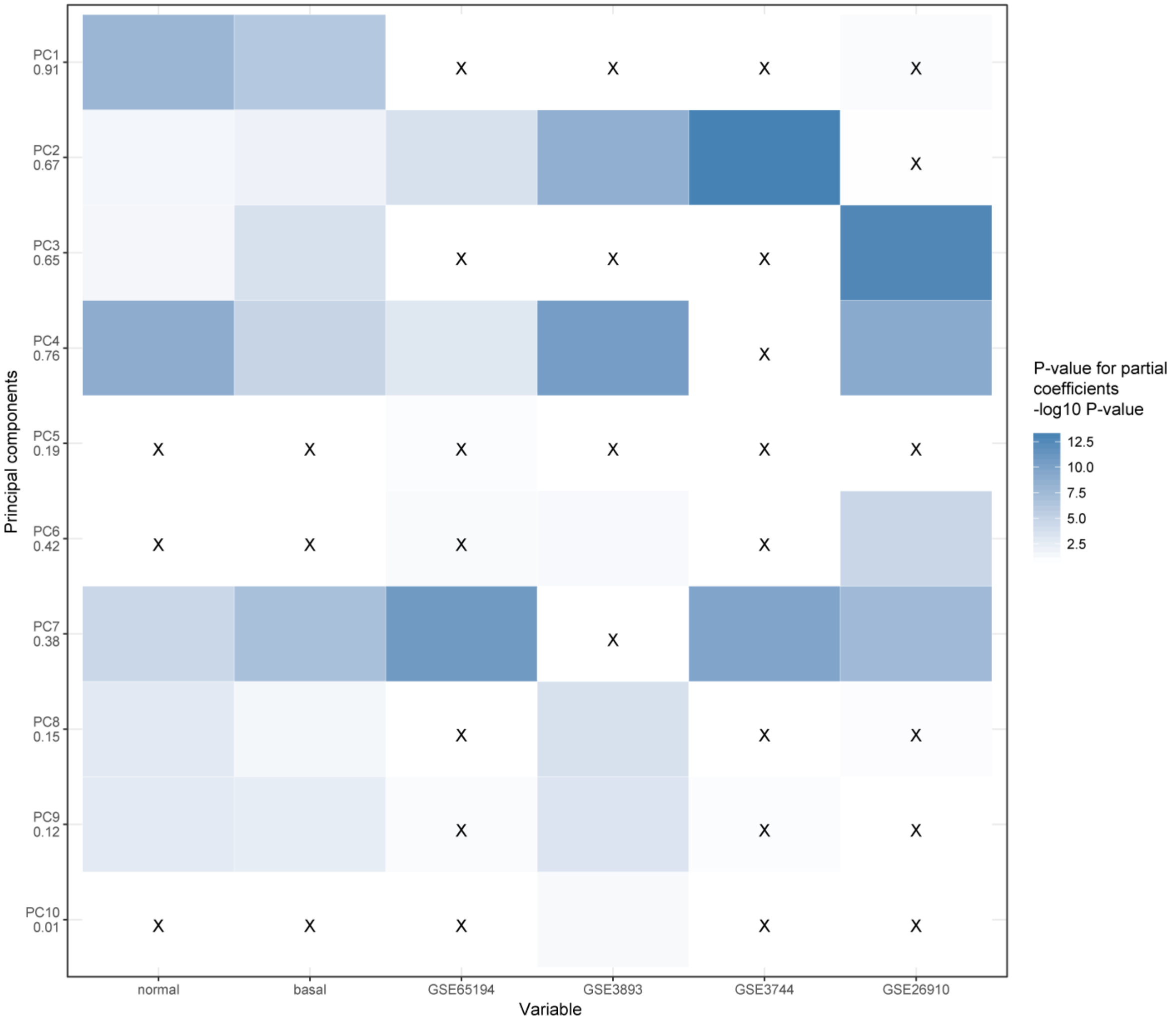
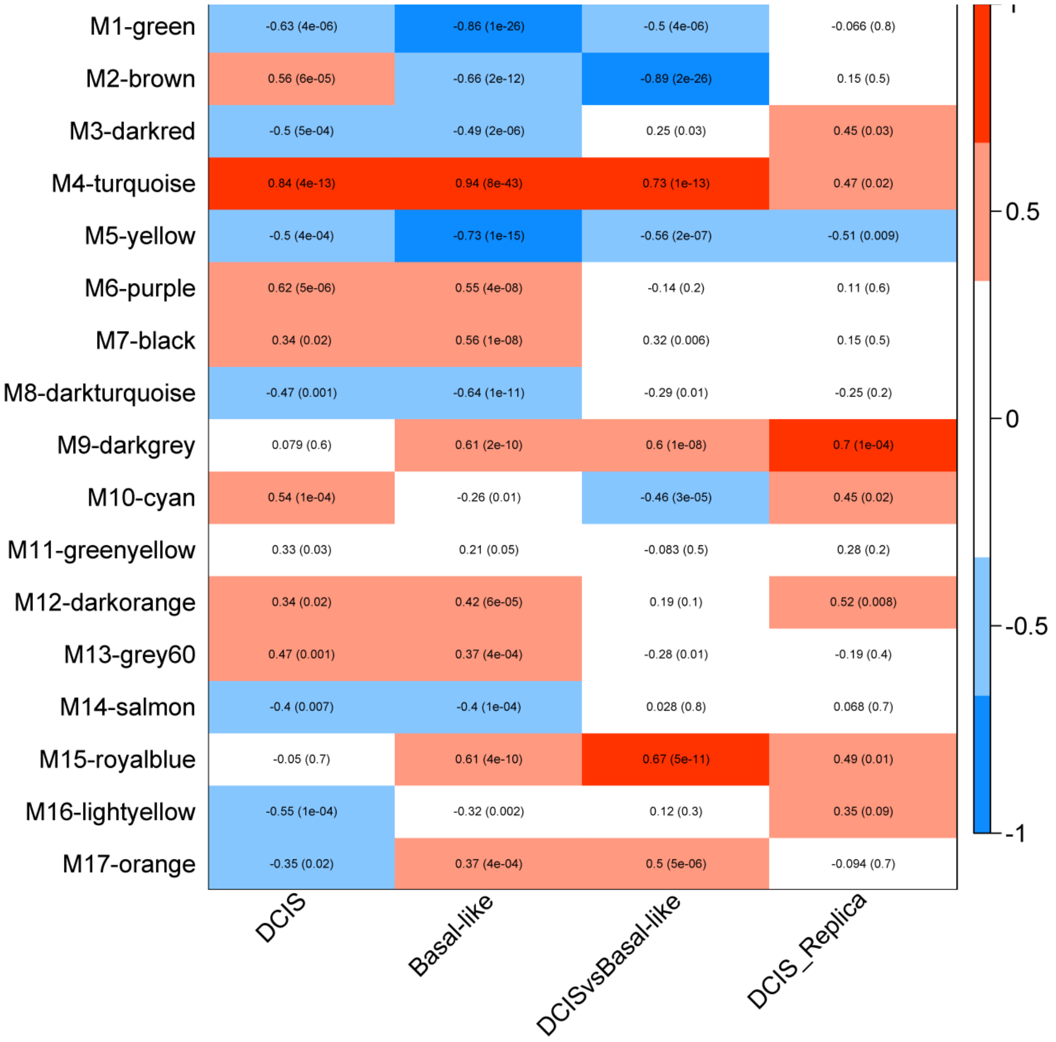
Transcriptome evolution from breast epithelial cells to basal-like tumors

SUPPLEMENTARY MATERIALS



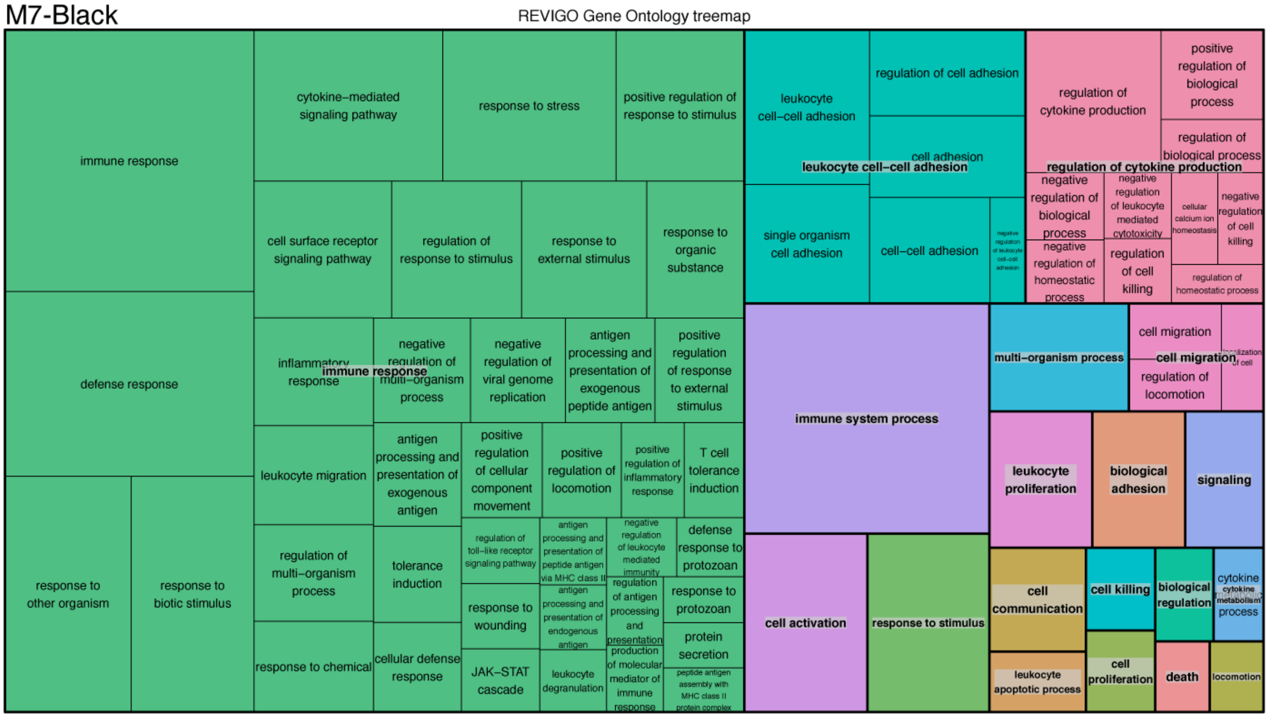
Supplementary Figure 1: Heatmap representation of the –log10 *P*-values for the partial coefficients of the multiple lineal model of each one of the 10 first principal components, predicted by Disease and Batch variables.



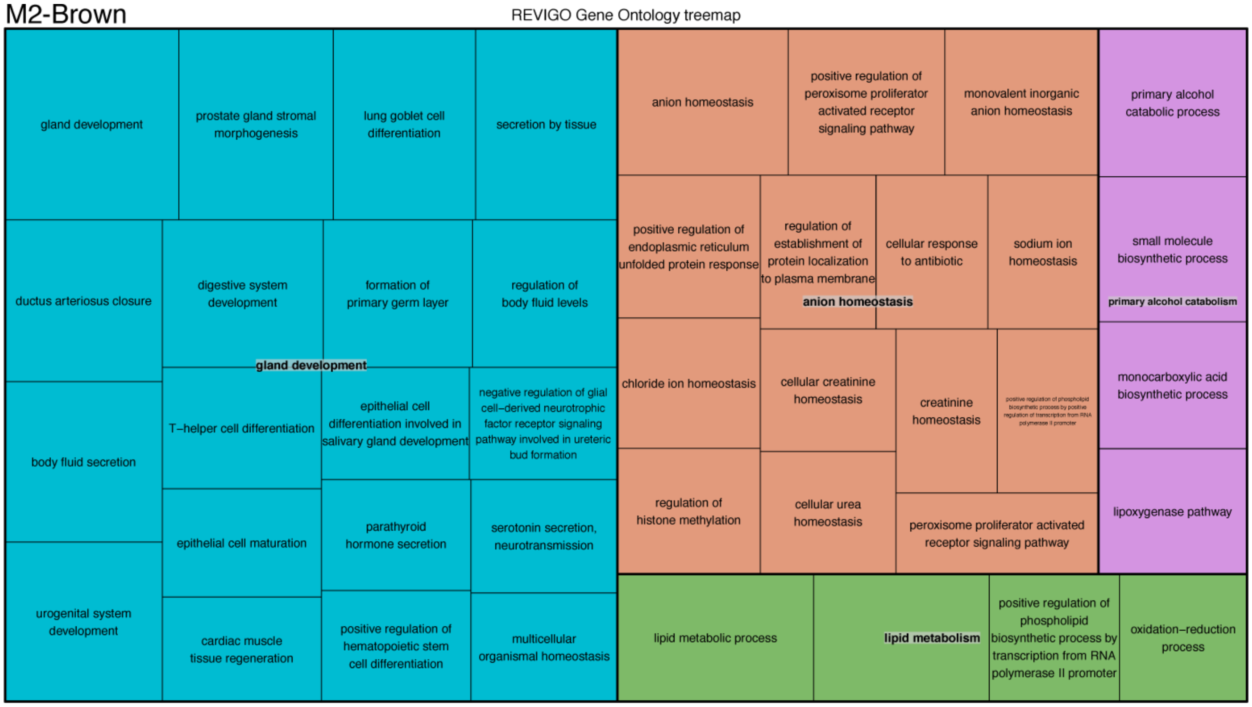
	DCIS	Basal-like	DCISvsBasal-like	DCIS_Replica
M1-green	-0.63 (4e-06)	-0.86 (1e-26)	-0.5 (4e-06)	-0.066 (0.8)
M2-brown	0.56 (6e-05)	-0.66 (2e-12)	-0.89 (2e-26)	0.15 (0.5)
M3-darkred	-0.5 (5e-04)	-0.49 (2e-06)	0.25 (0.03)	0.45 (0.03)
M4-turquoise	0.84 (4e-13)	0.94 (8e-43)	0.73 (1e-13)	0.47 (0.02)
M5-yellow	-0.5 (4e-04)	-0.73 (1e-15)	-0.56 (2e-07)	-0.51 (0.009)
M6-purple	0.62 (5e-06)	0.55 (4e-08)	-0.14 (0.2)	0.11 (0.6)
M7-black	0.34 (0.02)	0.56 (1e-08)	0.32 (0.006)	0.15 (0.5)
M8-darkturquoise	-0.47 (0.001)	-0.64 (1e-11)	-0.29 (0.01)	-0.25 (0.2)
M9-darkgrey	0.079 (0.6)	0.61 (2e-10)	0.6 (1e-08)	0.7 (1e-04)
M10-cyan	0.54 (1e-04)	-0.26 (0.01)	-0.46 (3e-05)	0.45 (0.02)
M11-greenyellow	0.33 (0.03)	0.21 (0.05)	-0.083 (0.5)	0.28 (0.2)
M12-darkorange	0.34 (0.02)	0.42 (6e-05)	0.19 (0.1)	0.52 (0.008)
M13-grey60	0.47 (0.001)	0.37 (4e-04)	-0.28 (0.01)	-0.19 (0.4)
M14-salmon	-0.4 (0.007)	-0.4 (1e-04)	0.028 (0.8)	0.068 (0.7)
M15-royalblue	-0.05 (0.7)	0.61 (4e-10)	0.67 (5e-11)	0.49 (0.01)
M16-lightyellow	-0.55 (1e-04)	-0.32 (0.002)	0.12 (0.3)	0.35 (0.09)
M17-orange	-0.35 (0.02)	0.37 (4e-04)	0.5 (5e-06)	-0.094 (0.7)

Supplementary Figure 2: Heatmap showing correlation and *P*-values for each module eigengene and disease categories. Last column uses module eigengene values from matched genes from another external dataset of DCIS and normal samples.

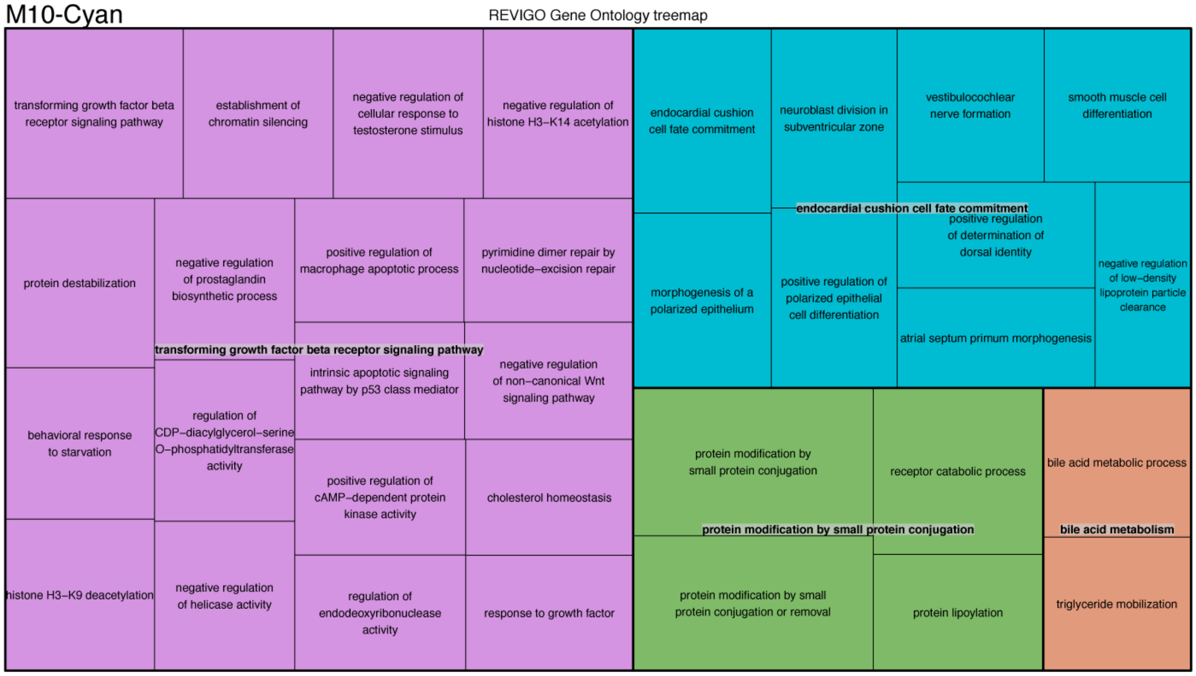
M7-Black



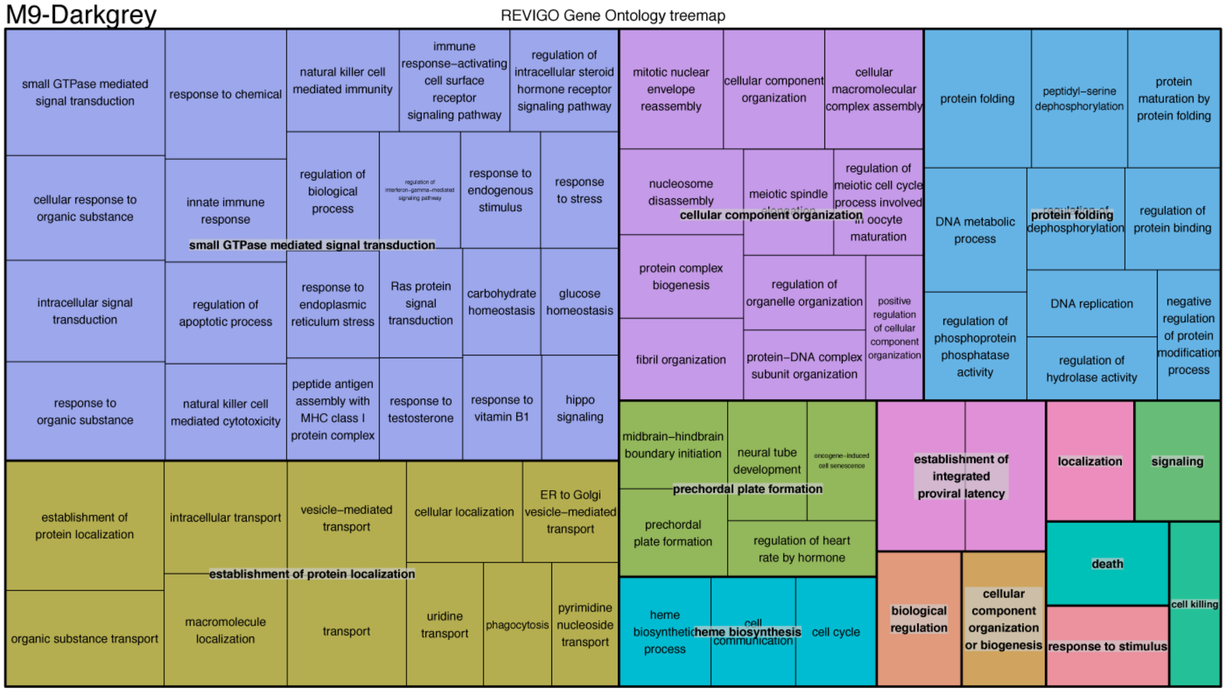
M2-Brown



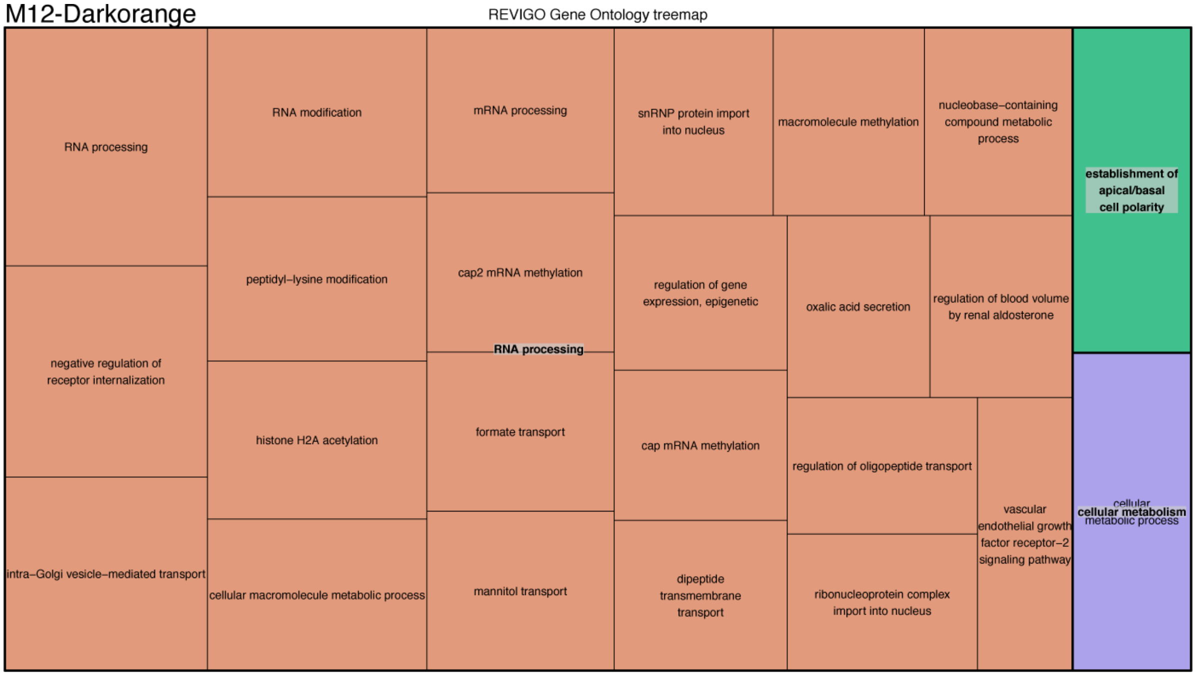
M10-Cyan



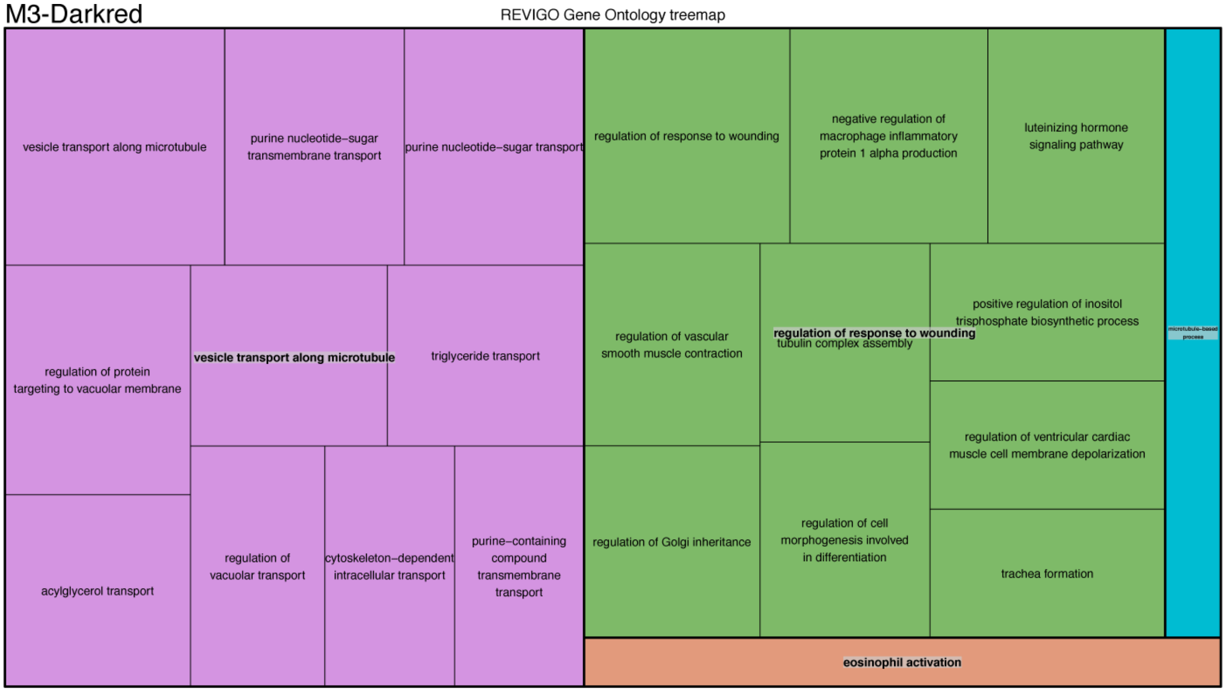
M9-Darkgrey



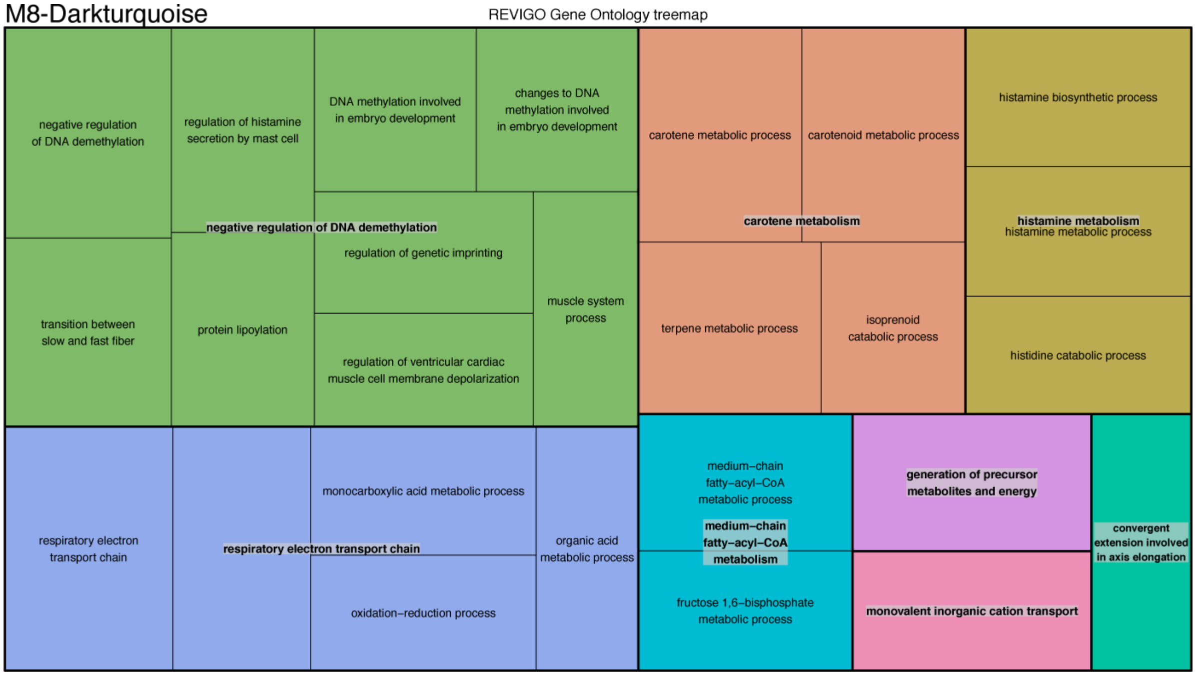
M12-Darkorange



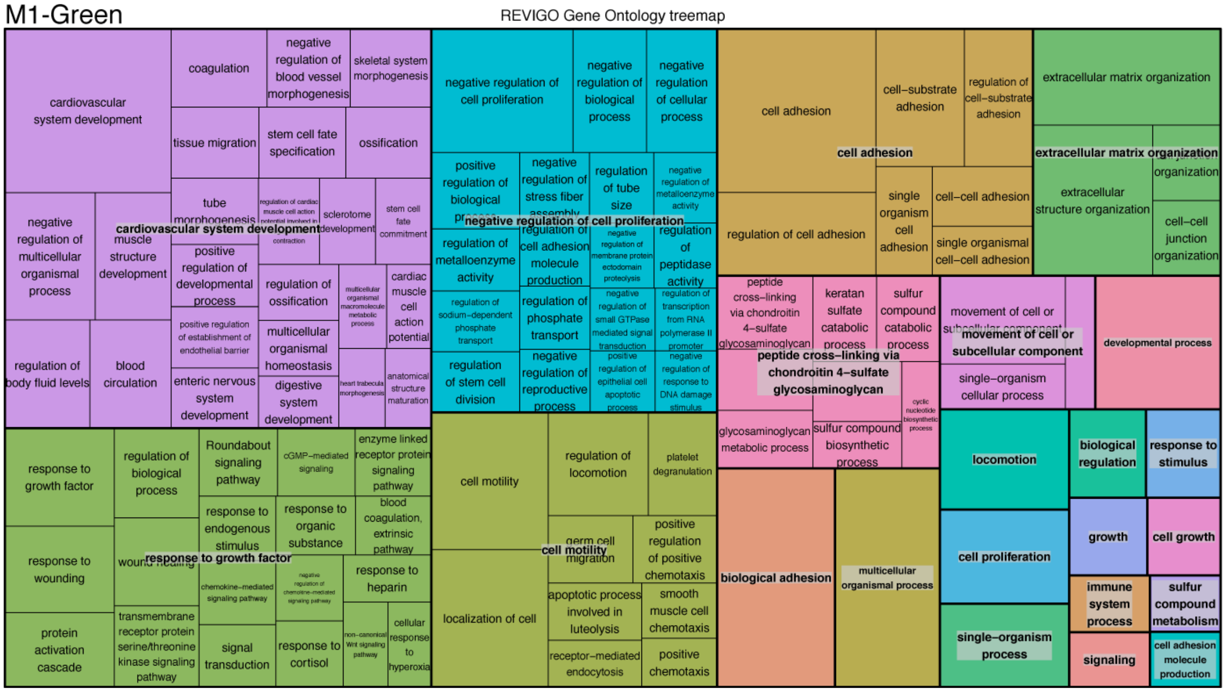
M3-Darkred



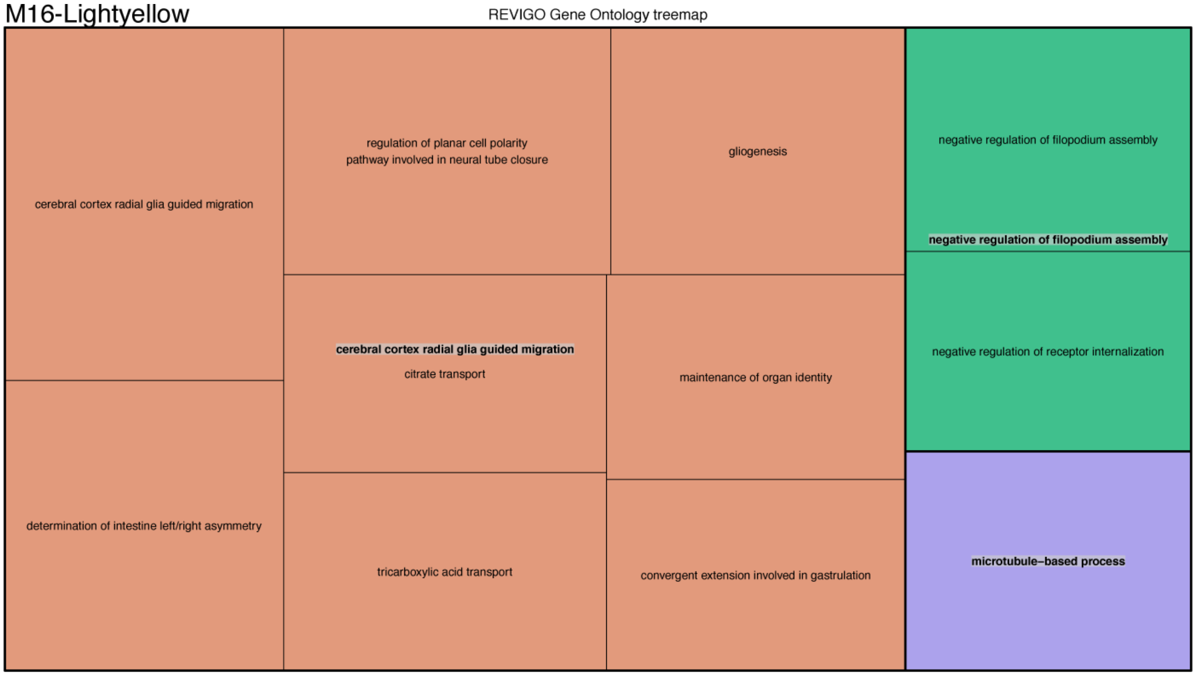
M8-Darkturquoise



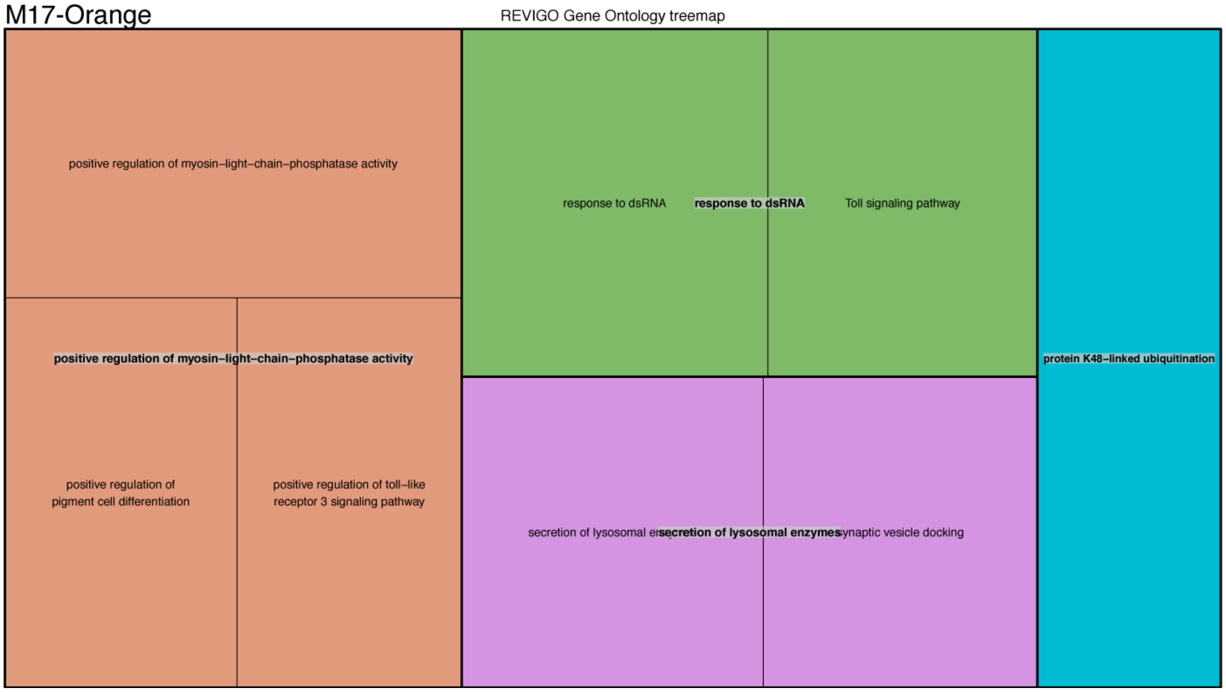
M1-Green



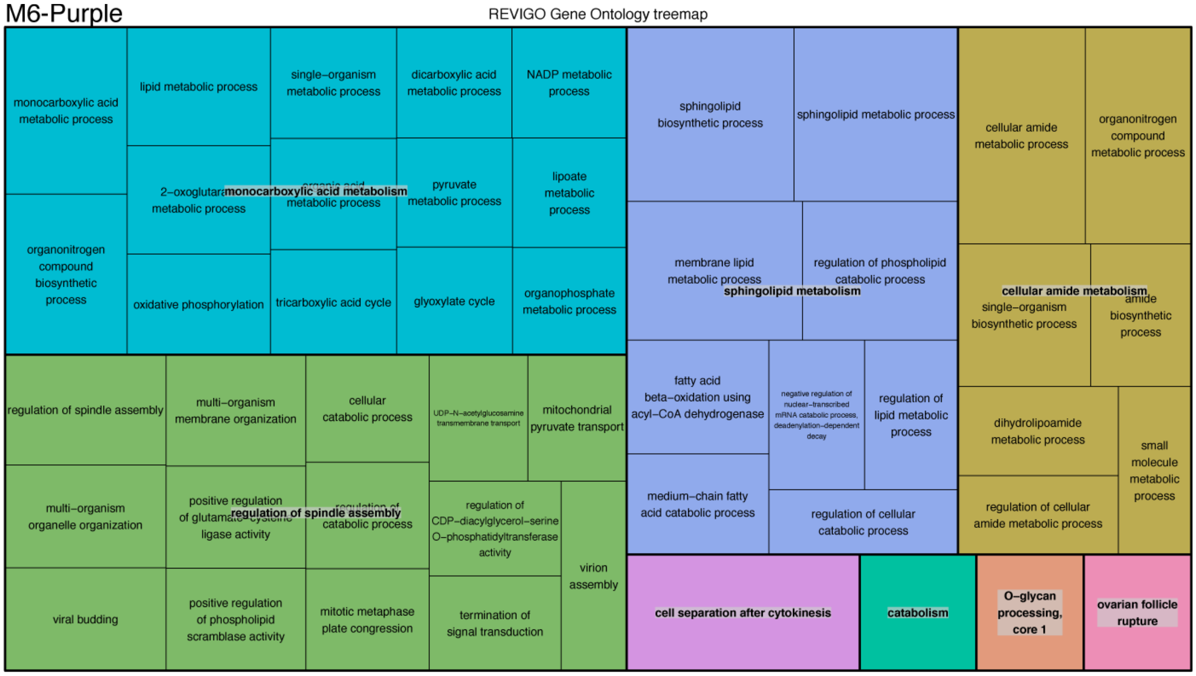
M16-Lightyellow



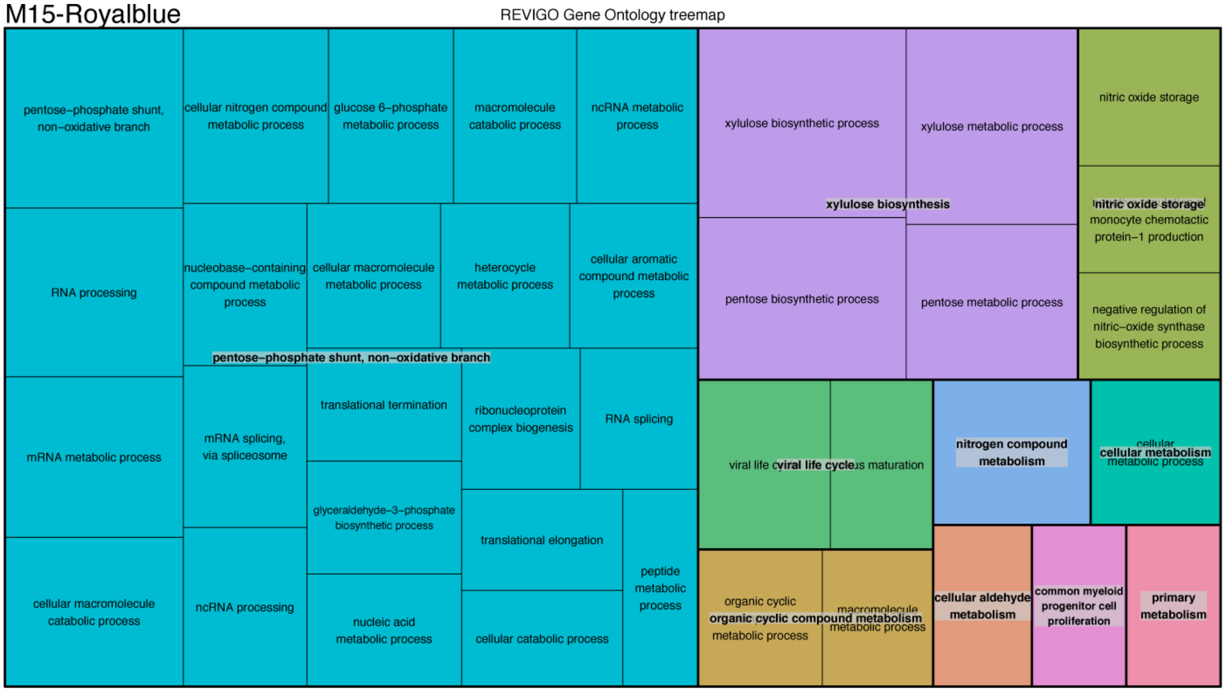
M17-Orange



M6-Purple

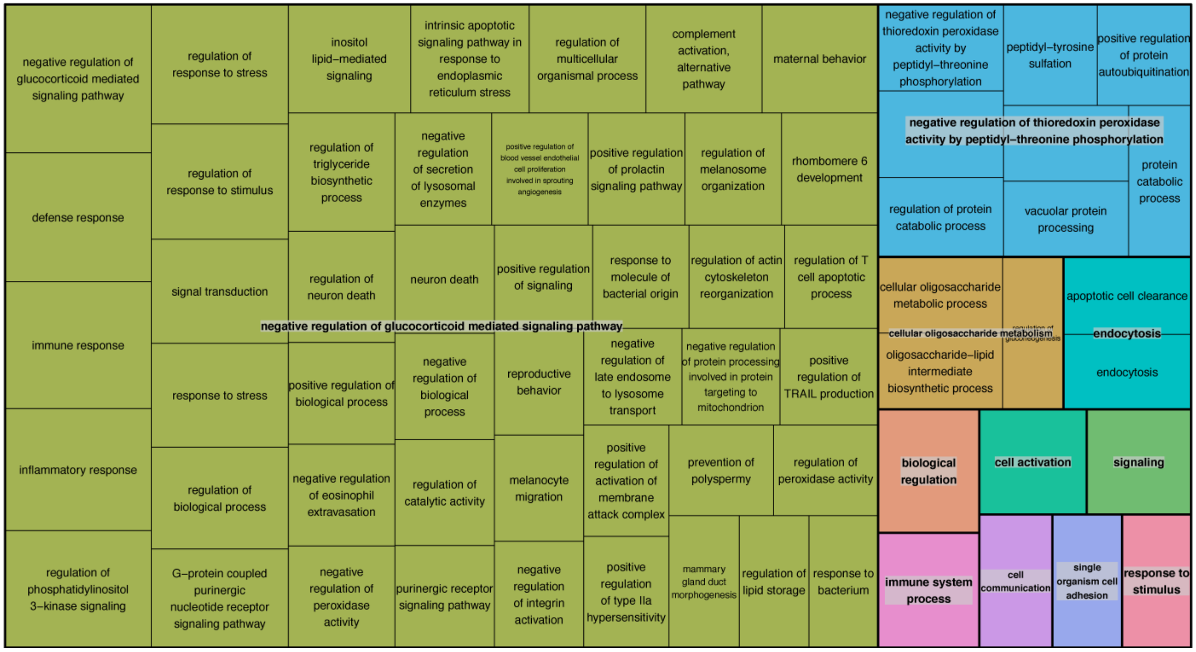


M15-Royalblue



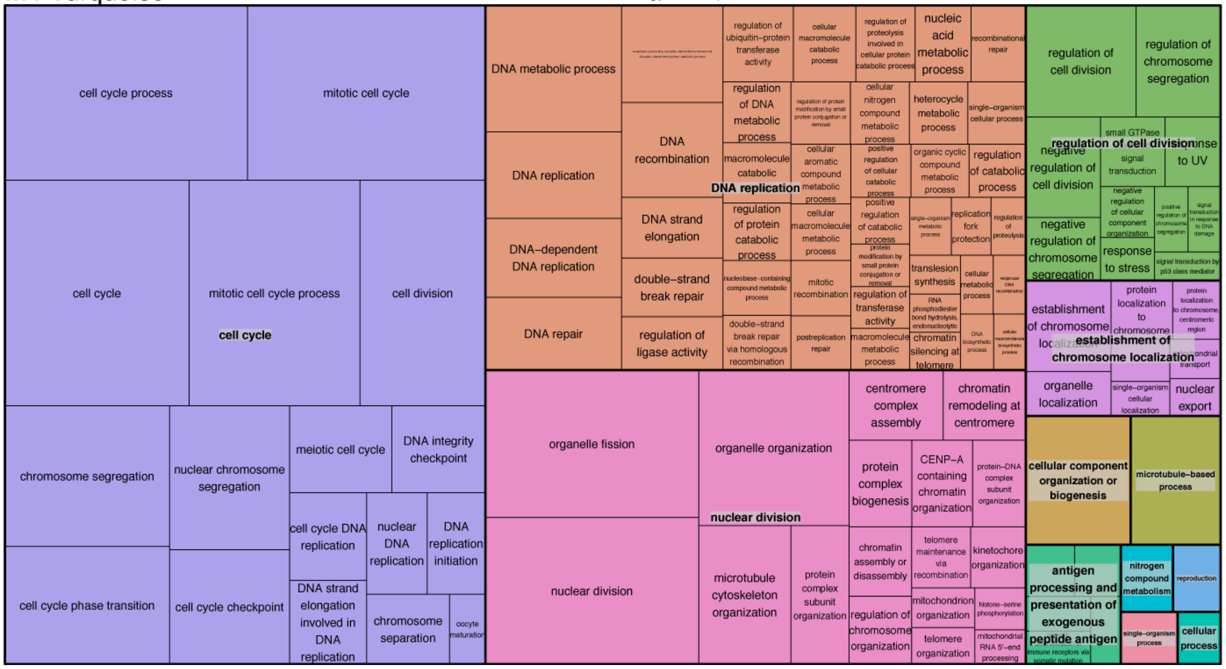
M14-Salmon

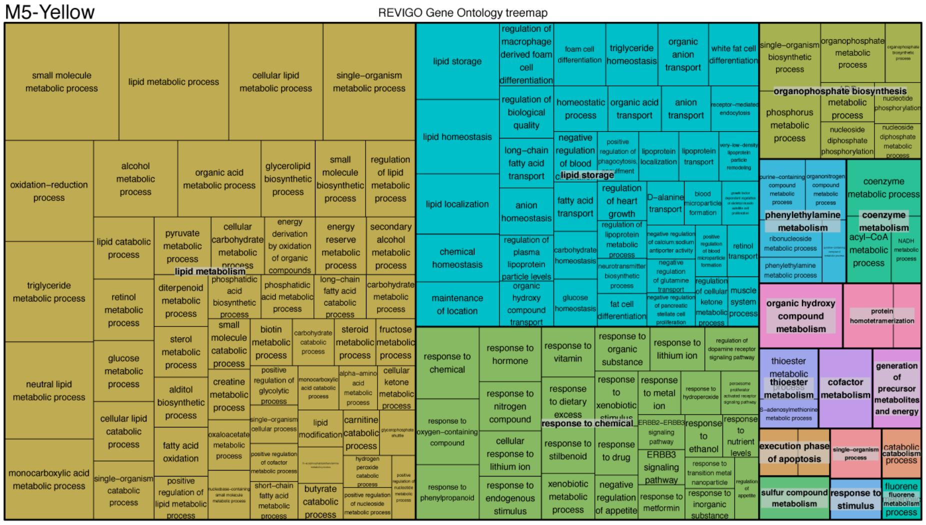
REVIGO Gene Ontology treemap



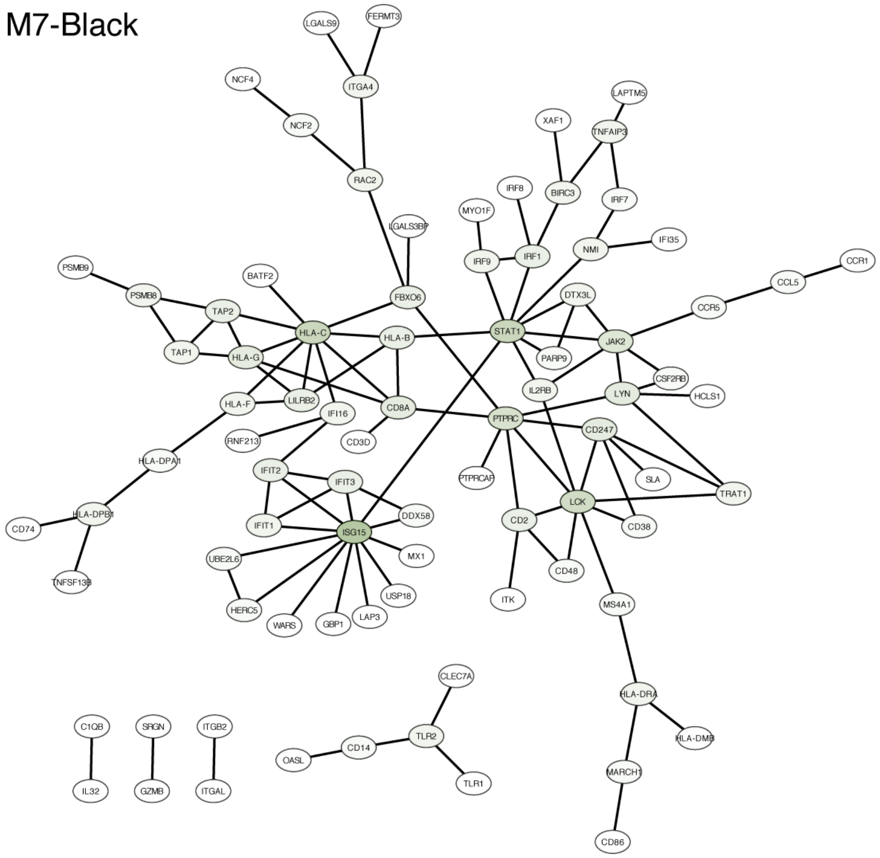
M4-Turquoise

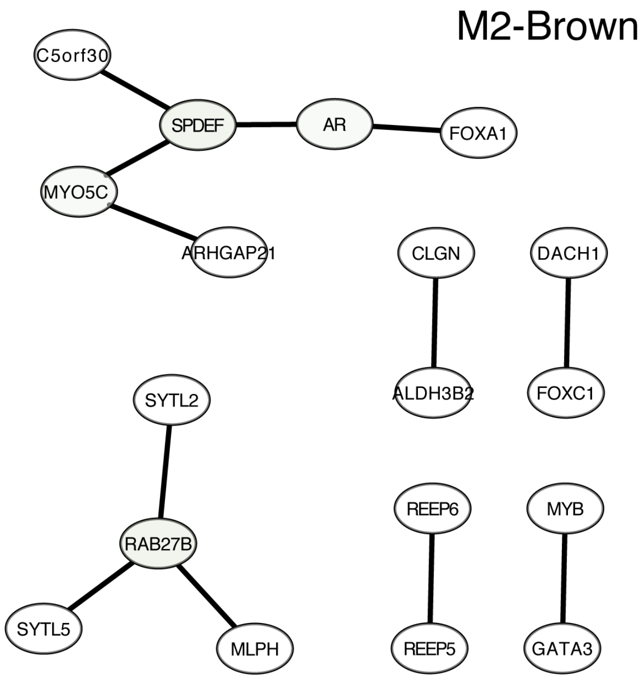
REVIGO Gene Ontology treemap



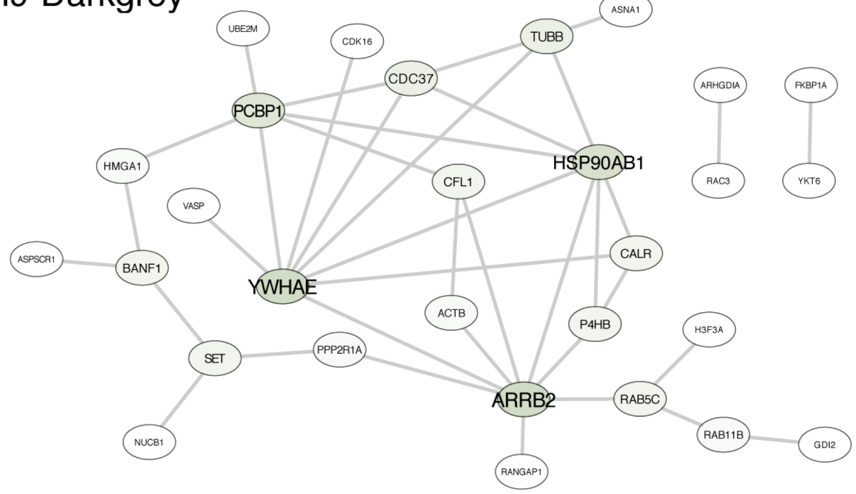


Supplementary Figure 3: ReviGO visualization of significantly enriched gene ontology terms among genes of each module.

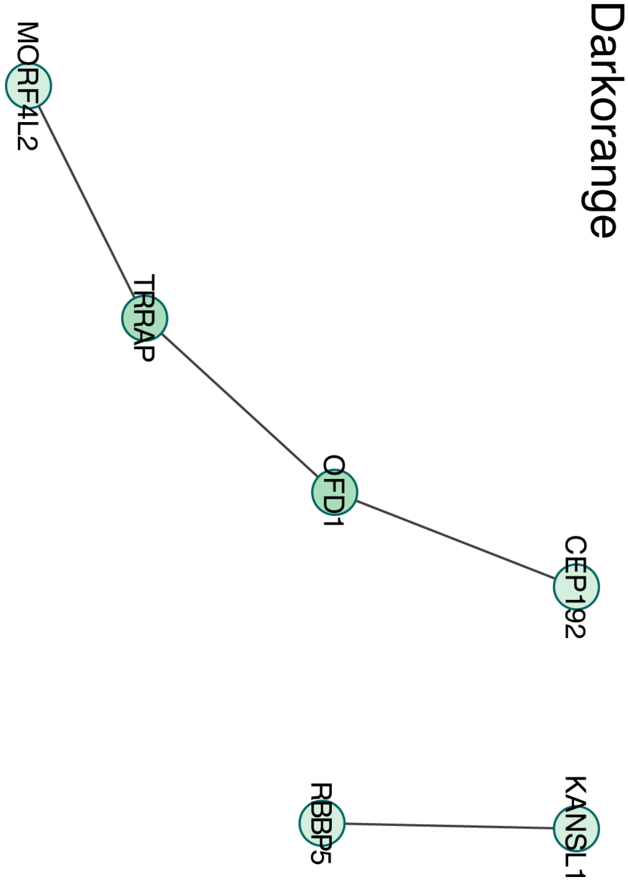

M7-Black

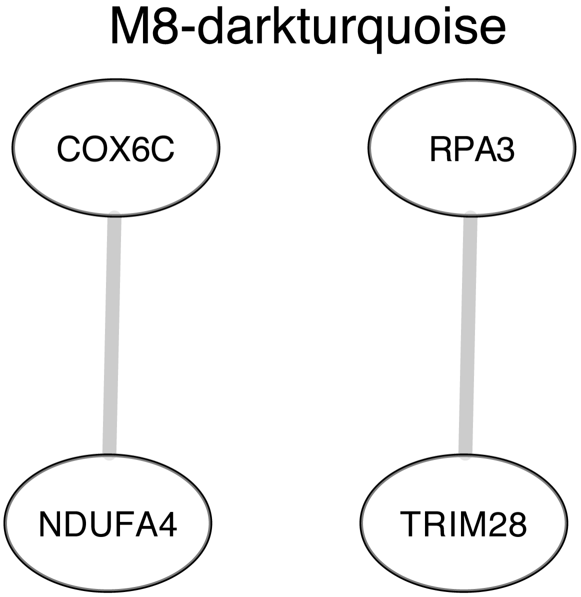

M2-Brown

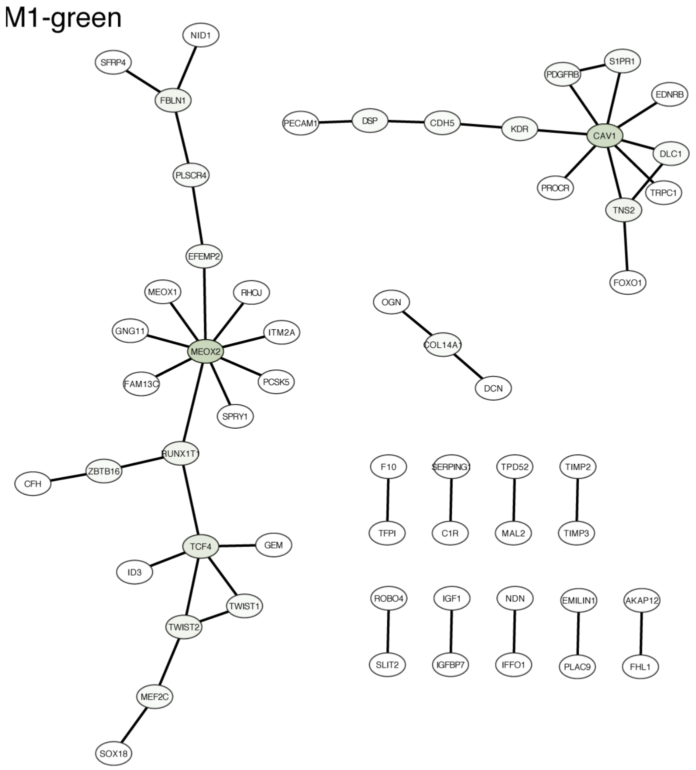
M9-Darkgrey



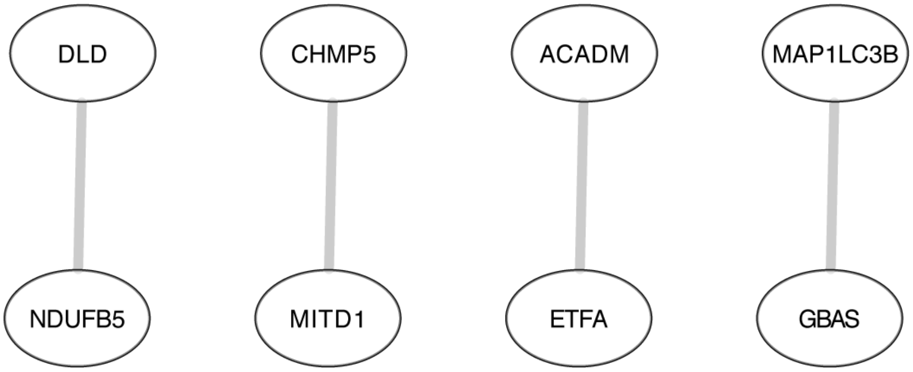
M12-Darkorange

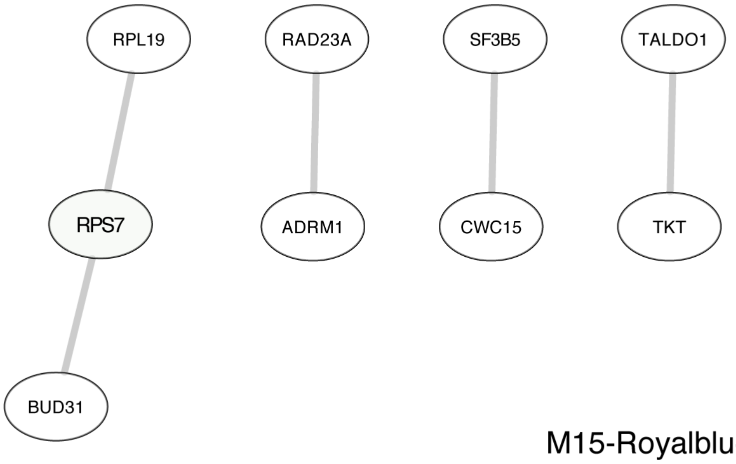



M8-darkturquoise
COX6C
RPA3
NDUFA4
TRIM28


M1-green
NID1
SFRP4
FBLN1
PLSCR4
EFEMP2
MEOX1
RHOJ
GNG11
ITM2A
MEOX2
FAM13C
PCSK5
SPRY1
RUNX1T1
ZBTB16
CFH
TCF4
GEM
ID3
TWIST1
TWIST2
MEF2C
SOX18
PECAM1
DSP
CDH5
KDR
CAV1
PDGFRB
S1PR1
EDNRB
DLC1
PROCR
TRPC1
TNS2
FOXO1
OGN
COL14A1
DCN
F10
TFPI
SERPING1
C1R
TPD52
MAL2
TIMP2
TIMP3
ROBO4
SLIT2
IGF1
IGFBP7
NDN
IFFO1
EMILIN1
PLAC9
AKAP12
FHL1

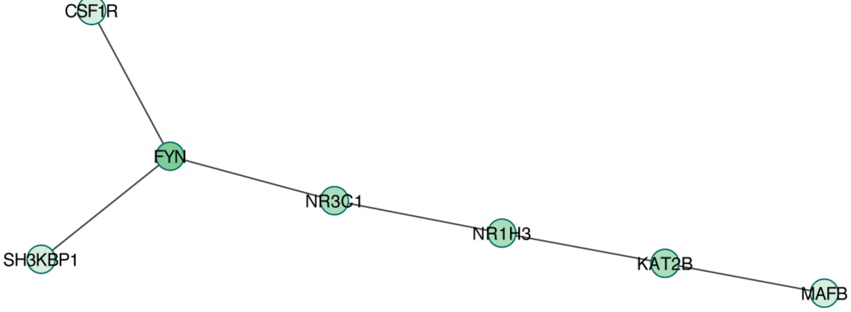
M6-Purple

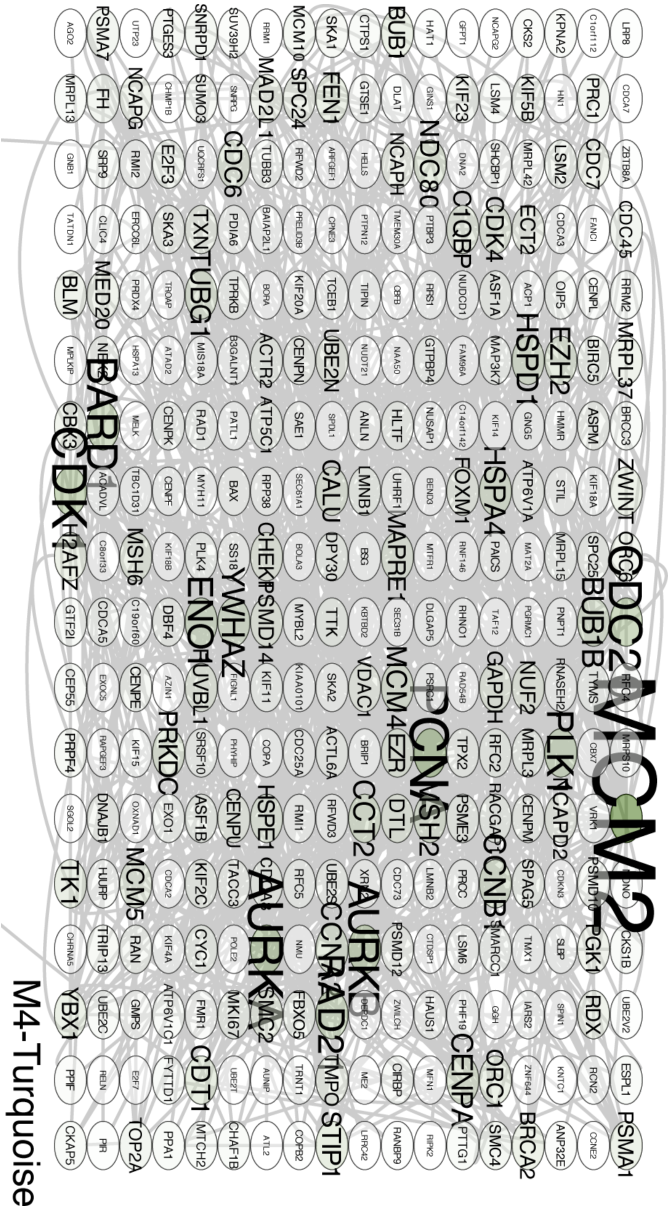


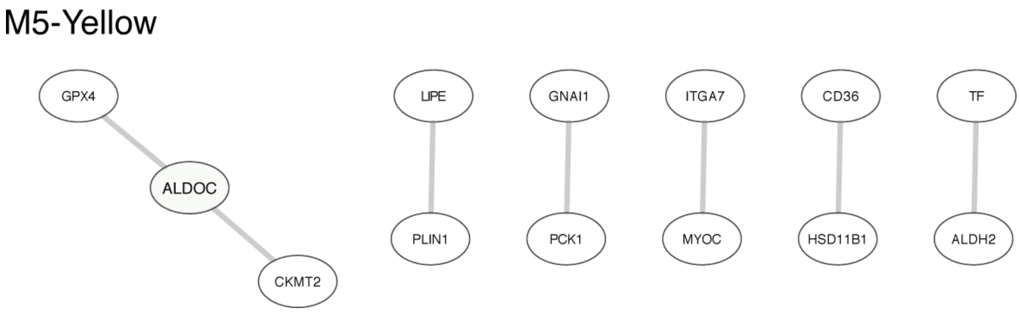


M15-Royalblue

M14-Salmon

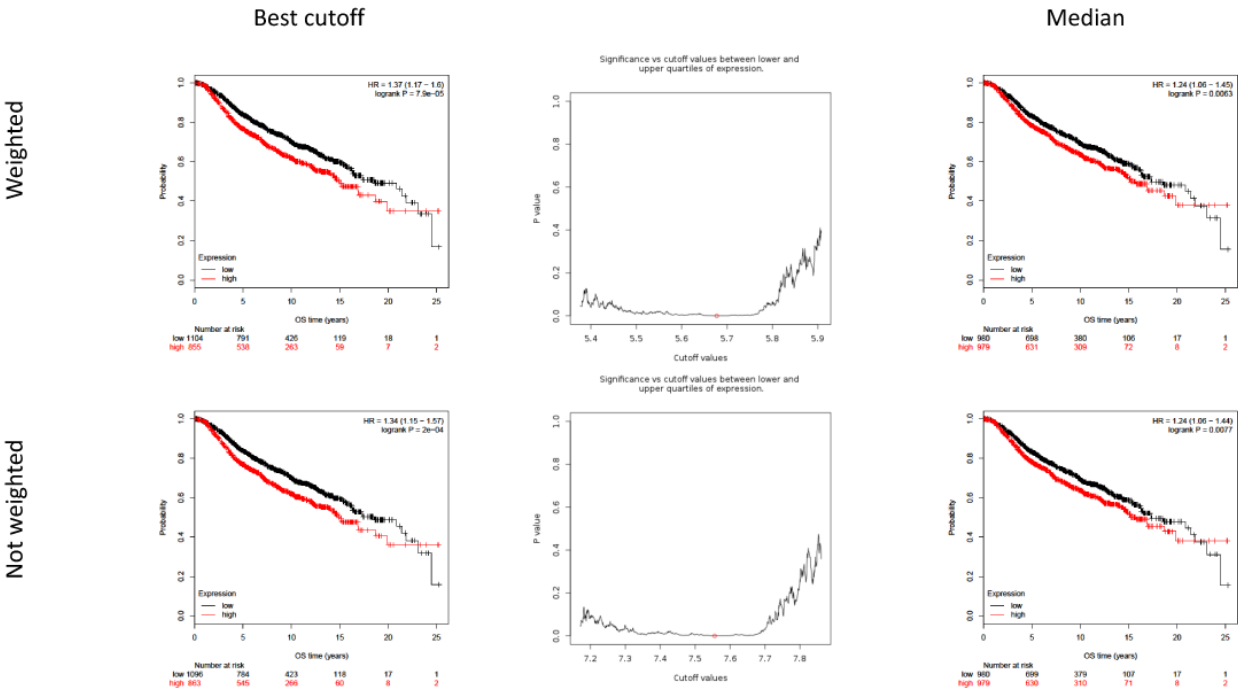




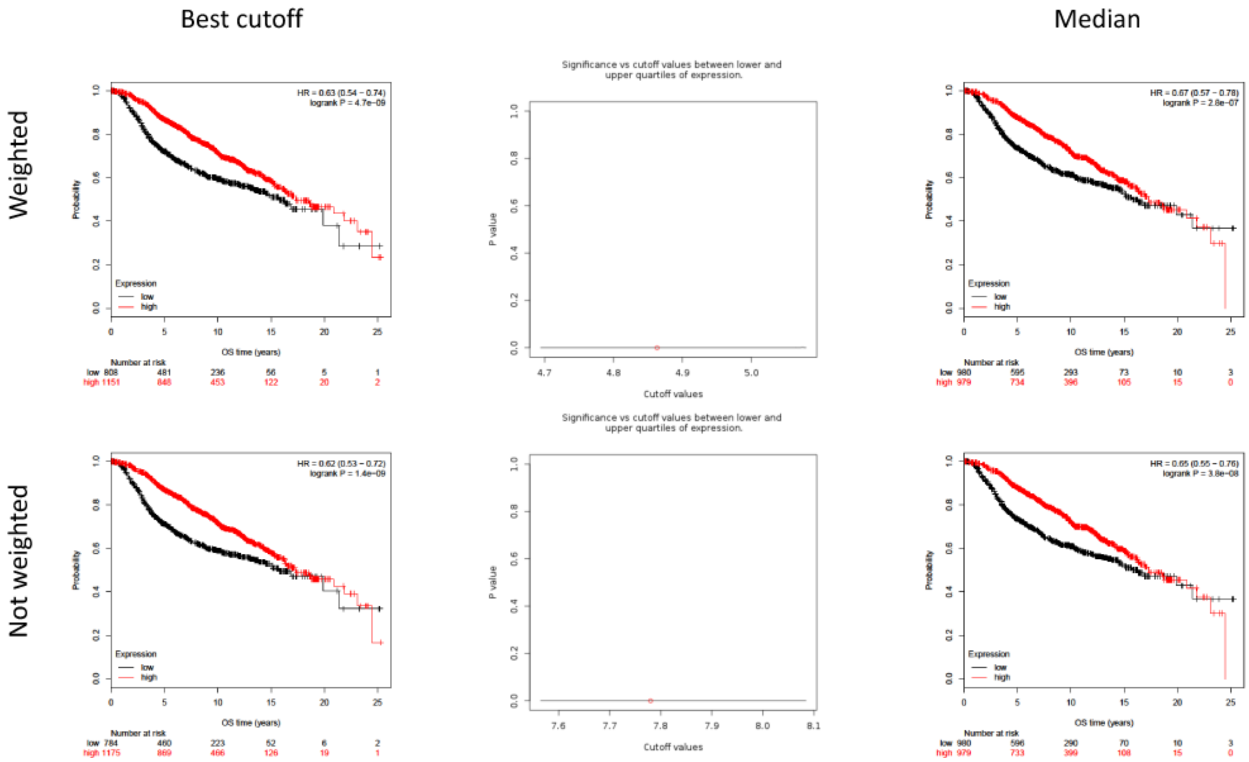


Supplementary Figure 4: Protein-protein interaction network for genes in each module. Green color shade indicates node degree.

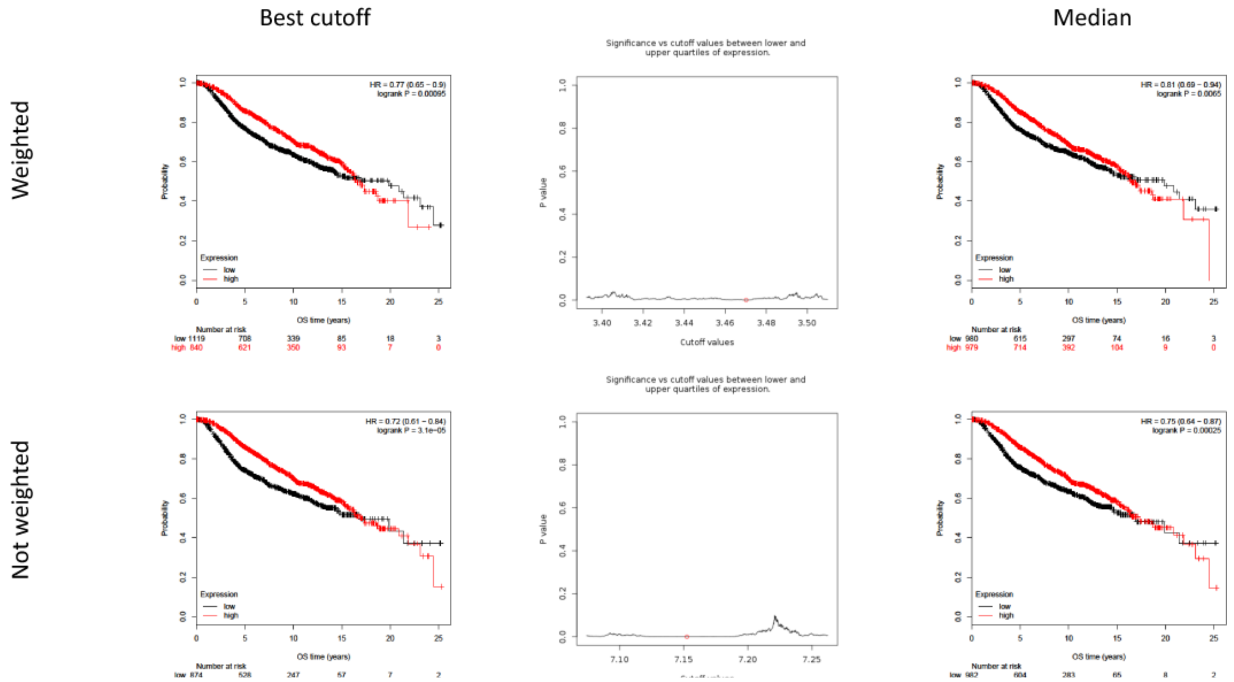
BLACK


Best cutoff
Median
Weighted
Not weighted
HR = 1.37 (1.17 − 1.6)
logrank P = 7.9e−05
Probability
OS time (years)
Expression
low
high
Number at risk
low 1104 791 426 119 18 1
high 855 538 263 59 7 2
Significance vs cutoff values between lower and upper quartiles of expression.
P value
Cutoff values
5.4 5.5 5.6 5.7 5.8 5.9
HR = 1.24 (1.06 − 1.45)
logrank P = 0.0063
low 980 698 380 106 17 1
high 979 631 309 72 8 2
HR = 1.34 (1.15 − 1.57)
logrank P = 2e−04
low 1096 784 423 118 17 1
high 863 545 266 60 8 2
7.2 7.3 7.4 7.5 7.6 7.7 7.8
HR = 1.24 (1.06 − 1.44)
logrank P = 0.0077
low 980 699 379 107 17 1
high 979 630 310 71 8 2

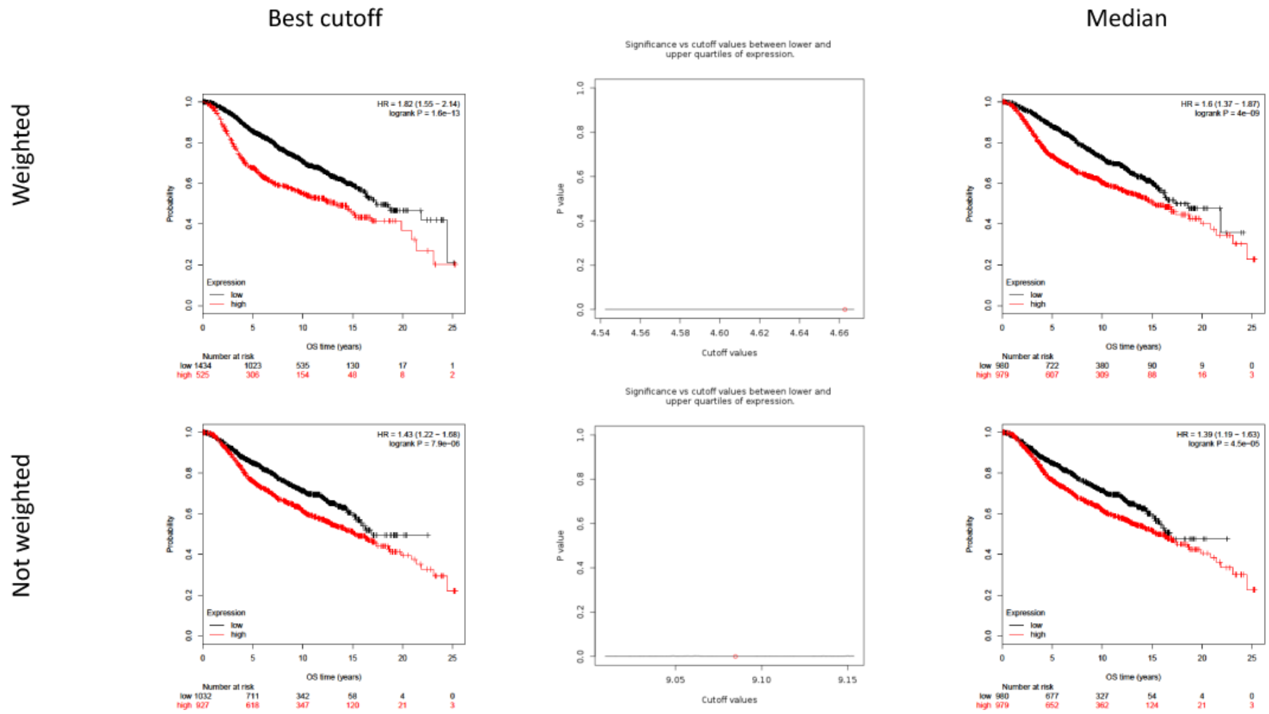
BROWN


Best cutoff
Median
Weighted
Not weighted
HR = 0.63 (0.54 − 0.74)
logrank P = 4.7e−09
Probability
OS time (years)
Expression
low
high
Number at risk
low 808 481 236 56 5 1
high 1151 848 453 122 20 2
Significance vs cutoff values between lower and upper quartiles of expression.
P value
Cutoff values
4.7 4.8 4.9 5.0
HR = 0.67 (0.57 − 0.78)
logrank P = 2.8e−07
low 980 595 293 73 10 3
high 979 734 396 105 15 0
HR = 0.62 (0.53 − 0.72)
logrank P = 1.4e−09
low 784 460 223 52 6 2
high 1175 869 466 126 19 1
7.6 7.7 7.8 7.9 8.0 8.1
HR = 0.65 (0.55 − 0.76)
logrank P = 3.8e−08
low 980 596 290 70 10 3
high 979 733 399 108 15 0

CYAN



DARKGREY

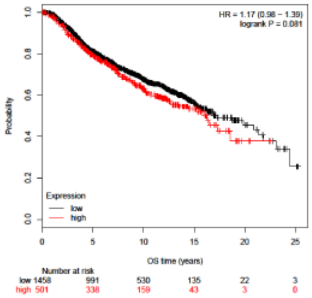


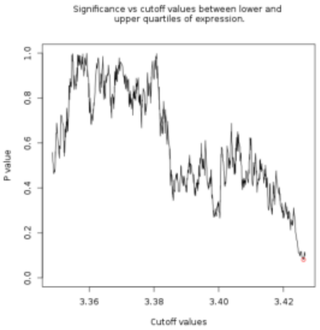
DARKORANGE

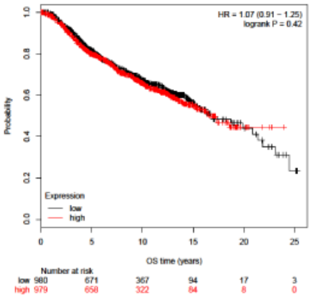
Best cutoff

Median

Weighted







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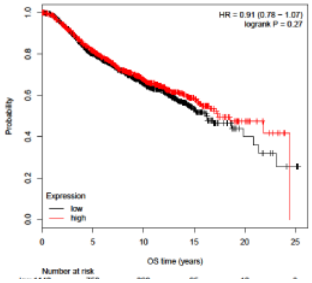
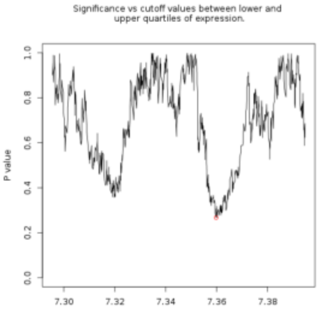
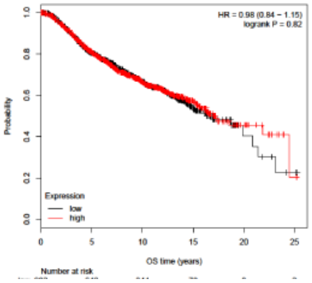




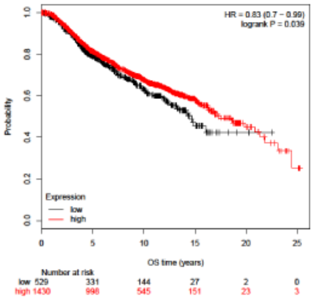


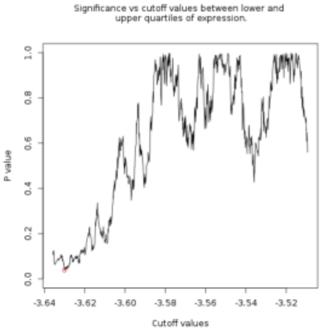
DARKRED

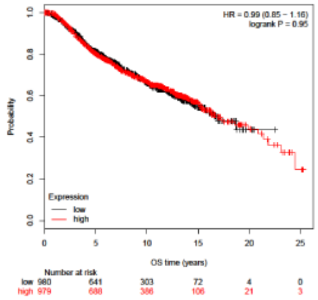
Best cutoff

Median

Weighted







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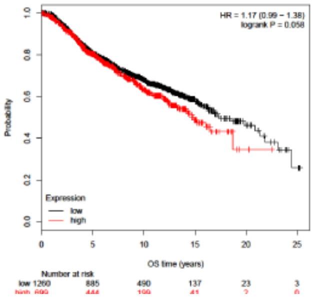
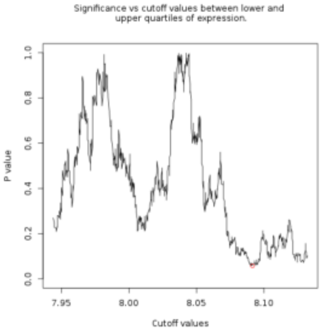
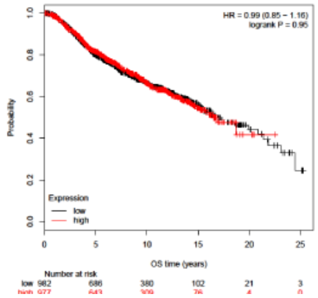




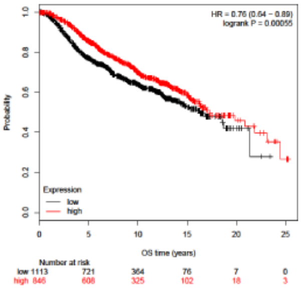


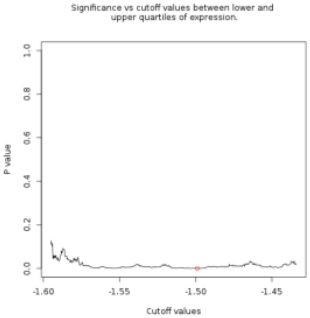
DARKTURQUOISE

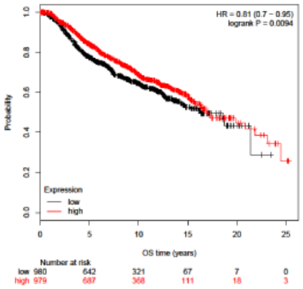
Best cutoff

Median

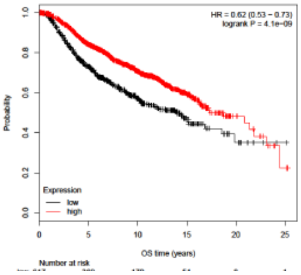
Weighted

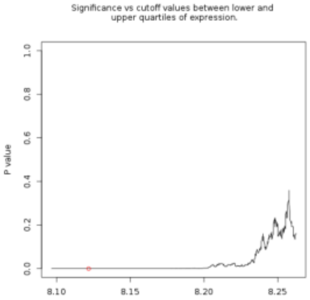


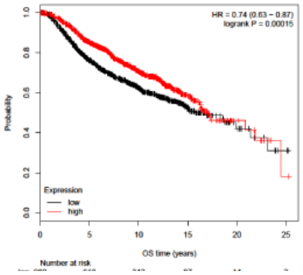

Significance vs cutoff values between lower and upper quartiles of expression.



Not weighted




Significance vs cutoff values between lower and upper quartiles of expression.

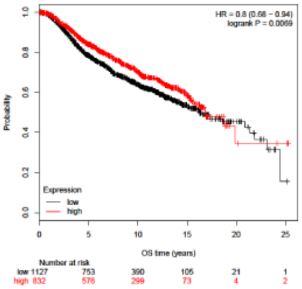


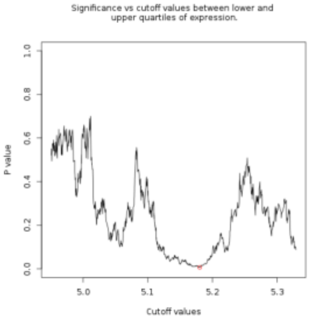
GREEN

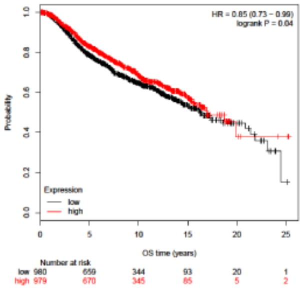
Best cutoff

Median

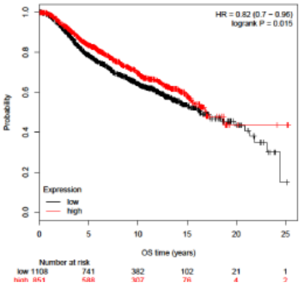
Weighted

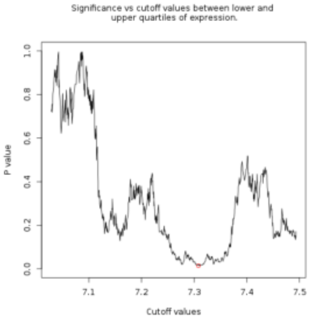


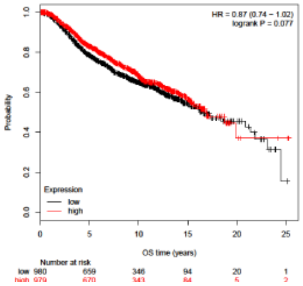

Significance vs cutoff values between lower and upper quartiles of expression.



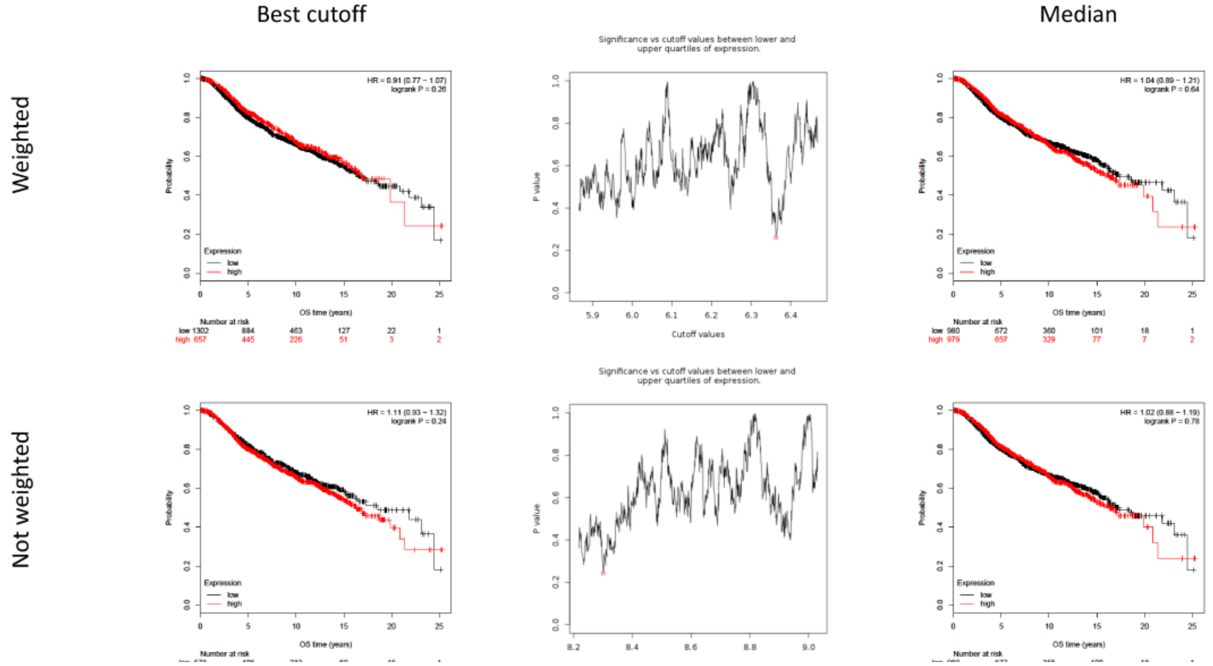
Not weighted



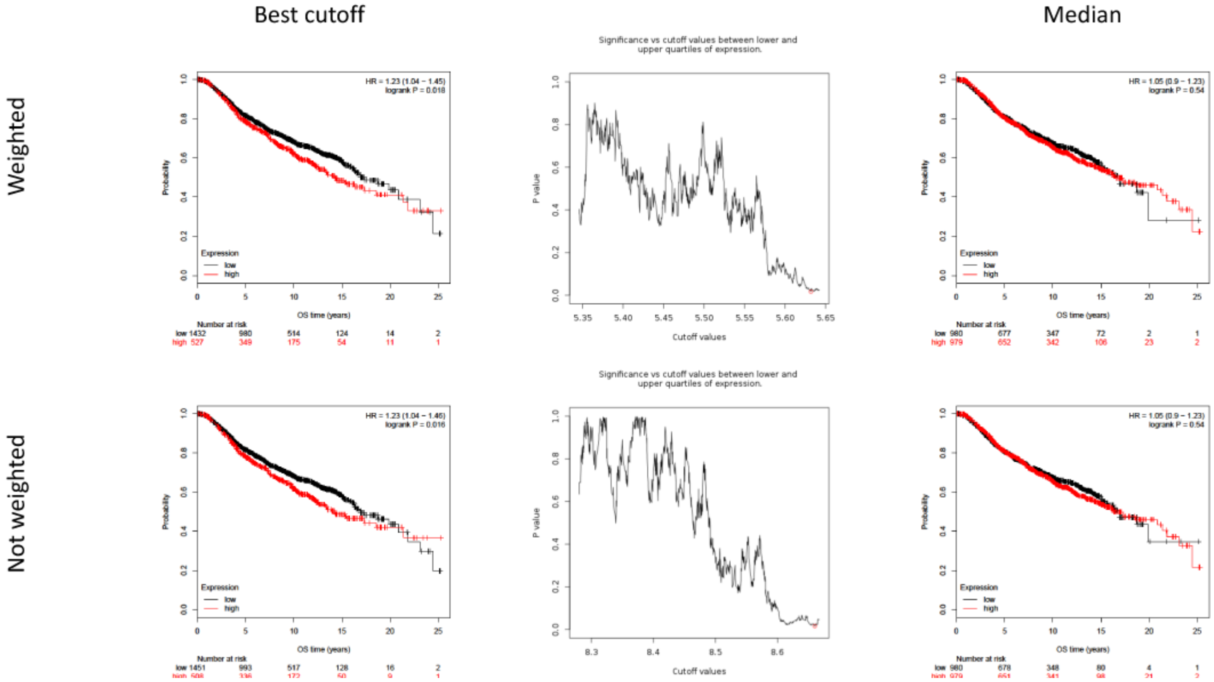

Significance vs cutoff values between lower and upper quartiles of expression.



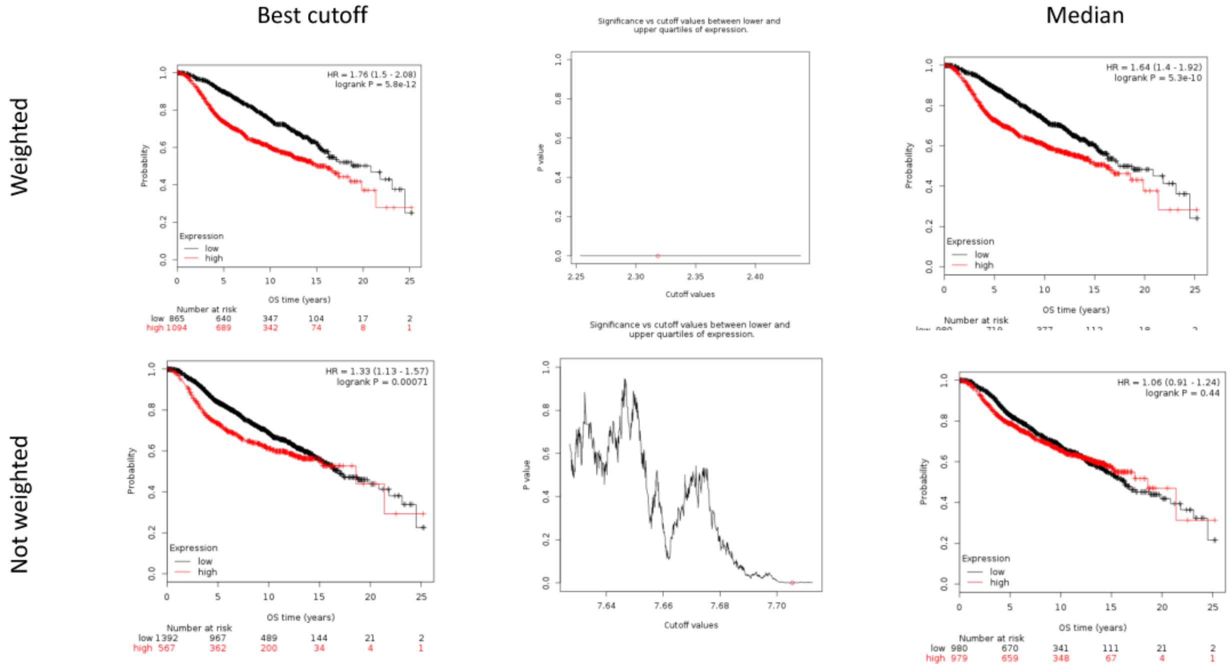
GREENYELLOW



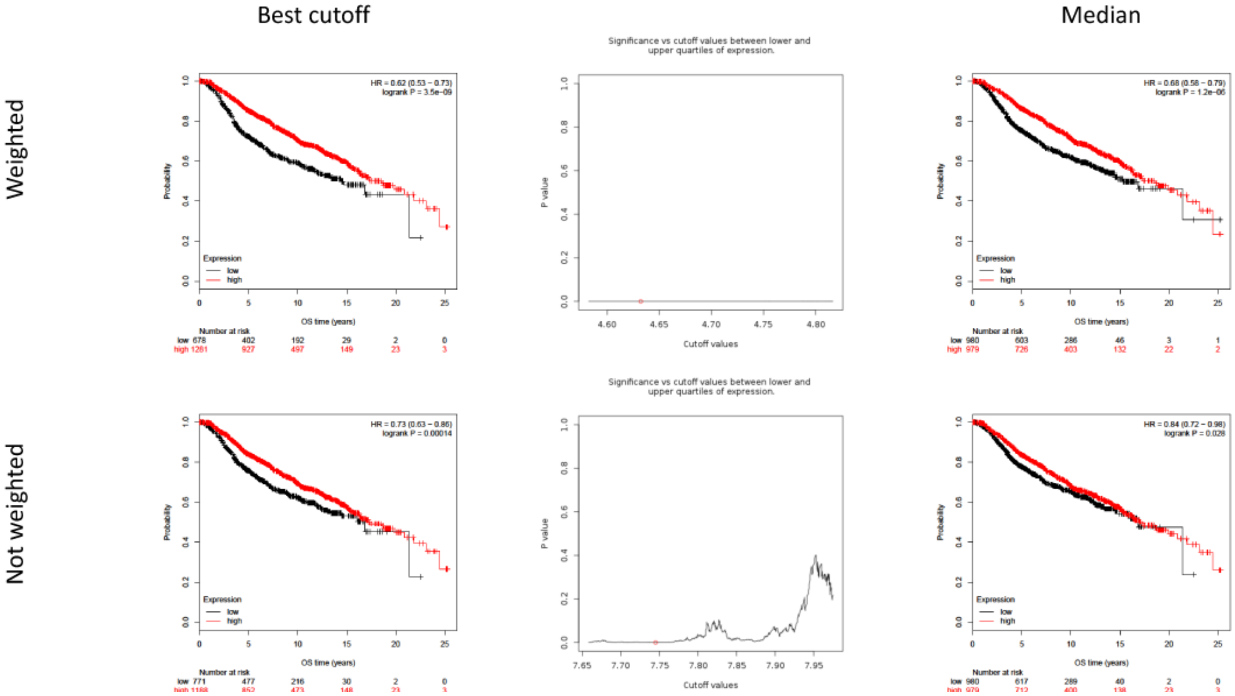
GREY60



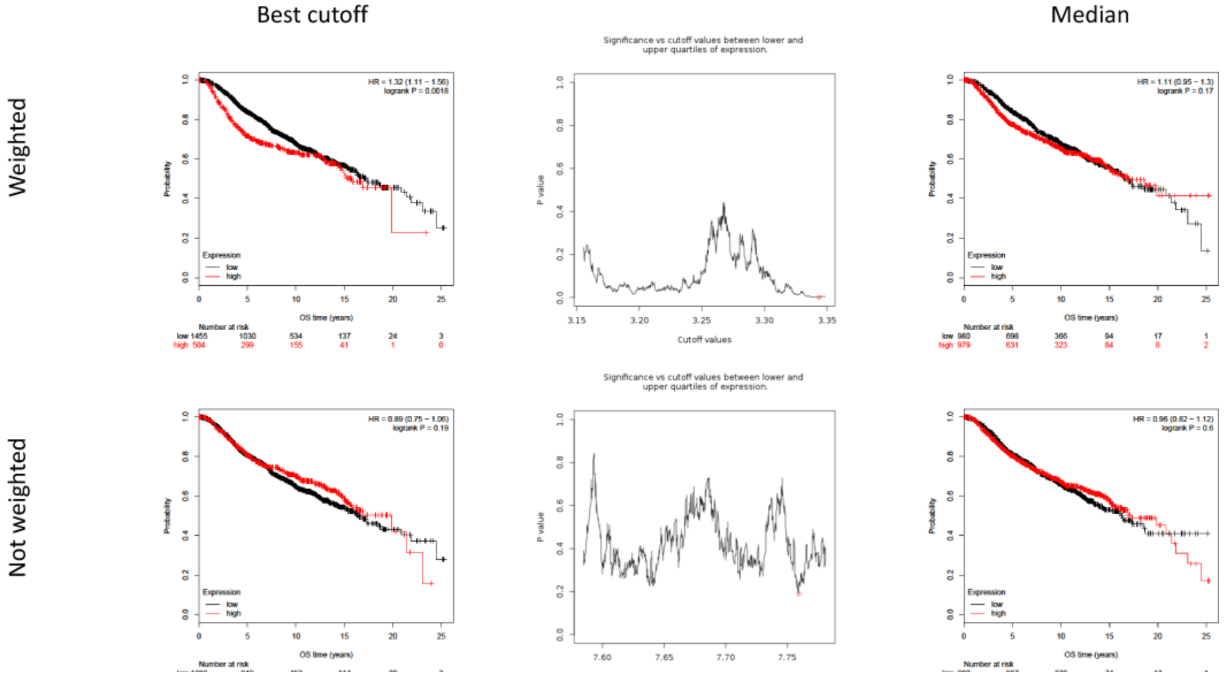
GREY500



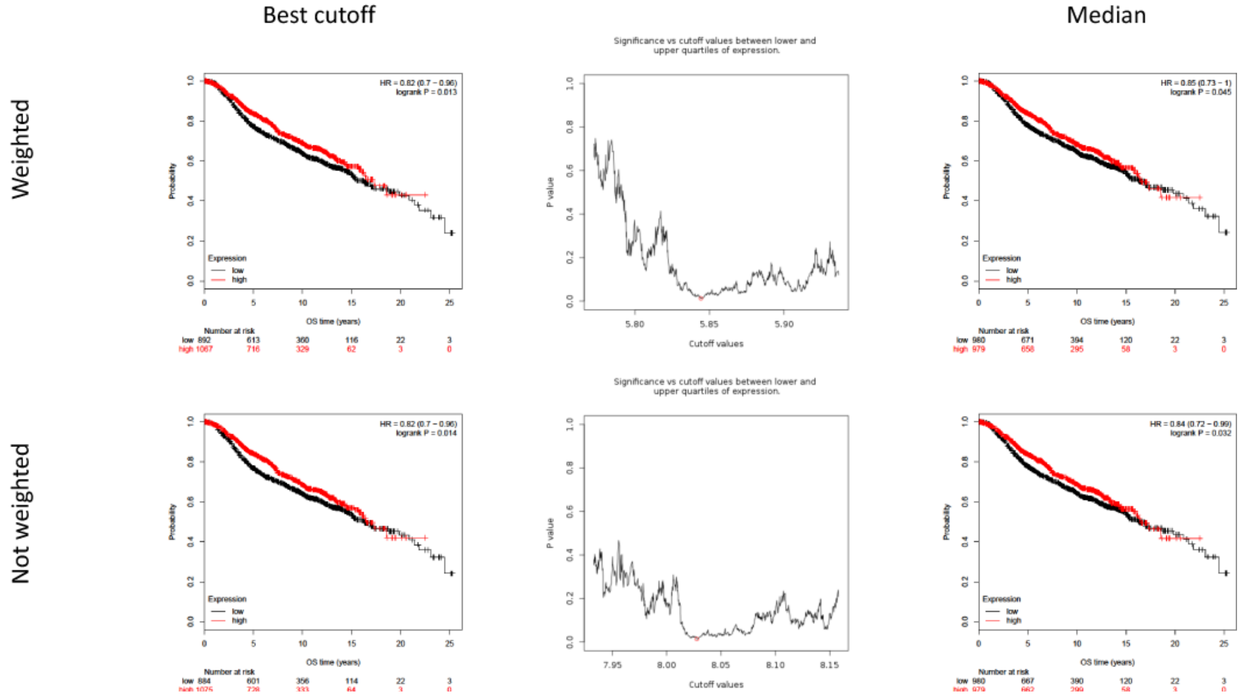
LIGHTYELLOW



ORANGE



PURPLE

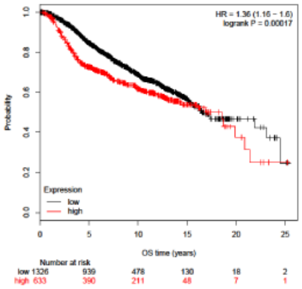


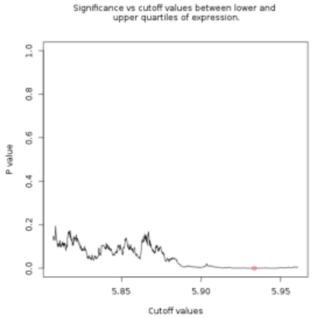
ROYALBLUE

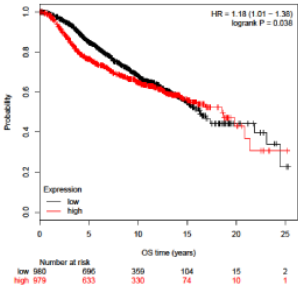
Best cutoff

Median

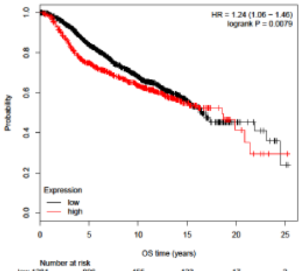
Weighted

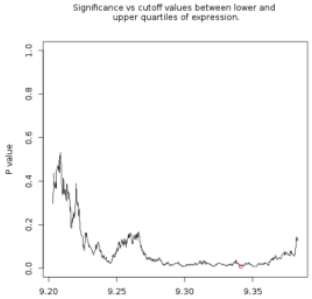


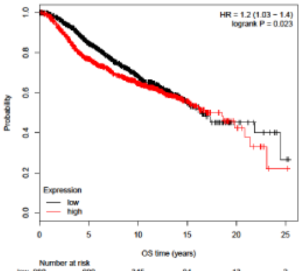




Not weighted





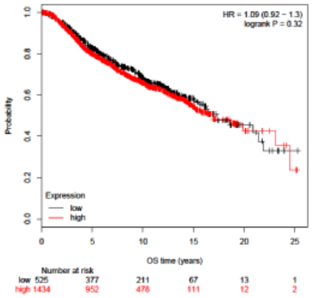


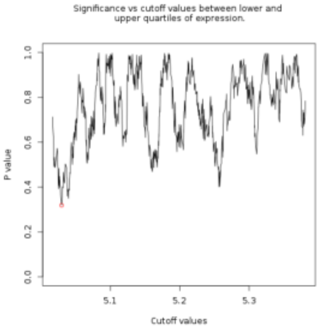
SALMON

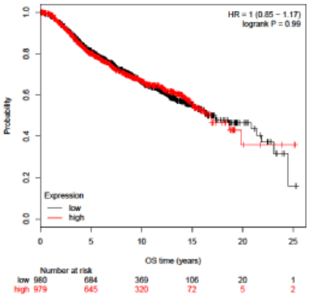
Best cutoff

Median

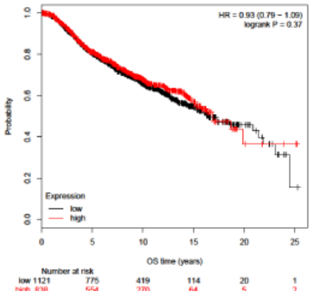
Weighted

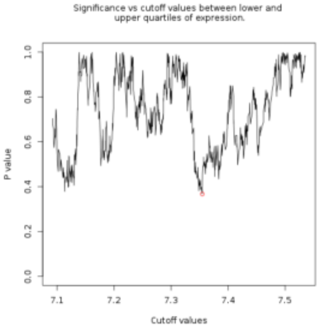


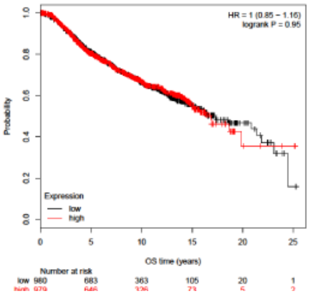


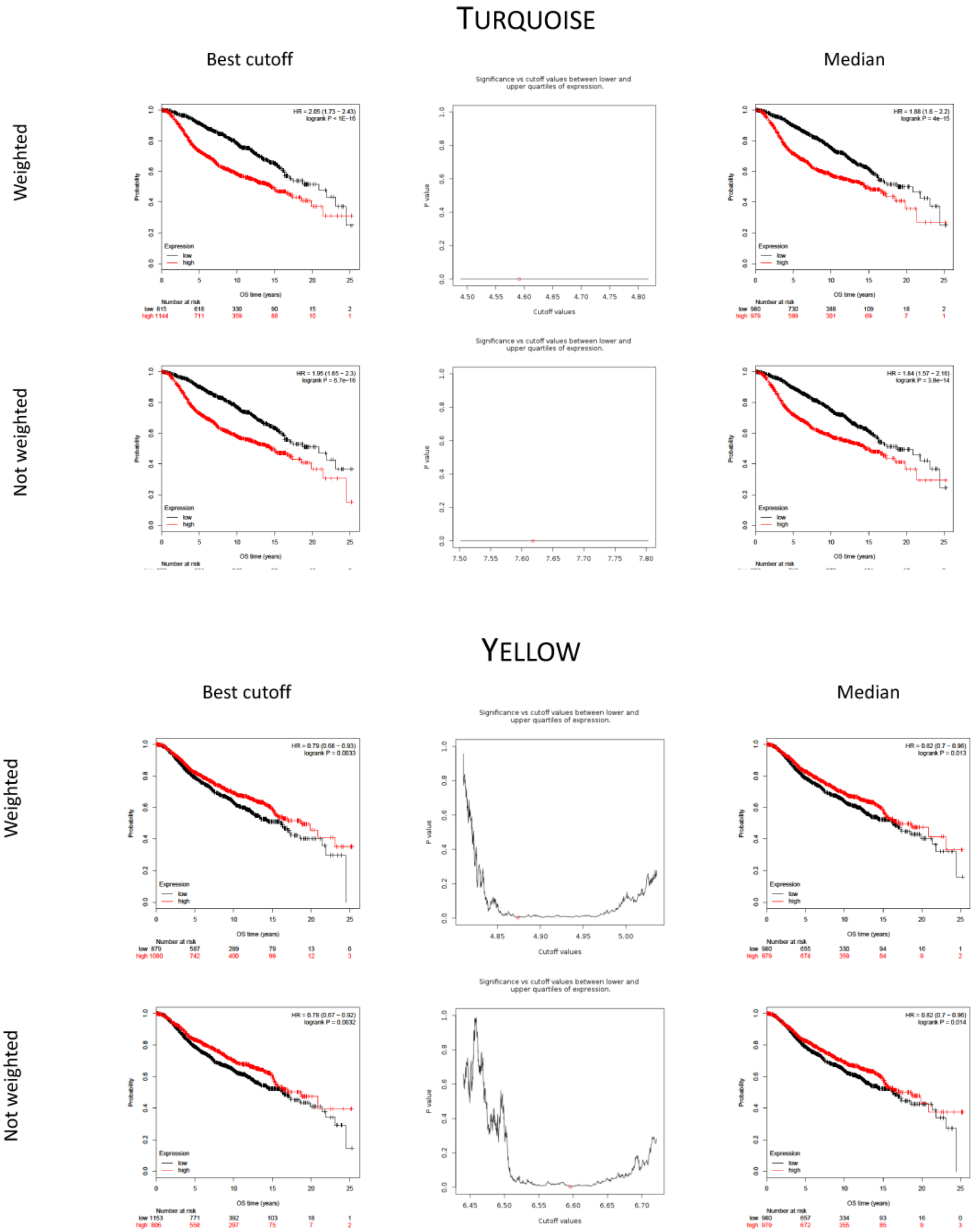


Not weighted









Supplementary Figure 5: KM plots for genes in modules splitting Metabric samples in low-expressing and high-expressing gene sets. Upper panels labeled show results using genes values weighted by gene membership in the corresponding module.

Supplementary Table 1: Overlaps between genes in modules and previously reported breast cancer dysregulated genes. *P*-values were obtained by means of a Fisher's exact test. See Supplementary_Table_1

Supplementary Table 2: Expression summary statistics of genes in modules in normal and tumor Metabric samples. Rows are colored according to the direction of changes (green, up-regulated and red, down-regulated)

sample	genelist	min	Q1	median	Q3	max	*p*_value
normal	black	9.846	10.095	10.183	10.32	11.005	
tumour	black	8.268	10.411	10.81	11.282	12.911	3.79E–42
normal	brown	9.584	10.014	10.266	10.501	11.183	
tumour	brown	9.079	10.753	11.144	11.438	12.322	8.81E–40
normal	cyan	10.059	10.178	10.215	10.262	10.373	
tumour	cyan	8.407	10.171	10.279	10.375	10.788	2.07E–08
normal	darkgrey	11.807	11.884	11.925	11.975	12.089	
tumour	darkgrey	10.443	12.951	13.04	13.129	13.577	1.12E–88
normal	darkorange	10.159	10.28	10.349	10.4	10.539	
tumour	darkorange	8.446	10.429	10.5	10.576	10.949	1.86E–55
normal	darkred	10.318	10.514	10.576	10.654	10.87	
tumour	darkred	8.932	10.819	10.917	11.024	11.62	2.75E–68
normal	darkturquoise	11.099	11.225	11.272	11.33	11.617	
tumour	darkturquoise	9.559	11.72	11.837	11.959	12.478	1.26E–86
normal	green	10.128	10.943	11.194	11.363	11.642	
tumour	green	8.479	10.106	10.378	10.661	12.027	6.26E–62
normal	greenyellow	10.243	10.789	10.964	11.168	12.182	
tumour	greenyellow	9.617	11.485	12.02	12.531	14.175	3.66E–56
normal	grey	10.283	10.396	10.432	10.452	10.49	
tumour	grey	8.595	10.484	10.536	10.589	10.768	4.88E–59
normal	grey60	9.086	9.883	10.346	10.553	10.917	
tumour	grey60	8.749	10.877	11.106	11.288	11.892	2.20E–69
normal	lightyellow	10.555	10.728	10.808	10.898	11.209	
tumour	lightyellow	8.488	10.551	10.705	10.879	11.619	2.85E–09
normal	orange	10.136	10.512	10.587	10.657	10.807	
tumour	orange	8.364	10.367	10.484	10.621	11.156	5.00E–11
normal	purple	10.562	10.799	10.889	11.007	11.238	
tumour	purple	9.37	11.261	11.428	11.573	12.624	2.66E–68
normal	royalblue	11.33	11.428	11.48	11.541	11.749	
tumour	royalblue	10.078	12.233	12.335	12.445	13.087	1.12E–88
normal	salmon	9.905	10.347	10.498	10.7	11.221	
tumour	salmon	8.219	10.237	10.468	10.722	11.846	0.103305466
normal	turquoise	10.261	10.325	10.35	10.401	10.914	
tumour	turquoise	8.941	10.856	11.049	11.26	12.003	1.36E–86
normal	yellow	9.846	10.454	11.16	11.874	12.84	
tumour	yellow	7.864	9.607	9.724	9.926	13.217	1.07E–76

Supplementary Table 3: Gene Ontology categories enriched in each gene module. See Supplementary_Table_3

Supplementary Table 4: List of drugs associated to hub genes in modules. See Supplementary_Table_4

Supplementary Table 5: Achieved hazard rate and *p*-values for each module

	weighted						**unweighted**					
	HR		***p*_value**		**cutoff**		**HR**		***p*_value**		**cutoff**	
	best_ cutoff	**median**	**best_ cutoff**	**median**	**best_ cutoff**	**median**	**best_ cutoff**	**median**	**best_ cutoff**	**median**	**best_ cutoff**	**median**
M7-black	1.37	1.24	0.000079	0.0063	5.68	5.62	1.34	1.24	0.0002	0.0077	7.56	7.49
M2-brown	0.63	0.67	4.7E–09	0.00000028	4.86	4.93	0.62	0.65	1.4E–09	0.000000038	7.78	7.88
M10-cyan	0.77	0.81	0.00095	0.0065	3.47	3.46	0.72	0.75	0.000031	0.00025	7.15	7.17
M9-darkgrey	1.82	1.6	1.6E–13	0.000000004	4.66	4.6	1.43	1.39	0.0000079	0.000045	9.08	9.08
M12-darkorange	1.17	1.07	0.081	0.42	3.43	3.39	0.91	0.98	0.27	0.82	7.36	7.34
M3-darkred	0.83	0.99	0.039	0.95	–3.63	–3.57	1.17	0.99	0.058	0.95	8.09	8.04
M8-darkturquoise	0.76	0.81	0.00055	0.0094	–1.5	–1.52	0.62	0.74	4.1E–09	0.00015	8.12	8.18
M1-green	0.8	0.85	0.0069	0.04	5.18	5.13	0.82	0.87	0.015	0.077	7.31	7.26
M11-greenyellow	0.91	1.04	0.26	0.64	6.36	6.18	1.11	1.02	0.24	0.78	8.3	8.64
M0-grey	1.76	1.64	5.80E–12	5.30E–10	2.32	2.34	1.33	1.06	0.00071	0.44	7.71	7.67
M13-grey60	1.23	1.05	0.018	0.54	5.63	5.51	1.23	1.05	0.016	0.54	8.66	8.49
M16-lightyellow	0.62	0.68	3.5E–09	0.0000012	4.63	4.7	0.73	0.84	0.00014	0.028	7.75	7.8
M17-orange	1.32	1.11	0.0018	0.17	3.34	3.25	0.89	0.96	0.19	0.6	7.76	7.68
M6-purple	0.82	0.85	0.013	0.045	5.84	5.86	0.82	0.84	0.014	0.032	8.03	8.05
M15-royalblue	1.36	1.18	0.00017	0.038	5.93	5.88	1.24	1.2	0.0079	0.023	9.34	9.29
M14-salmon	1.09	1	0.32	0.99	5.03	5.18	0.93	1	0.37	0.95	7.35	7.29
M4-turquoise	2.05	1.88	1E–16	4E–15	4.59	4.64	1.95	1.84	6.7E–16	3.8E–14	7.62	7.64
M5-yellow	0.79	0.82	0.0033	0.013	4.87	4.89	0.78	0.82	0.0032	0.014	6.6	6.54