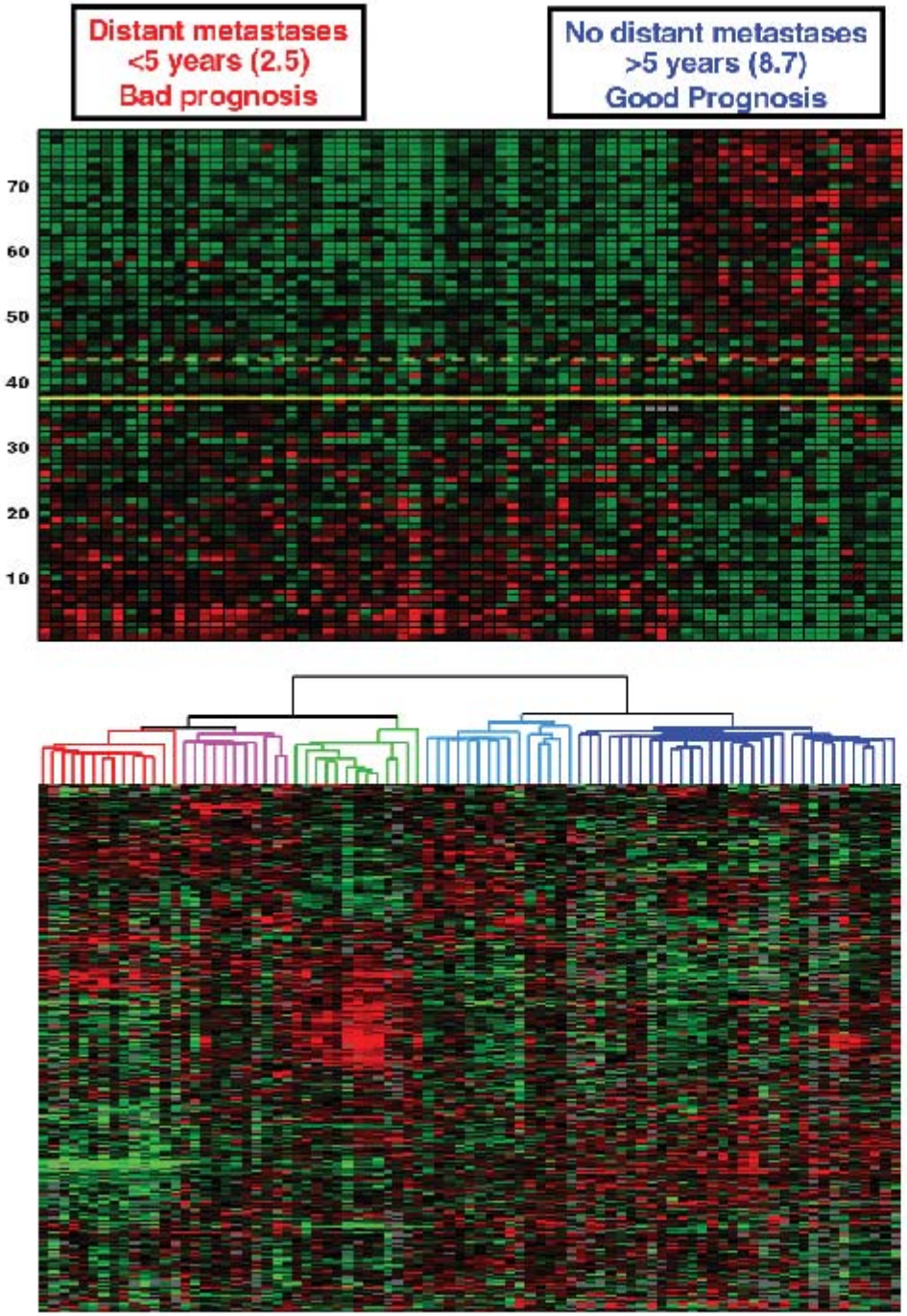


BTG family, member 2
methylmalonate-semialdehyde dehydrogenase
acyl-Coenzyme A dehydrogenase, short/branched chain

high expression predicts favorable outcome

preferentially expressed antigen in melanoma
N-myc downstream regulated
ceruloplasmin ferroxidase
Pirin
budding uninhibited by benzimidazoles 1 yeast homolog
cathepsin S
phosphofructokinase, platelet
cell division cycle 25B
ribonucleotide reductase M2 polypeptide
gamma-glutamyl hydrolase conjugase, folylpolygammaglutamyl hydrolase
serine/threonine kinase 15
enhancer of zeste Drosophila homolog 2
thyroid hormone receptor interactor 13
centromere protein F 350/400kD, mitosin
minichromosome maintenance deficient mis5, S. pombe 6
cyclin E
KIAA0008 gene product
transferrin receptor p90, CD71

high expression predicts poor outcome



Gene Expression Profiling Clinical Implications

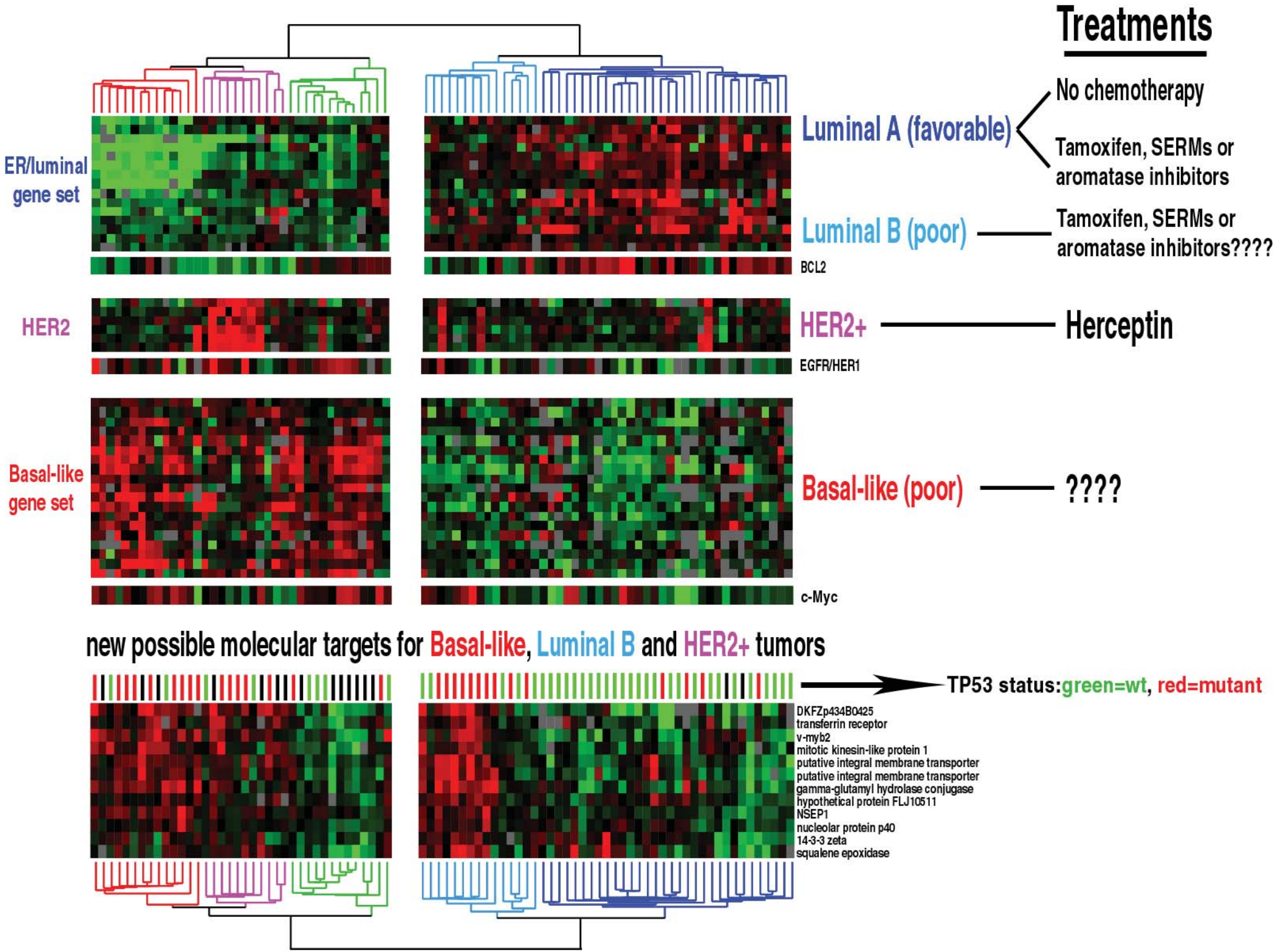
1. showed significance in a multivariate analysis - adding value

2. suggests that some patients may not need therapy (20-40%)

3. these data sets, and others to come, will form the basis for new diagnostics based on preoperative tumor biopsies (cores or FNAs)

   -who to treat (van't Veer et al.)

   -how to treat, which will likely be dependent upon tumor subtype biology


Treatments
ER/luminal gene set
Luminal A (favorable)
No chemotherapy
Tamoxifen, SERMs or aromatase inhibitors
Luminal B (poor)
Tamoxifen, SERMs or aromatase inhibitors????
BCL2
HER2
HER2+
Herceptin
EGFR/HER1
Basal-like gene set
Basal-like (poor)
????
c-Myc
new possible molecular targets for Basal-like, Luminal B and HER2+ tumors
TP53 status:green=wt, red=mutant
DKFZp434B0425
transferrin receptor
v-myb2
mitotic kinesin-like protein 1
putative integral membrane transporter
putative integral membrane transporter
gamma-glutamyl hydrolase conjugase
hypothetical protein FLJ10511
NSEP1
nucleolar protein p40
14-3-3 zeta
squalene epoxidase

Future studies and directions

- "Systems Biology" or Cell Biology approach to the study of human cancers: coordinated use of multiple techniques on the same samples to create predictive models. Collaboration with Stephen Channock, Bob Strausberg (NCI) and Anne-Lise Børresen-Dale (Radium Hospital/Norway) to perform on each of our breast tumors
  - Microarray
  - IHC, western blots and proteomic analyses for signaling pathway investigations
  - DNA sequence variation analysis on 100 genes in 100 tumors to identify somatic mutations and gene variants/polymorphisms.
  - Genome-wide genotyping using SNPs and/or microsatellites

- Validate our existing findings on large clinical cohorts of homogenously treated patients
  - May require alternative sample collection methods (fresh frozen)
  - Correlative studies first, then predictive studies second

- Mandate from funding agencies for full data release.

- Develop therapies based upon cell type of origin and a molecular understanding of the altered genes/proteins and pathways in each tumor subtype – combination therapies.

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