Supporting Information for "Pathway-based personalized analysis of cancer" by Drier Y, Sheffer M, Domany E.

Principal Curves

The concept of principal curve was first proposed by Hastie and Stuetzle (1) as a non-parametric nonlinear extension of the linear Principal Component Analysis. We denote by *f(λ)* a curve in *p*-dimensional space, where *λ* is a single parameter whose variation traces all the points along the curve. A curve *f* is defined to be a principal curve *associated with a distribution P(x)* defined over some space, if and only if it is a smooth, one dimensional non intersecting curve that is *self-consistent*, i.e. each point *y* on the curve is the expected value of all the points *x* whose projection onto the curve is *y.* Let the projection index $\lambda_f(x)$ be the λ for which the projection of *x* on the curve is *f(λ)*: $\lambda_f(x) = \sup_{\lambda}\left\{\lambda : \|x - f(\lambda)\| = \inf_{\mu}\|x - f(\mu)\|\right\}$ The condition for self-consistency is simply $f(\lambda) = \mathbb{E}\left(X \middle| \lambda_f(X) = \lambda\right)$. Since in practice we are given a finite data set *X,* of *n* points in d_P dimensional space $X \in M_{n\times d_P}(\mathbb{R})$, while the distribution it is sampled from is not known, scatterplot smoothing is used. Hastie and Stuetzle also offer a two-steps iterative algorithm for finding such a principal curve:

1. Conditional-Expectation step: Fix $\lambda = \{\lambda_i\}_{i=1}^n$ and minimize $\mathbb{E}\|X - f(\lambda)\|$ by setting $f(\lambda_i)$ to be the local average (of the points projected onto a neighborhood of $f(\lambda_i)$, e.g. the points x_j for which $\lambda_j \cong \lambda_i$).
2. Projection step: Given $f = \{f(\lambda_i)\}_{i=1}^n$ find for each x_i the corresponding value of $\lambda_i = \lambda_f(x_i)$ assuming *f* is piecewise linear.

The line along the first linear principal component is used as a starting curve, and the algorithm is iterated until convergence.

Implementation and Availability

The code is implemented in R and uses "princurve 1.1-10" by Andreas Weingessel (http://cran.r-project.org/web/packages/princurve/index.html), which is in turn based on the original S/Fortran code princurv by Hastie. The code is available at http://www.weizmann.ac.il/pathifier/ and on Bioconductor (http://www.bioconductor.org/).

Data and preprocessing

GBM mRNA expression data was downloaded from TCGA data portal on April 2011 (2). To reduce batch effects of arrays and protocols, we used only Agilent G4502A arrays measured at the UNC medical school, yielding 455 samples, 10 of which were from normal tissue. Additionally, 228 glioblastoma samples and 28 normal brain samples were obtained from REMBRANDT (3). Subtypes classification was taken from Verhaak et al. (4) Classification of the REMBRANDT data and additional TCGA samples was done using the same genes. Colorectal mRNA data was taken from Sheffer et al. (5) which contains 313 samples including normal tissue (52 samples), polyps (49), primary tumors (182) and metastases from the liver (21) and lung (9); Sveen et al. (6) containing 13 normals and 76 primary tumors of stages 2,3 (one tumor sample was removed); and Kogo et al. (7) containing 9 normal and 132 primary tumors of all stages.

For TCGA data we used level 3 already processed data and for Kogo data we used the downloaded processed data. For all the rest, data was summarized with PLIER and normalized with cyclic LOWESS (8), For the Sheffer dataset, batch correction was applied before LOWESS. To eliminate noisy genes only the 5000 most varying genes for each cancer type (sum of variation on all 2 or 3 datasets) were selected for further analysis.

Assembly of pathway associated gene sets

Gene sets were imported from three pathway databases, KEGG (9, 10), BioCarta (11) (both downloaded from MSigDB (12)) and the NCI-Nature curated Pathway Interaction Database (13). Identity of genes in gene sets was decided according to their official gene symbols. Gene sets with less than 3 genes varying in the data were omitted, leaving 173 KEGG pathways, 188 BioCarta pathways and 197 NCI-Nature PID pathways.

Chromosomal Instability Index

Chromosomal instability index (CIN) was deduced from the normalized gene expression, following reference (5). For a given tumor sample, each chromosomal arm was scored as follows. For every gene *i* calculate fc_i the fold change versus the median expression of the gene in the normal samples. The median fold change of the chromosomal arm *a* is defined as $fc_a = \underset{i\in a}{median}\, fc_i$. The total chromosomal instability index is the sum (over all arms) of the squared median fold changes $CIN = \sum_a fc_a^2$. Spearman correlation between the CIN index and the deregulation score of every pathway was calculated across each colorectal dataset. We recorded the list of pathways passing 5% FDR for every dataset. We applied Fisher exact test to evaluate the significance of the similarity between every pair of pathway lists.

Pathway deregulation scores that are correlated with necrosis levels of glioblastoma

The PDS of 242 pathways significantly correlate with the necrosis levels of the samples, as quantified by TCGA (Spearman correlation, FDR<1%), see Table S2. Some of these pathways are indeed expected to cause cell death, such as: *SODD* signaling, *FAS* pathway, *NEF* pathway, *BAD* phosphorylation pathway, apoptosis, caspase pathway, Notch signaling, Induction of apoptosis through DR3 and DR4/5 Death Receptors, p75(NTR)-mediated signaling, oxidative stress induced gene expression via *NRF2* and *ERK5* in neuronal survival. Many of the other pathways are growth factor pathways, such as: *NGF*, *ERBBs*, *PDGFRB*, IGF, and Trk receptor pathways. A few hypoxia and angiogenesis related pathways are also correlated with necrosis (*VEGF* pathways, HIF pathways, angiopoietin receptor pathway, lymphangiogenesis pathway, Hypoxia and p53 in the Cardiovascular system).

Pathway clusters in the TCGA GBM dataset

Pathway cluster TgP1 consists of cell cycle arrest and cell death pathways; TgP2 contains cell cycle pathways and many of KEGG's "cancer" pathways (including glioma) which capture cancer progression and signaling; TgP3 contains mainly cell death and DNA repair pathways and is deregulated mostly on the Neural and Proneural samples; The pathways of cluster TgP4 correspond to the EGF activated pathways mentioned above; Cluster TgP5 contains pathways that are deregulated mostly on the Classical samples. Some of them are indeed suspected to be specific to this subtype, such as hedgehog-GLI signaling (4) and GPCR/CXCR4 signaling (14) while the deregulation of some others in this subtype is a new prediction: such as PAR1(*F2R*)-mediated thrombin signaling, axon guidance, etc.; Half of the TgP6 pathways involve alpha synuclein amyloids; All TgP7 pathways involve phospholipase C; the pathways that comprise clusters TgP8-TgP10, TgP12-TgP15 belong to the 242 pathways that were correlated with necrosis that were mentioned above, and are also highly expressed on many Mesenchymal samples. As mentioned, many of these pathways (and specifically the pathways of TgP8-TgP10, TgP13 and TgP15) are related to hypoxia and angiogenesis, and we find, in agreement with previous knowledge, that they score higher in Mesenchymal glioblastoma (15). Clusters TgP8 and TgP12 contain several Epithelial-Mesenchymal Transition (EMT) related pathways (such as N-cadherin signaling, epithelial tight junctions, Rho/Rac/CDC42 signaling, regulation of actin cytoskeleton, ECM-receptor, Focal adhesion) obviously related to Mesenchymal tumors; 7 of the 8 pathways of TgP11 are key signaling pathways involving caveolin; TgP12 contains many of the pathways correlated with NF1 mutation (P3 in Fig. 2C); TgP14 contains mostly cell death pathways; TgP15 pathways all involve phospholipase A2; TgP16 contains many immune pathways. The full details of the pathways in each cluster can be found in Dataset S1.

Matching between REMBRANDT and TCGA GBM pathway clusters

Cluster ReP1 matches TgP1, ReP2 matches TgP2, ReP3 matches TgP15, ReP4 matches TgP16, ReP7 matches TgP3, ReP8 matches TgP14, ReP9 includes parts of TgP10-TgP13 (most strongly related to TgP12), and ReP10 includes parts of TgP4-TgP9 (most strongly related to TgP5 and TgP9). Under this mapping, similar characteristics of the deregulation profiles of sample types emerge (Fig. 2B). Some of the Neurals/Proneurals are mostly not deregulated (ReS1/ReS2 vs. TgS7/TgS15/TgS13) and some are deregulated on TgP1/TgP2/TgP3 or the matching ReP1/ReP2/ReP7. Classical tumors are deregulated on TgP4/TgP5 and possibly TgP6/TgP7 as well as on the matching ReP10 (and unmatched ReP6/ReP7). Pathways of clusters TgP8-TgP16 as well as the matching ReP10/ReP9/ReP8/ReP3/ReP4 (and unmatchable ReP5) are highly deregulated in the Mesenchymal samples. The Classical-Mesenchymal cluster TgS4 matches ReS8, and indeed the corresponding samples are deregulated on TgP4-TgP5/TgP10-TgP12/TgP14-TgP15 and, respectively, on the matching ReP10/ReP9/ReP8/ReP3 (as well as on the unmatchable ReP5).

Deregulation scores of many pathways are correlated with survival of GBM patients

35 pathways were found to be related to survival in both GBM datasets (see Table S3), many of them make biological sense: Agrin deregulation may temper the blood-brain barrier in glioblastoma (16); Growth hormone (GH) plays a crucial role in stimulating and controlling the growth, metabolism and differentiation of many mammalian cells, and hence clearly relevant for cancer aggressiveness (17); The hematopoiesis pathway contains cytokines and it is suspected to be related to cancer progression and drug resistance by interactions with the immune system (18-20); Linolenic acids and their products were suggested to prolong cancer patient survival (21); FcεRI may protect against cancer by IgE antitumor immunity (22); Cell-matrix adhesions are clearly related to invasion and metastasis (23); *GnRH* is a neurohormone that may drive proliferation in glioblastoma and other cancers, and therefore is also a suggested drug target (24-29); Phosphatidyl-inositol 3- and 4-kinases, key ingredients of the inositol phosphate pathway, are known to have important roles in glioblastoma and cancer in general, and hence are possible drug targets (30-32); Surprisingly, cholera toxin was also found related to glioblastoma; WNT signaling has a key role in brain and other cancers, and is related to cancer stem-like cells and poor prognosis (33-35); Alterations in E-cadherin mediated cell-cell adhesion are associated with an increase in carcinoma cell motility, invasiveness and metastasis (36); Glypican-1 is crucial for efficient growth, metastasis, and angiogenesis of cancer, and lack of it slows down pancreatic tumor progression (37); Fas and TNF-alpha are key players in apoptosis whose deregulation is a clear hallmark of cancer (38, 39); α4β1 integrin is related to angiogenesis (40), and is involved the survival and chemoresistance of several types of cancer (41); β2 integrins are known to predict poor survival in blood cancers (42, 43), and may cause fibrinolysis via uPA/uPAR; α6

integrin regulated stemness and invasiveness in glioblastoma (44, 45), and has a prognostic value in breast cancer (46); P53 is a key player in glioblastoma and cancer in general; *PTPN1* (aka PTP1B) may promote apoptosis in cancer and is a possible drug target for gliomas (47); Reelin is a secreted glycoprotein guiding migratory neurons, it is downregulated in neuroblastoma, which may contribute to metastasis (48, 49); Syndecans induce proliferation and invasion (50-52), and may serve as a prognostic predictor (53, 54).

Deregulation scores of many pathways are correlated with CIN in colorectal tumors

84 pathways were found to have significant positive correlation with the estimated CIN level in the tumors. To check that this correlation does not reflect only the differences between the MSI-high (most with low CIN) and MSS (most with high CIN) subtypes, we re-calculated the correlations for the subset of MSS and MSI-low tumors of the Sheffer and Sveen datasets. 71 pathways were significant ($p<0.046$, for every dataset pair, Fisher exact test), with an overlap of 55 with the previously found 84 pathways, suggesting that the correlations between CIN and deregulation of tumorigenic pathways is not only due to the differences between MSS and MSI-high tumors.

Deregulation scores in MSS colorectal tumors compared with MSI-high

In the Sheffer dataset, 325 pathways are differentially deregulated between MSS and MSI-high tumors (Mann–Whitney, 10% FDR, Supplementary Tables S6 and S7). 120 pathways are more deregulated on MSI-high tumors: They include Mismatch repair, nucleotide excision repair, ATM pathway, ATR pathway, cell cycle, MCM, DNA replication, RB1 pathway, oxidative stress, chemokines and cytokines signaling, and different interleukin pathways. This differential deregulation is in agreement with the fact that DNA mismatch repair is deregulated in MSI tumors (55), which are usually characterized by higher levels of inflammation and tumor infiltrating lymphocytes (56). A significant part of these pathways was also deregulated in the MSI-high tumors in the Sveen dataset ($p=1.92\times10^{-5}$ for MSS deregulated pathways, $p=0.022$ for MSI-high, Fisher exact test, Supplementary Tables S6 and S7)**.** It is reassuring that the mismatch repair pathway is deregulated in MSI-high tumors, in both datasets. Almost all pathways that are deregulated in MSS in the Sheffer dataset (200/205, 98%) also show significant positive correlation with the CIN index. Interestingly, in the MSS tumors, where p53 mutation is frequent, pathways downstream of p53 are highly deregulated (KEGG's p53 signaling pathway and PID's direct p53 effectors, which focus of the downstream effects of p53, as well as many death pathways), while in the MSI tumors, where p53 is often functional, many pathways upstream of p53 are deregulated (i.e. DNA damage and cell cycle). Indeed, we found that 123 out of 140 pathways that are differentially deregulated between wild type and mutant p53 (Mann–Whitney, 5% FDR) were shared with the group of 325 pathways deregulated in either MSI-high or MSS.

Pathway clusters in the Sheffer colorectal dataset

ShP1 includes B-cell receptor and T-cell receptor pathways, and ShP2 includes antigen processing and presentation, T-cell differentiation, T helper cell surface molecules, T cytotoxic cell surface molecules, Graft-versus-host disease, Autoimmune thyroid disease etc. Clusters ShP4 and ShP5 include ECM pathways, focal adhesion, syndecan pathways, integrin pathways such as α9/β1 that induce adhesion and migration of endothelial and cancer cells (57); interleukines that mediate inflammation and angiogenesis (58); toll like receptors, that are involved in innate immune response and HIF2, a transcription factor that induces the hypoxia response. Other pathways are related to metabolism, such as glycolysis and drug metabolism. Cluster ShP7 includes regulation of actin cytoskeleton, cell adhesion, JAK/STAT signaling, MAPK signaling and complement and coagulation cascades pathway. Interestingly, this cluster is also deregulated in the polyps (cluster ShS2), although polyps show low level of CIN. Cluster ShP8 includes various cAMP-dependent signaling pathways, triggered by receptor binding to GPCRs involving the G-Protein such as insulin and BAD phosphrylation. Other pathways include metabolism of different amino acids and TGF-beta signaling. Cluster ShP9 includes a number of death associated pathways such as apoptosis, T-cell apoptosis, p53 downstream signaling, lysosome and *FAS* signaling. In addition, it includes also fatty acid metabolism, VEGF, mTOR, and notch signaling. Cluster ShP10 includes mitochondrial metabolic pathways such as pyruvate metabolism, TCA cycle, metabolism of sugars and oxidative phosphorylation. Cluster ShP11 includes cell cycle related pathways such as G1/S check point, aurora pathway, p53 upstream regulation, E2F, RB1, MCM, DNA replication, mismatch repair, purine metabolism, and more.

72 pathways out of the 106 that exhibited increase of PDS with progression of the disease (see above) belong to clusters ShP8, ShP9 and ShP10 ($p<10^{-3}$ for all three clusters, Fisher exact test). This group of pathways consists of cell death, cAMP-dependent signaling and mitochondrial metabolism pathways, along with p53 pathways.

Comparison to PARADIGM

PARADIGM is useful for integrating many types of data, but it does not handle well complex pathways when information is missing. The reason is that PARADIGM is based on full knowledge and understanding of all the interactions in the pathway; in complex pathways, however, much of these interactions depend on protein-level information, such as abundance, activity, location and structure (e.g. whether it is phosphorylated or not). When all this information is available, we believe informative and reliable results are produced by PARADIGM. However, in most cases, when much of the necessary information is missing, it is very hard to deduce the behavior of the pathway by following all the details of the interactions within the pathway.

Pathifier implicitly assumes that when all or most of the genes in the pathway are taken into account, a lot of the information on the pathway's activity status is coded in their readily available mRNA abundances. The details are context depended and cannot be fully deduced, but a data based analysis, specific for the pathway and the type of cancer, is likely to reveal the differences between the samples. Clearly, the validity of this assumption cannot be generally proven, but testing the results obtained for different cancers and different datasets of the same cancer types does support it strongly.

Despite the differences in approach and philosophy we compared the results of PARADIGM and Pathifier, to assess what high-level findings are in agreement between the methods, and what additional information can be uncovered by Pathifier. We repeated the analyses described above using the scores derived obtained by PARADIGM. EGFR gene and EGFR complexes were indeed found to be correlated to EGFR mutations as expected (FDR<1%). However, no pathways were found to be correlated to the EGFR mutations. Not much more could be inferred by the analysis based on PARADIGM scores (Supplementary Figure S10). As reported in (59), some stratification of glioblastoma is possible by PARADIGM IPA's, but it does not match strongly the known subtypes. Though it successfully detected a relevant cluster of *HIF1A* low and E2F high tumors, PARADIGM missed many of the observations we mention above. Moreover, none of the IPA's is found to be related to survival with FDR<19%. Therefore we conclude that while PARADIGM is a very useful method to integrate different types of data and deduce simple complexes and downstream activations (such as EGF receptor activation), Pathifier provides additional clinically relevant and easy to interpret information about the deregulation of complex pathways.

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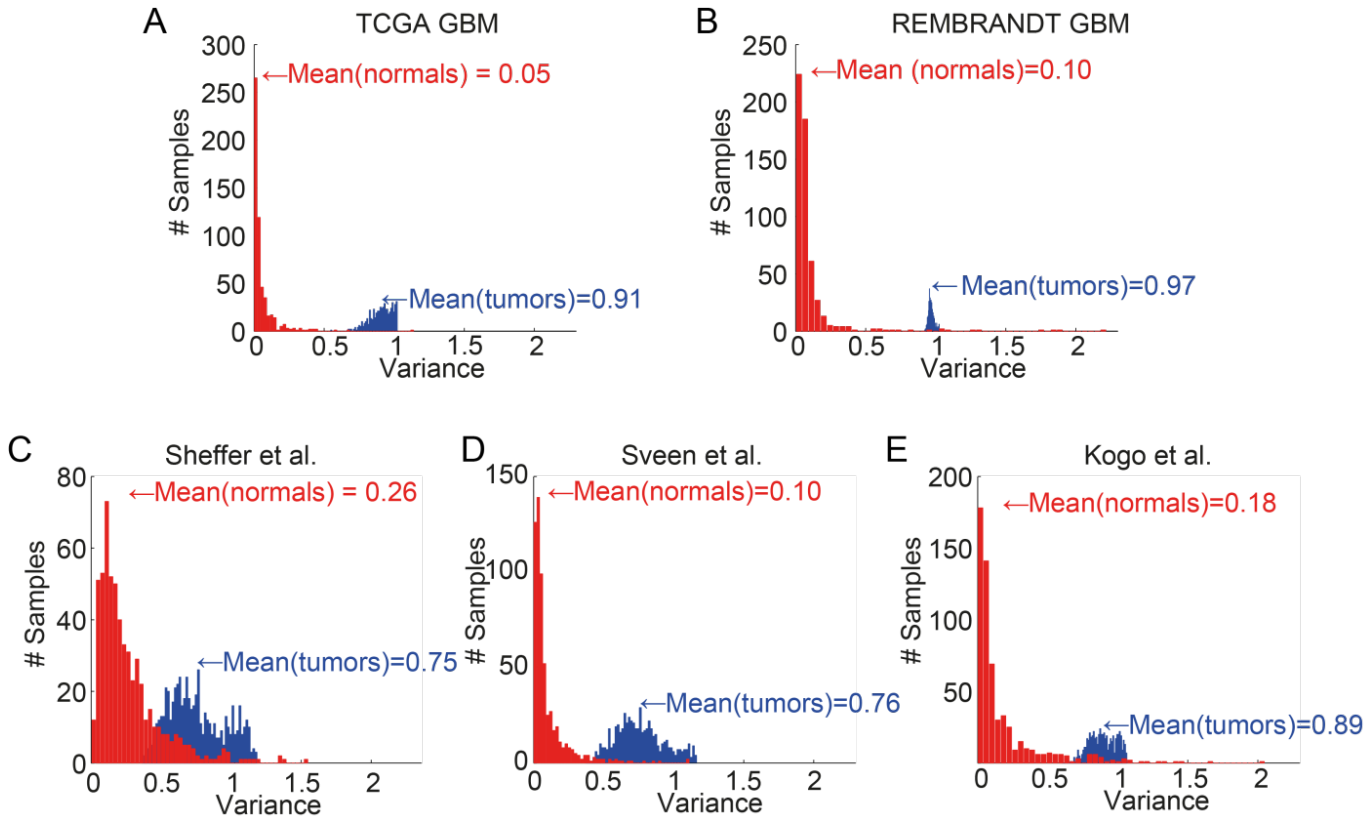
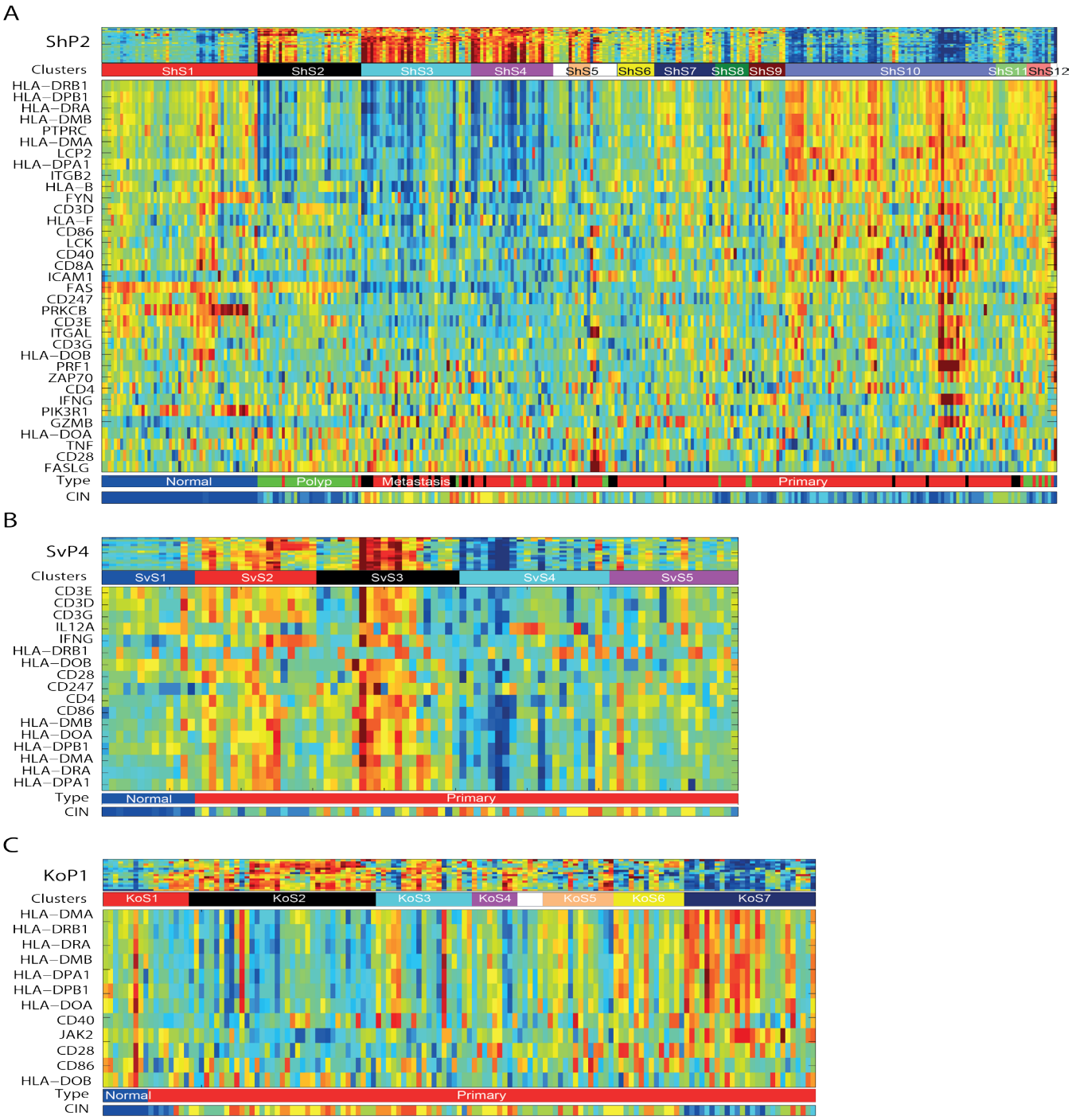
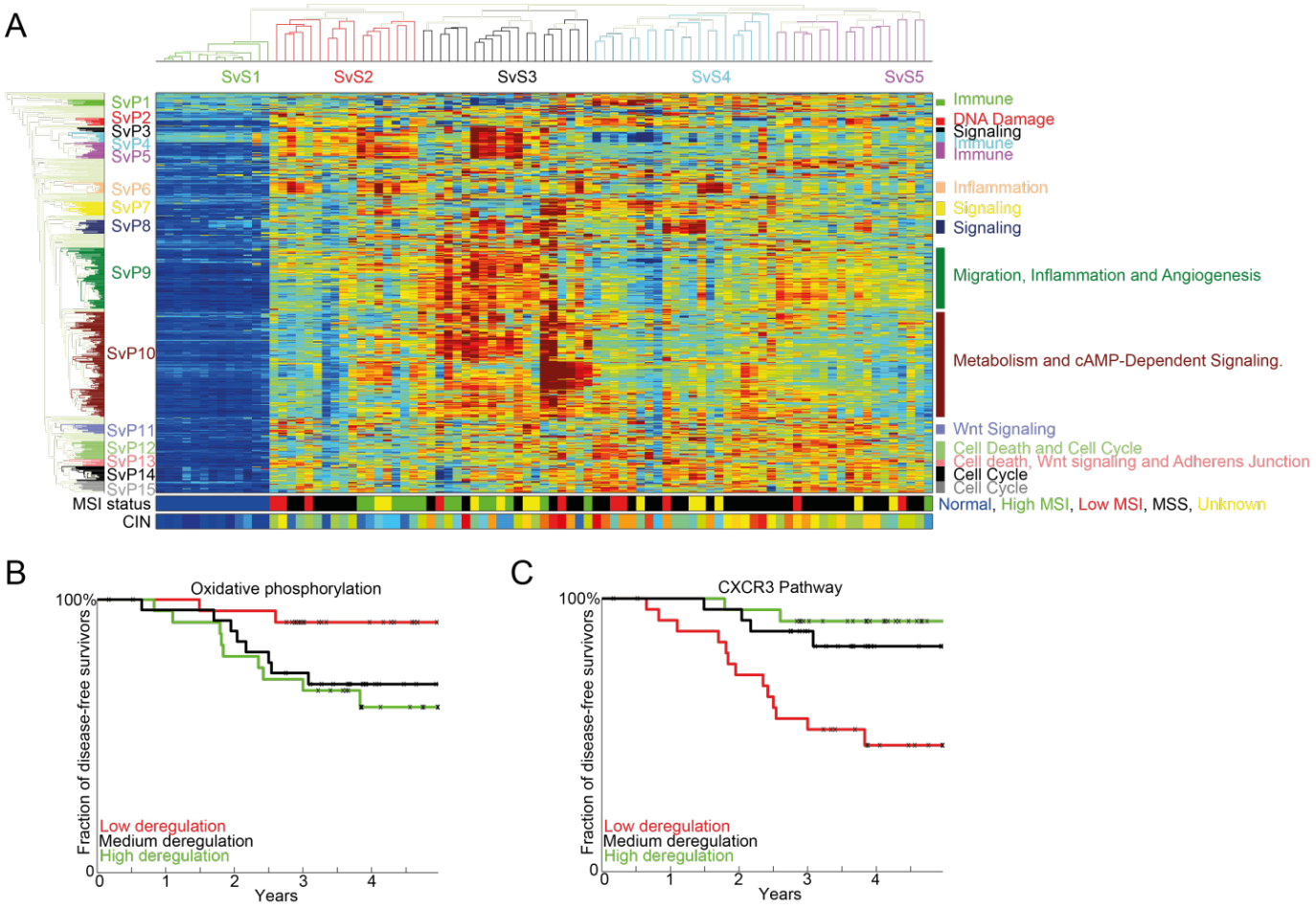


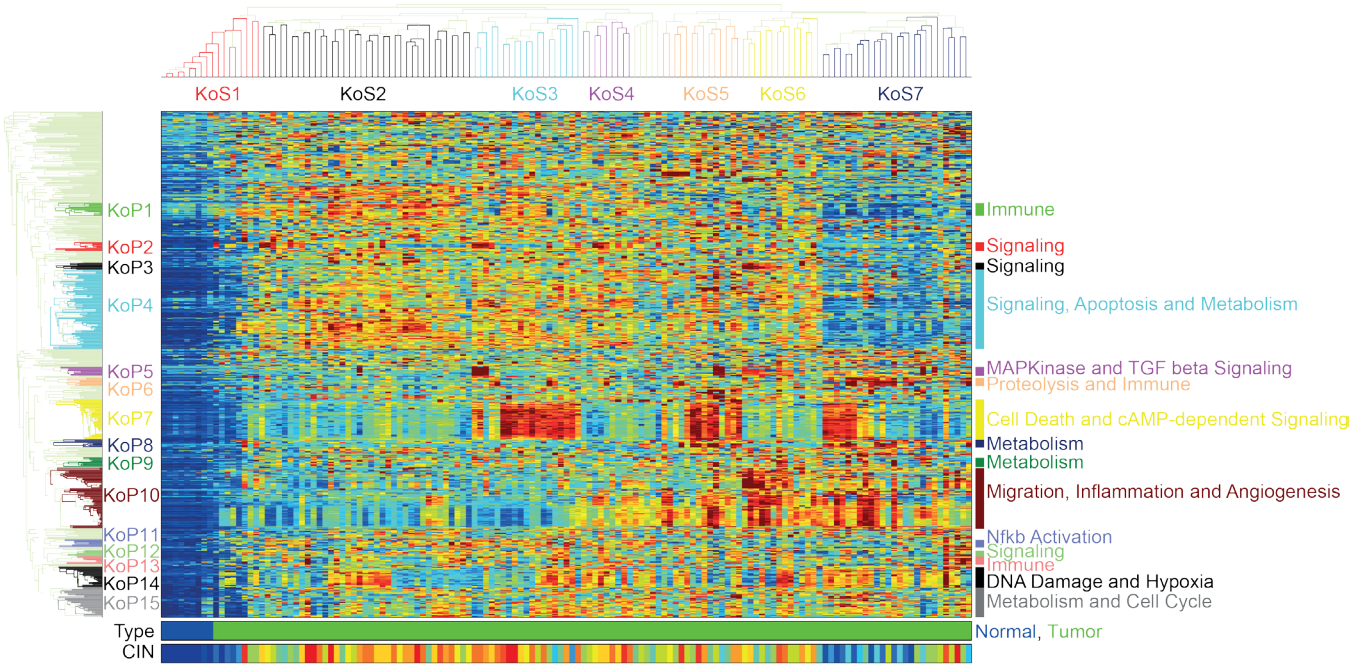
Supplementary Figure S1 - Histograms of the Pathifier PDS's variance in each dataset. The variance over the normal samples (red) and over the tumor samples (blue) was calculated for each pathway, showing much lower variance over the normal samples. The mean variance for these two groups is indicated for GBM (**A.** TCGA **B.** REMBRANDT) and colorectal cancer (**C.** Sheffer **D.** Sveen **E.** Kogo) datasets.



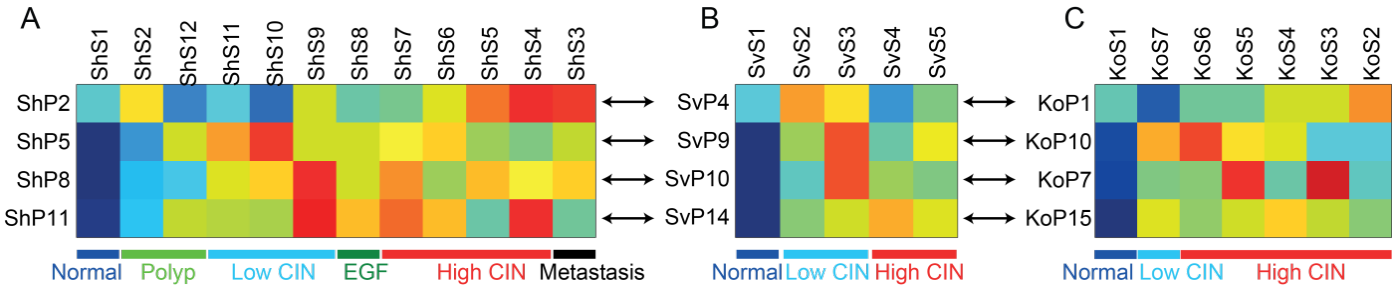
Supplementary Figure S2 - Expression of genes shared between pathways in the immune clusters. A. Cluster ShP2 of the Sheffer dataset. The upper panel shows the PDS of cluster ShP2. As the PDS of the normal samples is around zero (green-blue), highly positive PDS (dark red) and highly negative PDS (dark blue) correspond to pathway deregulation, but in different directions. The lower panel shows the expression of genes that participate in at least five of the pathways in ShP2: each row represent a gene, blue corresponds to low expressions and red to high expressions. The color bars at the bottom correspond to the tissue type of the tumor (normal, polyp, tumor and metastasis) and the CIN index (equally distributed into 10 bins). These genes are related to lymphocytes, and may represent TILs (tumor infiltrating lymphocytes). Note that positive PDS co-occur with low expression (mostly in metastatic samples and in some of the polyps), while negative PDS correlate with high expression (mostly found among the tumors with low CIN). **The Cluster SvP4 (Sveen dataset) and the Cluster KoP1 (Kogo dataset) are shown in B, C** in a similar manner. Note that in SvP4 positive PDS co-occur with high expression and in KoP1 positive PDS co-occur with low expression, which is explained by the fact that the direction of the curve is chosen according to the normal samples. The association between high expression and low CIN is reconstructed in both SvP4 and in KoP1.



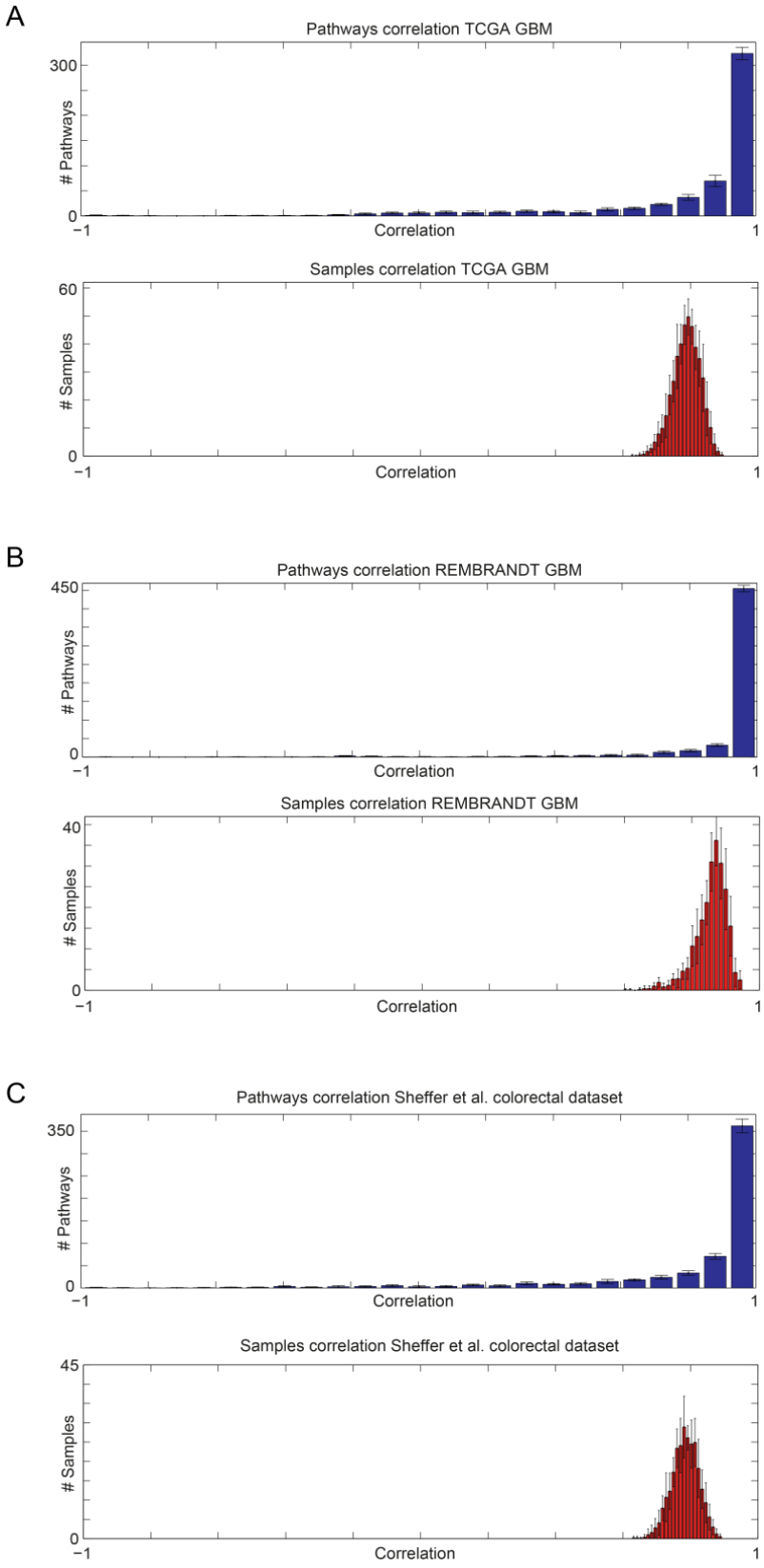
Supplementary Figure S3 - A. Clustering analysis of all the PDS in the Sveen dataset. Each row corresponds to a pathway and each column to a sample. Pathways and samples are clustered according to PDS. For most pathways the PDS of the normal samples are minimal (dark blue), and hence the higher the PDS are the more deregulated the pathway is. For a few pathways (mostly in SvP4) the PDS of normal samples are around zero (green-blue), and hence highly positive PDS (dark red) and highly negative PDS (dark blue) both correspond to pathway deregulation, but in different directions. The color bars at the bottom correspond to the MSI status of the tumor (normal, low high, MSS and unknown) and the CIN index (equally distributed into 20 bins). **B. Oxidative phosphorylation pathway is associated with survival**. Kaplan-Meier plots for the deregulation scores of oxidative phosphorylation in the Sveen dataset. The primary tumor samples were divided into three equal groups, based on their level of deregulation (high, medium and low). Low deregulation scores are associated with better prognosis. **C. CXCR3 pathway is associated with survival**. High deregulation scores are associated with better prognosis.



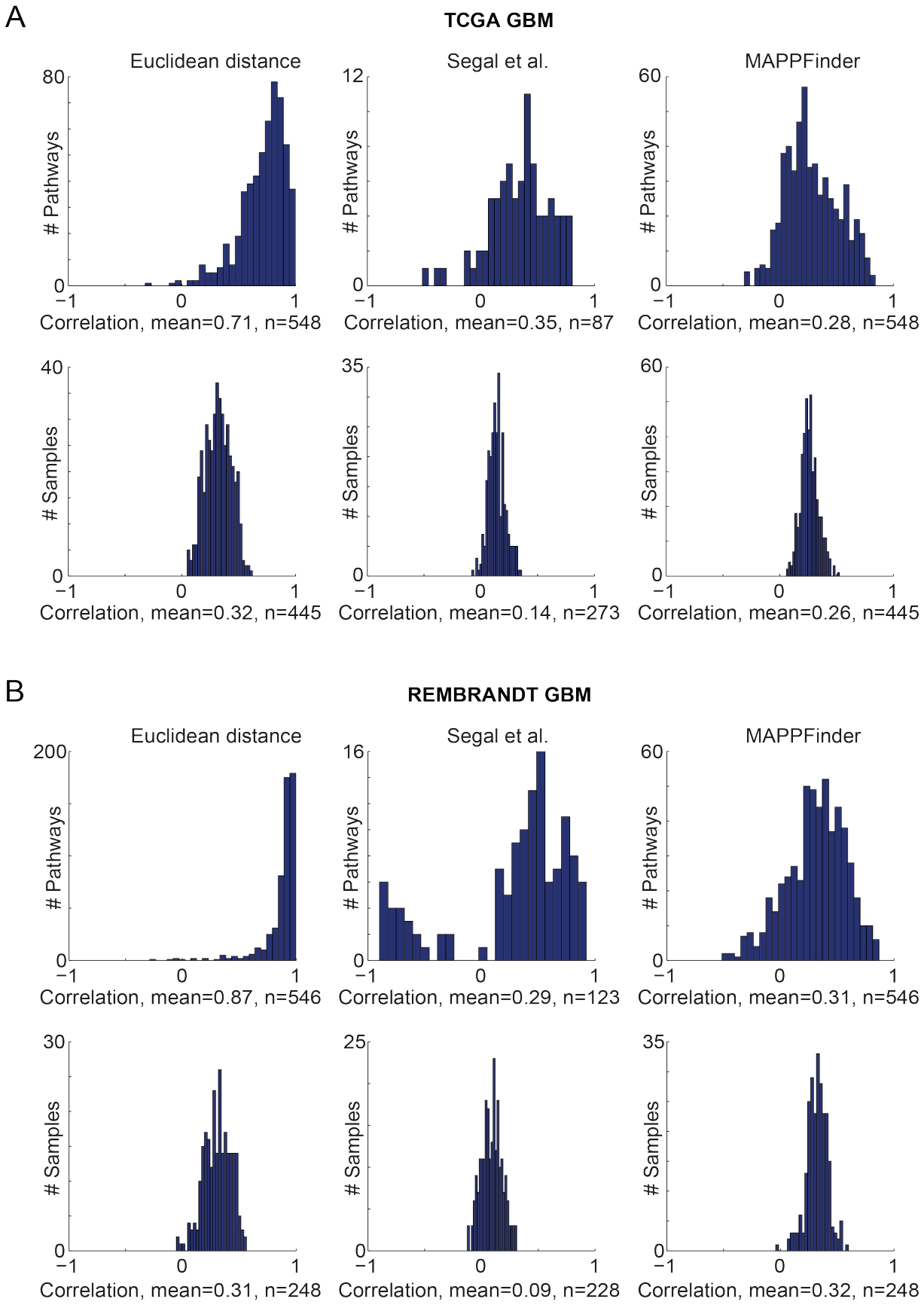
Supplementary Figure S4 - Clustering analysis of all the PDS in the Kogo dataset. Each row corresponds to a pathway and each column – to a sample. Pathways and samples are clustered according to PDS. For most pathways the PDS of the normal samples are minimal (dark blue), and hence the higher the PDS are the more deregulated the pathway is. For a few pathways (mostly in KoP1) the PDS of normal samples is around zero (green-blue), and hence highly positive PDS (dark red) and highly negative PDS (dark blue) both correspond to pathway deregulation, but in different directions. The color bars at the bottom correspond to the tissue type of the tumor (normal, tumors) and the CIN index (equally distributed into 20 bins).



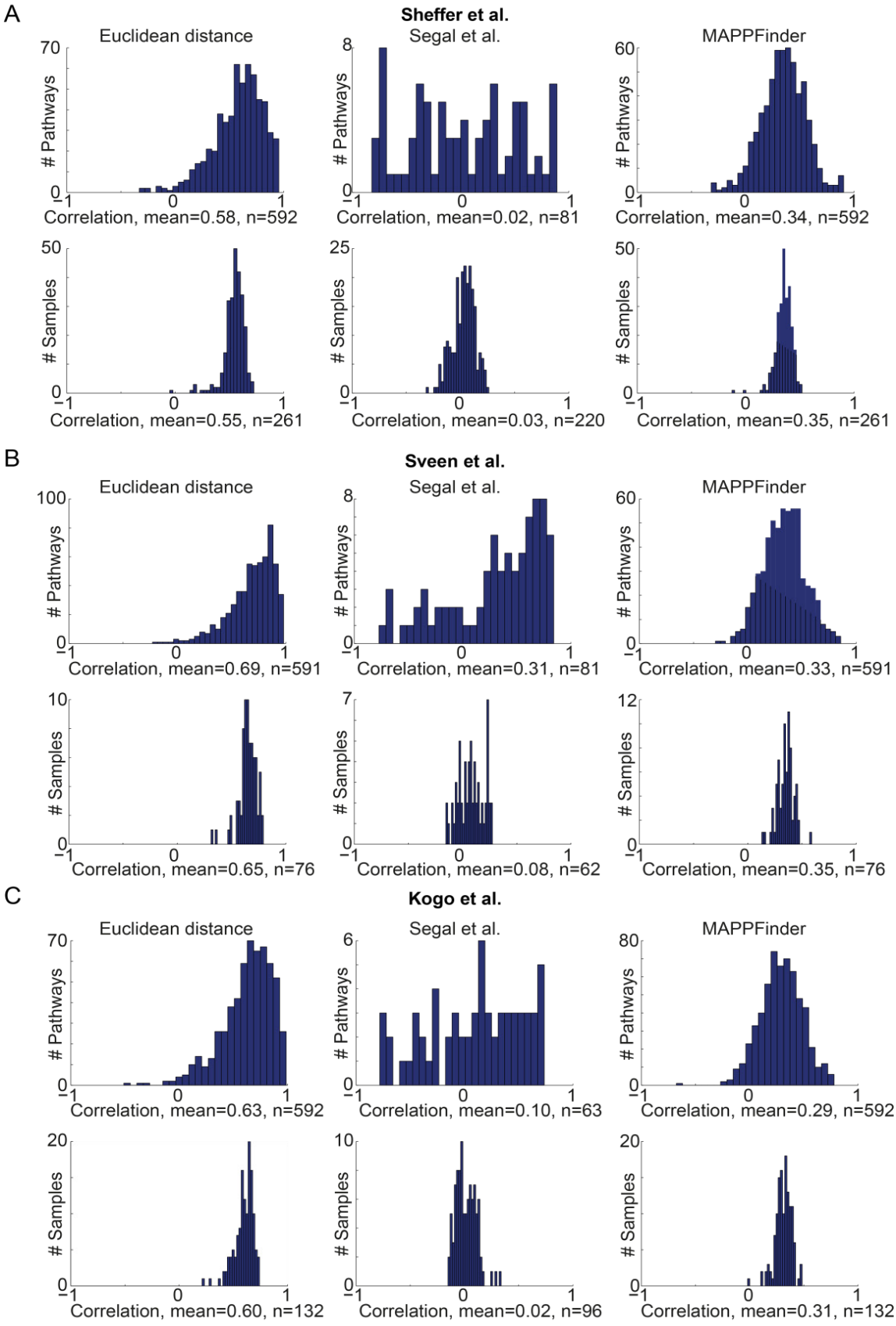
Supplementary Figure S5 - Summary of recurrent clusters in the colorectal datasets (A. Sheffer, B. Sveen, C. Kogo). Each row corresponds to a pathway cluster and each column to a sample cluster, displaying the median value of deregulation for each pair of clusters. These four pathway clusters were reproduced in all three datasets. In the first row are pathway clusters for which the PDS of the normal samples are minimal around zero (cyan), and hence highly positive PDS (dark red) and highly negative PDS (dark blue) both correspond to pathway deregulation, but in different directions. For all other clusters the PDS of the normal samples are minimal (dark blue), and hence the higher the PDS are the more deregulated the pathway is. Arrows connect between pathway clusters that match (that is, the pathways in the clusters significantly overlap).



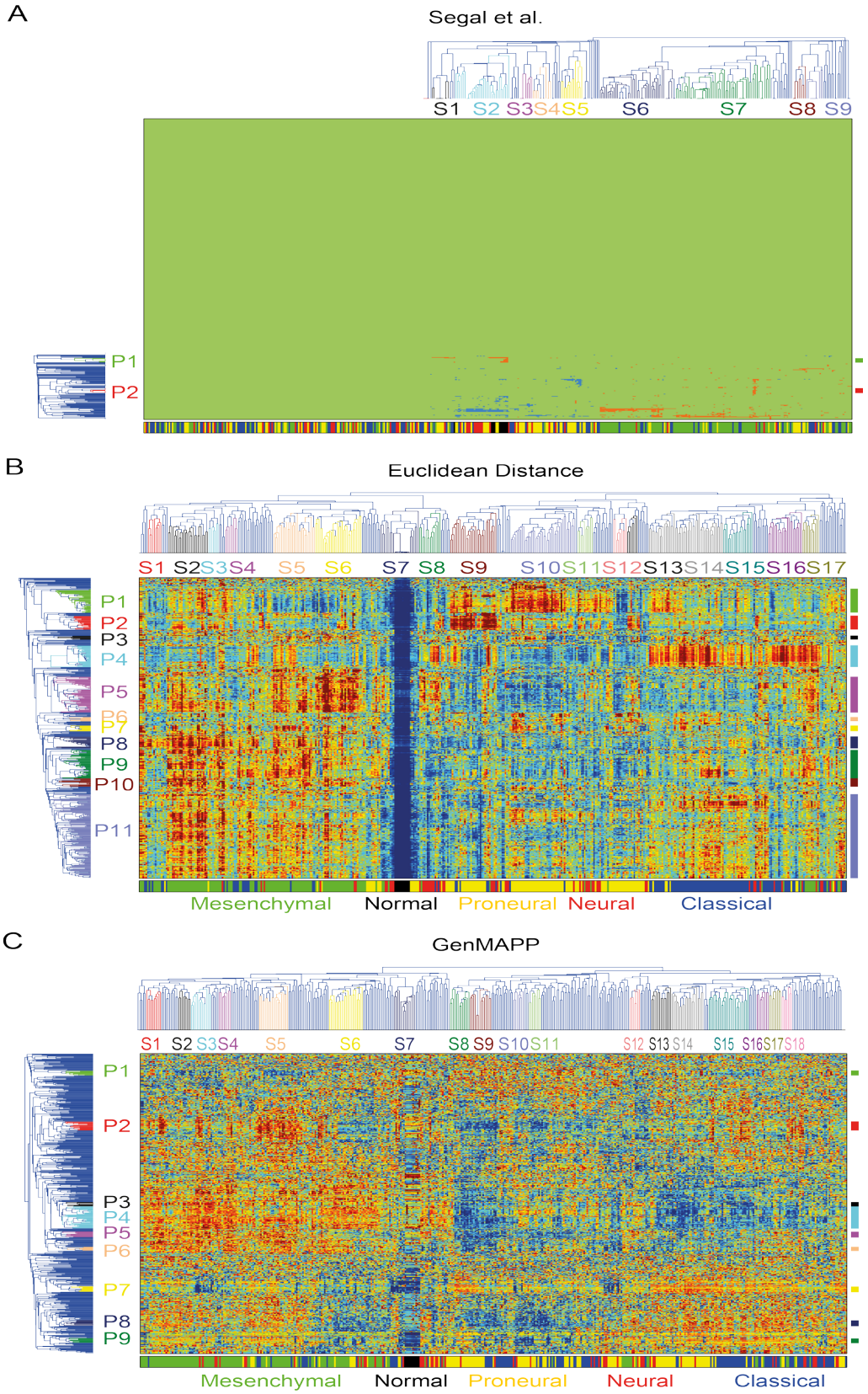
Supplementary Figure S6 - Normal samples sensitivity test. Histograms for the Pearson correlation coefficient between the Pathifier PDS scores using the full set of normal samples against ten different runs using 80% of randomly chosen normal samples. The correlation was measured for pathways (blue) and for samples (red), using the set of tumor samples. The average and standard deviation of the ten runs are shown, for each bin. Results are shown for **A.** TCGA GBM, **B.** Rembrant and **C.** Sheffer datasets.



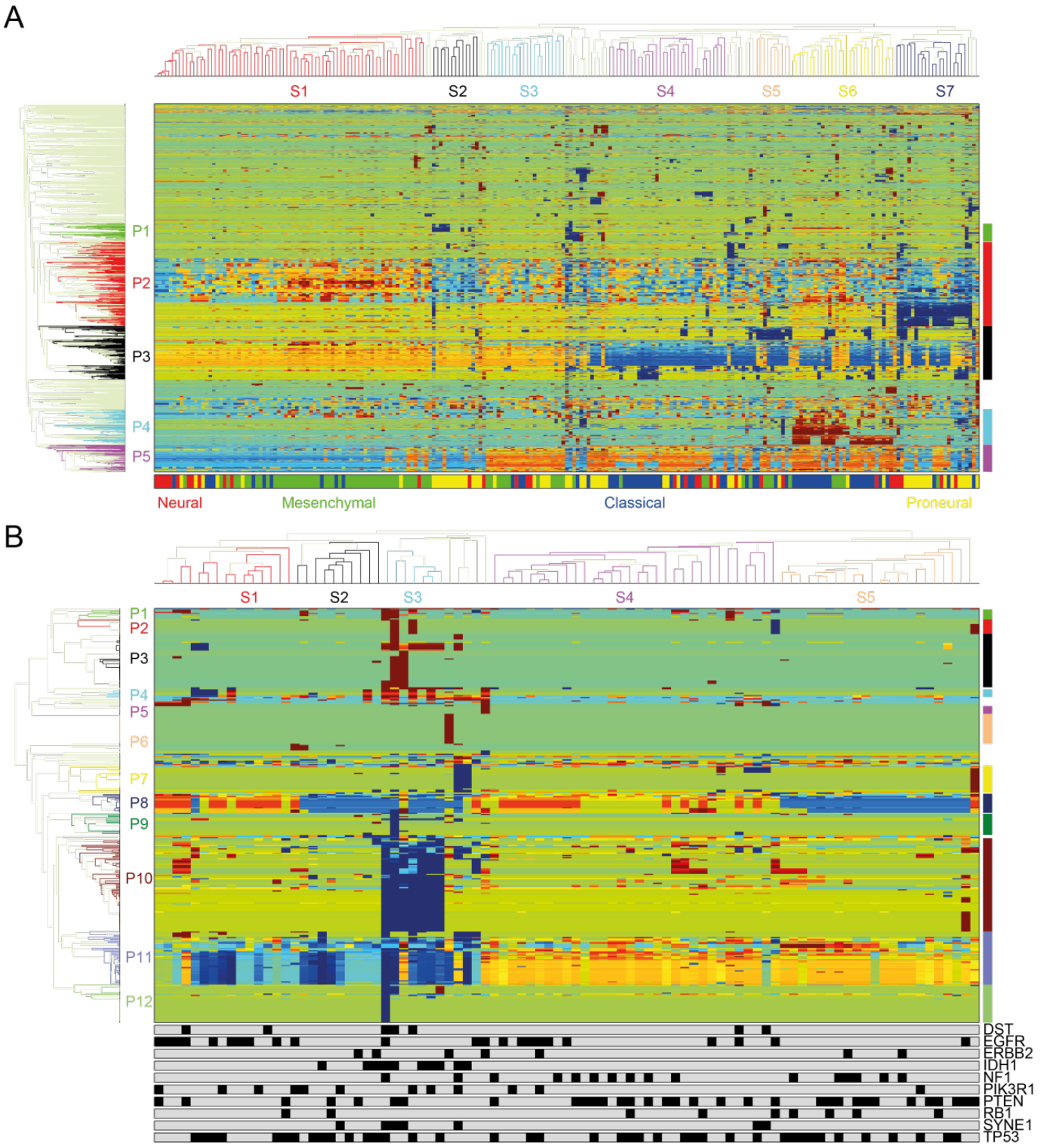
Supplementary Figure S7 - Histograms of Pearson correlations between Pathifier scores and alternative methods for GBM datasets- A. TCGA. **B.** REMBRANDT. The correlations between the three methods and Pathifier were calculated using the set of tumor samples, for pathways (upper) and for samples (lower). The correlations to Segal et al. and to GenMAPP are low.



Supplementary Figure S8 - Histograms of Pearson correlations between Pathifier scores and alternative methods for colorectal cancer datasets- A. Sheffer et al. **B.** Sveen et al. **C.** Kogo et al. The correlations between the three methods and Pathifier were calculated using the set of tumor samples, for pathways (upper) and for samples (lower). Note that the correlations to Segal et al. and to GenMAPP are low.



Supplementary Figure S9 - Clustered normalized pathways score of TCGA GBM using other methods (A. Segal et al. B. linear pathifter, scoring by Euclidean distance C. Adjusted GenMAPP/MAPPFinder score). Each row corresponds to a pathway and each column to a sample. Pathways and samples are clustered according to pathway scores. Blue color represents low score ("no deregulation"), and red high. The bottom bar represents the glioblastoma subtype. Segal et al. do not score most samples and most pathways are not scored (in green), due to strict significance requirements.



Supplementary Figure S10 - **A. PARADIGM's IPAs for the TCGA GBM dataset.** Each row corresponds to a PARADIGM "entity" and each column to a sample. Entities (pathways, interactions, complexes etc.) and samples are clustered according to the IPAs. Blue color represents low activity, and red high activity. The bottom bar displays the subtype. **B. PARADIGM's IPAs correlated with mutations.** The bottom bars display the mutation status for the corresponding gene.

Supplementary Table 1 - **Pathways whose deregulation corresponds to point mutation of selected genes (TCGA GBM data).** Pathways are ordered and numbered as in Figure 2C.

#	Pathway Name	Mutation	p-value	FDR	Cluster
1	ALK2 signaling events (PID)	IDH1	7.50E-05	6.32E-03	
2	Stress Induction of HSP Regulation (BIOCARTA)	IDH1	8.50E-05	6.47E-03	1
3	Peroxisome (KEGG)	IDH1	8.20E-05	6.47E-03	1
4	ABC transporters (KEGG)	IDH1	1.00E-06	1.24E-03	1
5	Alpha-synuclein signaling (PID)	IDH1	4.60E-05	4.72E-03	1
6	Retinol metabolism (KEGG)	DST	1.32E-04	8.01E-03	1
7	Histidine metabolism (KEGG)	IDH1	1.00E-06	1.24E-03	1
8	C-MYB transcription factor network (PID)	RB1	2.90E-05	3.69E-03	
9	AP-1 transcription factor network (PID)	RB1	1.00E-05	2.03E-03	
9	AP-1 transcription factor network (PID)	TP53	8.90E-05	6.53E-03	
10	TGF beta signaling pathway (BIOCARTA)	IDH1	1.14E-04	7.19E-03	
11	Calcium signaling pathway (KEGG)	EGFR	8.60E-05	6.47E-03	2
12	Sprouty regulation of tyrosine kinase signals (BIOCARTA)	IDH1	7.50E-05	6.32E-03	2
13	Keratinocyte Differentiation (BIOCARTA)	EGFR	4.00E-06	1.96E-03	2
14	Urokinase-type plasminogen activator (uPA) and uPAR-mediated signaling (PID)	EGFR	6.00E-06	1.96E-03	2
15	LPA receptor mediated events (PID)	EGFR	9.80E-05	6.94E-03	2
16	Angiotensin II mediated activation of JNK Pathway via Pyk2 dependent signaling (BIOCARTA)	EGFR	1.05E-04	7.11E-03	2
17	CBL mediated ligand-induced downregulation of EGF receptors (BIOCARTA)	EGFR	7.00E-06	1.96E-03	2
18	Arf6 signaling events (PID)	EGFR	1.08E-04	7.11E-03	2
19	Role of EGF Receptor Transactivation by GPCRs in Cardiac Hypertrophy (BIOCARTA)	EGFR	5.00E-06	1.96E-03	2
20	EGF receptor (ErbB1) signaling pathway (PID)	EGFR	2.50E-05	3.45E-03	2
21	Syndecan-3-mediated signaling events (PID)	EGFR	2.40E-05	3.45E-03	2
22	Trefoil Factors Initiate Mucosal Healing (BIOCARTA)	EGFR	2.60E-05	3.53E-03	2
23	Role of ERBB2 in Signal Transduction and Oncology (BIOCARTA)	EGFR	2.10E-05	3.33E-03	2
24	ErbB receptor signaling network (PID)	EGFR	7.70E-05	6.32E-03	2
25	mCalpain and friends in Cell motility (BIOCARTA)	EGFR	1.80E-05	3.00E-03	2
26	Regulation of Telomerase (PID)	EGFR	7.00E-06	1.96E-03	2
27	Endometrial cancer (KEGG)	EGFR	2.50E-05	3.45E-03	2
28	E-cadherin signaling in keratinocytes (PID)	EGFR	8.60E-05	6.47E-03	2
29	Erk1/Erk2 Mapk Signaling pathway (BIOCARTA)	EGFR	1.30E-05	2.32E-03	2
30	Thromboxane A2 receptor signaling (PID)	EGFR	8.00E-06	1.96E-03	2
31	EGF Signaling Pathway (BIOCARTA)	EGFR	1.00E-05	2.03E-03	2
32	Dorso-ventral axis formation (KEGG)	EGFR	8.00E-05	6.47E-03	2
33	a6b1 and a6b4 Integrin signaling (PID)	EGFR	4.00E-06	1.96E-03	2
33	a6b1 and a6b4 Integrin signaling (PID)	IDH1	4.30E-05	4.66E-03	2
34	Map Kinase Inactivation of SMRT Corepressor (BIOCARTA)	EGFR	3.00E-06	1.96E-03	2
34	Map Kinase Inactivation of SMRT Corepressor (BIOCARTA)	IDH1	3.90E-05	4.55E-03	2
35	Signaling events mediated by PTP1B (PID)	EGFR	4.40E-05	4.67E-03	2
36	Stabilization and expansion of the E-cadherin adherens junction (PID)	EGFR	2.00E-06	1.91E-03	2
37	Epithelial cell signaling in Helicobacter pylori infection (KEGG)	EGFR	6.00E-06	1.96E-03	2
37	Epithelial cell signaling in Helicobacter pylori infection (KEGG)	IDH1	1.72E-04	9.59E-03	2
38	ErbB1 downstream signaling (PID)	EGFR	2.80E-05	3.61E-03	2
38	ErbB1 downstream signaling (PID)	IDH1	1.47E-04	8.66E-03	2
39	Agrin in Postsynaptic Differentiation (BIOCARTA)	EGFR	1.70E-05	3.00E-03	2
40	ErbB signaling pathway (KEGG)	EGFR	2.00E-06	1.91E-03	2
41	Gap junction (KEGG)	EGFR	2.50E-05	3.45E-03	2
42	MAPK signaling pathway (KEGG)	IDH1	7.70E-05	6.32E-03	2
43	Retinoic acid receptors-mediated signaling (PID)	IDH1	1.00E-06	1.24E-03	
44	Multi-step Regulation of Transcription by Pitx2 (BIOCARTA)	IDH1	1.00E-06	1.24E-03	
45	ALK in cardiac myocytes (BIOCARTA)	IDH1	7.00E-06	1.96E-03	
46	IGF-1 Signaling Pathway (BIOCARTA)	NF1	1.21E-04	7.53E-03	3
47	ErbB2/ErbB3 signaling events (PID)	NF1	1.59E-04	9.07E-03	3
48	HIV Induced T Cell Apoptosis (BIOCARTA)	IDH1	1.56E-04	9.02E-03	3
49	Systemic lupus erythematosus (KEGG)	RB1	5.00E-06	1.96E-03	3
50	PDGFR-alpha signaling pathway (PID)	NF1	8.90E-05	6.53E-03	3
51	Ceramide signaling pathway (PID)	IDH1	4.00E-05	4.55E-03	3
52	SODD/TNFR1 Signaling Pathway (BIOCARTA)	IDH1	1.24E-04	7.61E-03	3
53	Proteoglycan syndecan-mediated signaling events (PID)	IDH1	4.00E-05	4.55E-03	3
54	Propanoate metabolism (KEGG)	IDH1	9.00E-06	2.03E-03	3
55	Long-term depression (KEGG)	IDH1	4.10E-05	4.60E-03	3
56	alpha-Linolenic acid metabolism (KEGG)	IDH1	5.30E-05	5.16E-03	3
57	Ether lipid metabolism (KEGG)	IDH1	1.90E-05	3.22E-03	3
58	Glycolysis / Gluconeogenesis (KEGG)	IDH1	3.60E-05	4.49E-03	3
59	Signaling events regulated by Ret tyrosine kinase (PID)	IDH1	1.33E-04	8.04E-03	3
60	Alpha6 beta4 integrin-ligand interactions (PID)	IDH1	1.52E-04	8.85E-03	3
61	Hedgehog signaling events mediated by Gli proteins (PID)	IDH1	7.20E-05	6.30E-03	3

62	p38 MAPK Signaling Pathway (BIOCARTA)	IDH1	5.70E-05	5.22E-03	3
63	Integrin family cell surface interactions (PID)	NF1	1.79E-04	9.83E-03	3
64	Validated transcriptional targets of TAp63 isoforms (PID)	IDH1	1.14E-04	7.19E-03	3
64	Validated transcriptional targets of TAp63 isoforms (PID)	NF1	4.30E-05	4.66E-03	3
65	Reelin signaling pathway (PID)	NF1	1.30E-05	2.32E-03	3
66	CXCR4-mediated signaling events (PID)	IDH1	1.77E-04	9.81E-03	3
67	Hypertrophic cardiomyopathy (HCM) (KEGG)	NF1	6.60E-05	5.80E-03	3
68	Extrinsic Prothrombin Activation Pathway (BIOCARTA)	NF1	6.30E-05	5.67E-03	3
69	Wnt signaling network (PID)	NF1	2.30E-05	3.45E-03	3
70	Presenilin action in Notch and Wnt signaling (PID)	NF1	1.09E-04	7.12E-03	3
71	Wnt signaling pathway (KEGG)	NF1	5.60E-05	5.21E-03	3
72	IL4-mediated signaling events (PID)	PTEN	1.13E-04	7.19E-03	3
73	Noncanonical Wnt signaling pathway (PID)	IDH1	1.38E-04	8.22E-03	3
74	Focal adhesion (KEGG)	IDH1	1.02E-04	7.06E-03	3
75	Canonical NF-kappaB pathway (PID)	IDH1	8.30E-05	6.47E-03	3
76	Syndecan-4-mediated signaling events (PID)	IDH1	5.00E-05	5.03E-03	3
77	Leukocyte transendothelial migration (KEGG)	IDH1	4.00E-05	4.55E-03	3
78	Cell adhesion molecules (CAMs) (KEGG)	IDH1	1.07E-04	7.11E-03	3
79	Chemokine signaling pathway (KEGG)	IDH1	2.00E-05	3.22E-03	3
80	Cytokine-cytokine receptor interaction (KEGG)	IDH1	5.40E-05	5.16E-03	3
81	Glycosaminoglycan degradation (KEGG)	NF1	1.04E-04	7.11E-03	3
82	Other glycan degradation (KEGG)	IDH1	8.00E-06	1.96E-03	3
83	IGF1 pathway (PID)	IDH1	1.83E-04	9.93E-03	3
83	IGF1 pathway (PID)	NF1	1.67E-04	9.43E-03	3
84	The IGF-1 Receptor and Longevity (BIOCARTA)	IDH1	6.00E-06	1.96E-03	3
85	Angiopoietin receptor Tie2-mediated signaling (PID)	NF1	4.70E-05	4.80E-03	3
86	IL3-mediated signaling events (PID)	NF1	5.50E-05	5.16E-03	3
87	Multiple antiapoptotic pathways from IGF-1R signaling lead to BAD phosphorylation (BIOCARTA)	NF1	1.00E-05	2.03E-03	3
88	Links between Pyk2 and Map Kinases (BIOCARTA)	NF1	1.00E-05	2.03E-03	3
89	Insulin Signaling Pathway (BIOCARTA)	NF1	8.00E-06	1.96E-03	3
90	IL 3 signaling pathway (BIOCARTA)	NF1	8.00E-06	1.96E-03	3
91	Nerve growth factor pathway (NGF) (BIOCARTA)	NF1	7.00E-06	1.96E-03	3
92	EPO Signaling Pathway (BIOCARTA)	NF1	7.00E-06	1.96E-03	3
93	Trka Receptor Signaling Pathway (BIOCARTA)	NF1	9.90E-05	6.94E-03	3
94	Role of Erk5 in Neuronal Survival (BIOCARTA)	NF1	9.40E-05	6.77E-03	3

Supplementary Table 2 - **Pathways whose deregulation correlates with necrosis levels (TCGA GBM data).** With significance measures, and Spearman correlation coefficient (denoted by ρ).

Pathway	p-value	FDR	ρ
HIF-2-alpha transcription factor network (PID)	1.54E-19	8.43E-17	0.41
HIF-1-alpha transcription factor network (PID)	1.60E-18	4.39E-16	0.40
Alpha9 beta1 integrin signaling events (PID)	1.45E-17	2.64E-15	0.39
S1P1 pathway (PID)	5.14E-17	7.04E-15	0.38
Nitrogen metabolism (KEGG)	3.21E-16	3.52E-14	0.38
Hypoxia-Inducible Factor in the Cardiovascular System (BIOCARTA)	2.64E-15	2.41E-13	0.36
VEGF and VEGFR signaling network (PID)	9.34E-15	7.28E-13	0.36
Validated transcriptional targets of AP1 family members Fra1 and Fra2 (PID)	1.06E-14	7.28E-13	0.36
Actions of Nitric Oxide in the Heart (BIOCARTA)	4.93E-14	3.00E-12	0.35
Signaling events mediated by VEGFR1 and VEGFR2 (PID)	8.91E-14	4.89E-12	0.34
VEGFR1 specific signals (PID)	1.04E-13	5.17E-12	0.34
mTOR signaling pathway (KEGG)	5.52E-13	2.52E-11	0.33
RXR and RAR heterodimerization with other nuclear receptor (PID)	7.07E-13	2.98E-11	0.33
Propanoate metabolism (KEGG)	9.96E-13	3.90E-11	0.33
Beta3 integrin cell surface interactions (PID)	1.61E-12	5.90E-11	0.33
VEGF, Hypoxia, and Angiogenesis (BIOCARTA)	3.19E-12	1.09E-10	0.32
IL1-mediated signaling events (PID)	5.99E-12	1.93E-10	0.32
Endothelins (PID)	1.34E-11	4.09E-10	0.31
PPAR signaling pathway (KEGG)	7.02E-11	2.02E-09	0.30
CD40/CD40L signaling (PID)	1.49E-10	3.99E-09	0.30
Valine, leucine and isoleucine degradation (KEGG)	1.53E-10	3.99E-09	0.30
Role of Mitochondria in Apoptotic Signaling (BIOCARTA)	2.13E-10	5.21E-09	0.30
Apoptosis (KEGG)	2.19E-10	5.21E-09	0.30
SODD/TNFR1 Signaling Pathway (BIOCARTA)	3.04E-10	6.94E-09	0.29
Syndecan-4-mediated signaling events (PID)	7.65E-10	1.61E-08	0.29
FAS (CD95) signaling pathway (PID)	7.77E-10	1.61E-08	0.29
HIV-1 Nef: Negative effector of Fas and TNF-alpha (PID)	7.94E-10	1.61E-08	0.29
Ceramide signaling pathway (PID)	8.23E-10	1.61E-08	0.29
Signaling mediated by p38-alpha and p38-beta (PID)	1.28E-09	2.42E-08	0.28
Melanogenesis (KEGG)	1.33E-09	2.43E-08	0.28
beta-Alanine metabolism (KEGG)	1.90E-09	3.36E-08	0.28
Alanine, aspartate and glutamate metabolism (KEGG)	2.15E-09	3.68E-08	0.28
p75(NTR)-mediated signaling (PID)	4.21E-09	6.99E-08	0.27
Neuroactive ligand-receptor interaction (KEGG)	4.70E-09	7.57E-08	0.27
Wnt signaling pathway (KEGG)	7.70E-09	1.18E-07	0.27
Neurotrophin signaling pathway (KEGG)	7.75E-09	1.18E-07	0.27
VEGF signaling pathway (KEGG)	8.31E-09	1.23E-07	0.27
VEGFR3 signaling in lymphatic endothelium (PID)	1.26E-08	1.82E-07	0.27
Adipocytokine signaling pathway (KEGG)	1.71E-08	2.37E-07	0.26
NOD-like receptor signaling pathway (KEGG)	1.73E-08	2.37E-07	0.26
Long-term potentiation (KEGG)	2.03E-08	2.71E-07	0.26
Phosphatidylinositol signaling system (KEGG)	2.31E-08	2.97E-07	0.26
Caspase cascade in apoptosis (PID)	2.36E-08	2.97E-07	0.26
Renal cell carcinoma (KEGG)	2.38E-08	2.97E-07	0.26
Osteopontin-mediated events (PID)	2.63E-08	3.20E-07	0.26
Glypican 1 network (PID)	2.83E-08	3.37E-07	0.26
Integrins in angiogenesis (PID)	2.97E-08	3.47E-07	0.26
Signaling events mediated by Hepatocyte Growth Factor Receptor (c-Met) (PID)	3.86E-08	4.41E-07	0.26
Calcium signaling in the CD4+ TCR pathway (PID)	5.60E-08	6.14E-07	0.25
Angiopoietin receptor Tie2-mediated signaling (PID)	5.60E-08	6.14E-07	0.25
FoxO family signaling (PID)	6.16E-08	6.56E-07	0.25
Alpha4 beta1 integrin signaling events (PID)	6.23E-08	6.56E-07	0.25
Syndecan-1-mediated signaling events (PID)	8.39E-08	8.64E-07	0.25
FGF signaling pathway (PID)	8.52E-08	8.64E-07	0.25
Beta1 integrin cell surface interactions (PID)	9.10E-08	9.06E-07	0.25
Inositol phosphate metabolism (KEGG)	9.34E-08	9.14E-07	0.25
Glycolysis / Gluconeogenesis (KEGG)	9.94E-08	9.55E-07	0.25
Direct p53 effectors (PID)	1.16E-07	1.09E-06	0.25
Glycosphingolipid biosynthesis - globo series (KEGG)	1.18E-07	1.10E-06	0.25
Notch signaling pathway (PID)	1.59E-07	1.43E-06	0.25
Fatty acid metabolism (KEGG)	2.35E-07	2.08E-06	0.24
Glycosphingolipid biosynthesis - lacto and neolacto series (KEGG)	2.39E-07	2.08E-06	0.24
p38 MAPK Signaling Pathway (BIOCARTA)	2.56E-07	2.18E-06	0.24
Cytokine-cytokine receptor interaction (KEGG)	2.58E-07	2.18E-06	0.24
Signaling events mediated by Stem cell factor receptor (c-Kit) (PID)	2.65E-07	2.20E-06	0.24
Fibrinolysis Pathway (BIOCARTA)	4.07E-07	3.33E-06	0.24

IL2 signaling events mediated by PI3K (PID)	6.33E-07	5.10E-06	0.23
Effects of Botulinum toxin (PID)	7.00E-07	5.56E-06	0.23
Gamma-aminobutyric Acid Receptor Life Cycle (BIOCARTA)	8.11E-07	6.35E-06	0.23
Butanoate metabolism (KEGG)	8.55E-07	6.60E-06	0.23
Lysine degradation (KEGG)	8.85E-07	6.74E-06	0.23
Ca++/ Calmodulin-dependent Protein Kinase Activation (BIOCARTA)	1.02E-06	7.67E-06	0.23
Insulin signaling pathway (KEGG)	1.04E-06	7.67E-06	0.23
Signaling events mediated by focal adhesion kinase (PID)	1.08E-06	7.78E-06	0.23
Trk receptor signaling mediated by PI3K and PLC-gamma (PID)	1.08E-06	7.78E-06	0.23
Chemokine signaling pathway (KEGG)	1.18E-06	8.40E-06	0.23
Long-term depression (KEGG)	1.24E-06	8.68E-06	0.23
EPHB forward signaling (PID)	1.60E-06	1.11E-05	0.23
TGF-beta receptor signaling (PID)	1.80E-06	1.23E-05	0.22
SNARE interactions in vesicular transport (KEGG)	2.11E-06	1.43E-05	0.22
Insulin Pathway (PID)	3.09E-06	2.04E-05	0.22
Regulation of PGC-1a (BIOCARTA)	3.13E-06	2.04E-05	0.22
Cardiac muscle contraction (KEGG)	3.25E-06	2.09E-05	0.22
Y branching of actin filaments (BIOCARTA)	3.34E-06	2.13E-05	0.22
Starch and sucrose metabolism (KEGG)	3.69E-06	2.33E-05	0.22
Validated targets of C-MYC transcriptional repression (PID)	3.95E-06	2.46E-05	0.22
Beta5 beta6 beta7 and beta8 integrin cell surface interactions (PID)	4.10E-06	2.52E-05	0.22
IL8- and CXCR2-mediated signaling events (PID)	4.29E-06	2.61E-05	0.22
amb2 Integrin signaling (PID)	4.37E-06	2.61E-05	0.22
Canonical NF-kappaB pathway (PID)	4.40E-06	2.61E-05	0.22
Taurine and hypotaurine metabolism (KEGG)	4.43E-06	2.61E-05	0.22
Regulation of eIF4e and p70 S6 Kinase (BIOCARTA)	4.57E-06	2.66E-05	0.22
Syndecan-2-mediated signaling events (PID)	4.95E-06	2.86E-05	0.22
Proximal tubule bicarbonate reclamation (KEGG)	5.24E-06	2.99E-05	0.21
Nicotinate and nicotinamide metabolism (KEGG)	5.58E-06	3.15E-05	0.21
Ascorbate and aldarate metabolism (KEGG)	6.12E-06	3.42E-05	0.21
Transcription factor CREB and its extracellular signals (BIOCARTA)	6.48E-06	3.59E-05	0.21
Neurotrophic factor-mediated Trk receptor signaling (PID)	7.50E-06	4.11E-05	0.21
Fructose and mannose metabolism (KEGG)	7.83E-06	4.25E-05	0.21
Arachidonic acid metabolism (KEGG)	7.93E-06	4.26E-05	0.21
Focal adhesion (KEGG)	8.32E-06	4.43E-05	0.21
Glycerophospholipid metabolism (KEGG)	8.56E-06	4.51E-05	0.21
RhoA signaling pathway (PID)	8.70E-06	4.54E-05	0.21
ECM-receptor interaction (KEGG)	9.32E-06	4.82E-05	0.21
Presenilin action in Notch and Wnt signaling (PID)	9.76E-06	5.00E-05	0.21
Oxidative Stress Induced Gene Expression Via Nrf2 (BIOCARTA)	1.00E-05	5.08E-05	0.21
Linoleic acid metabolism (KEGG)	1.09E-05	5.49E-05	0.21
Regulation of BAD phosphorylation (BIOCARTA)	1.16E-05	5.76E-05	0.21
Noncanonical Wnt signaling pathway (PID)	1.24E-05	6.12E-05	0.21
BCR signaling pathway (PID)	1.32E-05	6.47E-05	0.21
Caspase Cascade in Apoptosis (BIOCARTA)	1.60E-05	7.74E-05	0.20
Taste transduction (KEGG)	1.69E-05	8.14E-05	0.20
Downstream signaling in naïve CD8+ T cells (PID)	1.97E-05	9.36E-05	0.20
PDGFR-beta signaling pathway (PID)	1.98E-05	9.36E-05	0.20
Trk receptor signaling mediated by the MAPK pathway (PID)	2.14E-05	9.94E-05	0.20
Ether lipid metabolism (KEGG)	2.15E-05	9.94E-05	0.20
Regulation of ck1/cdk5 by type 1 glutamate receptors (BIOCARTA)	2.16E-05	9.94E-05	0.20
Vascular smooth muscle contraction (KEGG)	2.18E-05	9.94E-05	0.20
Canonical Wnt signaling pathway (PID)	3.12E-05	1.41E-04	0.20
Glutathione metabolism (KEGG)	3.18E-05	1.43E-04	0.20
NFkB activation by Nontypeable Hemophilus influenzae (BIOCARTA)	3.36E-05	1.50E-04	0.20
Insulin Signaling Pathway (BIOCARTA)	3.43E-05	1.52E-04	0.20
Cystic Fibrosis Transmembrane Conductance Regulator And Beta 2 Adrenergic Receptor Pathway (BIOCARTA)	3.62E-05	1.59E-04	0.20
CXCR3-mediated signaling events (PID)	3.69E-05	1.60E-04	0.19
Wnt signaling network (PID)	3.74E-05	1.61E-04	0.19
Phospholipase C-epsilon pathway (BIOCARTA)	3.81E-05	1.63E-04	0.19
IL8- and CXCR1-mediated signaling events (PID)	3.86E-05	1.64E-04	0.19
IFN-gamma pathway (PID)	4.21E-05	1.77E-04	0.19
Validated transcriptional targets of TAp63 isoforms (PID)	4.33E-05	1.80E-04	0.19
Phosphorylation of MEK1 by cdk5/p35 down regulates the MAP kinase pathway (BIOCARTA)	4.34E-05	1.80E-04	0.19
Beta2 integrin cell surface interactions (PID)	4.48E-05	1.85E-04	0.19
Hematopoietic cell lineage (KEGG)	4.68E-05	1.91E-04	0.19
Olfactory transduction (KEGG)	4.71E-05	1.91E-04	0.19
Growth Hormone Signaling Pathway (BIOCARTA)	5.46E-05	2.20E-04	0.19
Nerve growth factor pathway (NGF) (BIOCARTA)	5.93E-05	2.37E-04	0.19
Tight junction (KEGG)	6.50E-05	2.58E-04	0.19
Glycosaminoglycan biosynthesis - heparan sulfate (KEGG)	6.67E-05	2.63E-04	0.19

CDC42 signaling events (PID)	7.12E-05	2.79E-04	0.19
Leukocyte transendothelial migration (KEGG)	8.09E-05	3.14E-04	0.19
Role of Tob in T-cell activation (BIOCARTA)	8.39E-05	3.24E-04	0.19
Th1/Th2 Differentiation (BIOCARTA)	8.87E-05	3.40E-04	0.19
Arrhythmogenic right ventricular cardiomyopathy (ARVC) (KEGG)	9.02E-05	3.43E-04	0.19
Arf6 trafficking events (PID)	9.20E-05	3.48E-04	0.18
IL-2 Receptor Beta Chain in T cell Activation (BIOCARTA)	9.39E-05	3.52E-04	0.18
Regulation And Function Of ChREBP in Liver (BIOCARTA)	9.95E-05	3.71E-04	0.18
Bioactive Peptide Induced Signaling Pathway (BIOCARTA)	1.04E-04	3.85E-04	0.18
ALK1 signaling events (PID)	1.08E-04	3.96E-04	0.18
alpha-Linolenic acid metabolism (KEGG)	1.13E-04	4.13E-04	0.18
Integrin Signaling Pathway (BIOCARTA)	1.17E-04	4.25E-04	0.18
Regulation of actin cytoskeleton (KEGG)	1.37E-04	4.95E-04	0.18
Role of Erk5 in Neuronal Survival (BIOCARTA)	1.39E-04	4.95E-04	0.18
Nuclear Receptors in Lipid Metabolism and Toxicity (BIOCARTA)	1.39E-04	4.95E-04	0.18
EPO Signaling Pathway (BIOCARTA)	1.46E-04	5.17E-04	0.18
Extrinsic Prothrombin Activation Pathway (BIOCARTA)	1.47E-04	5.18E-04	0.18
Effects of calcineurin in Keratinocyte Differentiation (BIOCARTA)	1.75E-04	6.06E-04	0.18
Pathways in cancer (KEGG)	1.77E-04	6.10E-04	0.18
CXCR4-mediated signaling events (PID)	2.00E-04	6.84E-04	0.18
Monocyte and its Surface Molecules (BIOCARTA)	2.01E-04	6.84E-04	0.18
Aldosterone-regulated sodium reabsorption (KEGG)	2.06E-04	6.96E-04	0.18
Trka Receptor Signaling Pathway (BIOCARTA)	2.08E-04	6.98E-04	0.18
Proteoglycan syndecan-mediated signaling events (PID)	2.27E-04	7.57E-04	0.17
IL 3 signaling pathway (BIOCARTA)	2.42E-04	8.04E-04	0.17
IL-7 Signal Transduction (BIOCARTA)	2.45E-04	8.08E-04	0.17
GnRH signaling pathway (KEGG)	2.49E-04	8.15E-04	0.17
Endocytotic role of NDK, Phosphins and Dynamin (BIOCARTA)	2.51E-04	8.15E-04	0.17
T Cell Receptor Signaling Pathway (BIOCARTA)	2.51E-04	8.15E-04	0.17
a4b7 Integrin signaling (PID)	2.89E-04	9.33E-04	0.17
Multiple antiapoptotic pathways from IGF-1R signaling lead to BAD phosphorylation (BIOCARTA)	2.98E-04	9.55E-04	0.17
IL 6 signaling pathway (BIOCARTA)	3.07E-04	9.71E-04	0.17
Roles of fl-arrestin-dependent Recruitment of Src Kinases in GPCR Signaling (BIOCARTA)	3.15E-04	9.92E-04	0.17
HIV-I Nef: negative effector of Fas and TNF (BIOCARTA)	3.25E-04	1.02E-03	0.17
Cytokine Network (BIOCARTA)	3.87E-04	1.20E-03	0.17
Glycerolipid metabolism (KEGG)	3.92E-04	1.21E-03	0.17
LPA4-mediated signaling events (PID)	4.03E-04	1.22E-03	0.17
Role of fl-arrestins in the activation and targeting of MAP kinases (BIOCARTA)	4.04E-04	1.22E-03	0.17
fl-arrestins in GPCR Desensitization (BIOCARTA)	4.04E-04	1.22E-03	0.17
JNK signaling in the CD4+ TCR pathway (PID)	4.53E-04	1.36E-03	0.17
Oxidative phosphorylation (KEGG)	4.97E-04	1.49E-03	0.16
Stathmin and breast cancer resistance to antimicrotubule agents (BIOCARTA)	5.03E-04	1.50E-03	0.16
Thrombin signaling and protease-activated receptors (BIOCARTA)	5.42E-04	1.60E-03	0.16
MAPKinase Signaling Pathway (BIOCARTA)	5.53E-04	1.63E-03	0.16
The IGF-1 Receptor and Longevity (BIOCARTA)	5.93E-04	1.74E-03	0.16
Cell adhesion molecules (CAMs) (KEGG)	5.96E-04	1.74E-03	0.16
O-Glycan biosynthesis (KEGG)	6.47E-04	1.87E-03	0.16
Links between Pyk2 and Map Kinases (BIOCARTA)	7.33E-04	2.12E-03	0.16
Cells and Molecules involved in local acute inflammatory response (BIOCARTA)	7.58E-04	2.17E-03	0.16
Signal transduction through IL1R (BIOCARTA)	8.92E-04	2.55E-03	0.16
Selective expression of chemokine receptors during T-cell polarization (BIOCARTA)	9.60E-04	2.72E-03	0.16
N-Glycan biosynthesis (KEGG)	9.75E-04	2.75E-03	0.16
N-cadherin signaling events (PID)	9.96E-04	2.80E-03	0.16
Endocytosis (KEGG)	1.02E-03	2.84E-03	0.16
Angiotensin-converting enzyme 2 regulates heart function (BIOCARTA)	1.04E-03	2.88E-03	0.16
Signaling events regulated by Ret tyrosine kinase (PID)	1.23E-03	3.40E-03	0.15
TCR signaling in naïve CD8+ T cells (PID)	1.25E-03	3.45E-03	0.15
Regulation of p38-alpha and p38-beta (PID)	1.28E-03	3.52E-03	0.15
Bone Remodelling (BIOCARTA)	1.30E-03	3.55E-03	0.15
Dilated cardiomyopathy (KEGG)	1.35E-03	3.67E-03	0.15
Vasopressin-regulated water reabsorption (KEGG)	1.39E-03	3.74E-03	0.15
Hedgehog signaling events mediated by Gli proteins (PID)	1.40E-03	3.75E-03	0.15
Hypoxia and p53 in the Cardiovascular system (BIOCARTA)	1.49E-03	3.96E-03	0.15
Other glycan degradation (KEGG)	1.49E-03	3.96E-03	0.15
p38 MAPK signaling pathway (PID)	1.58E-03	4.19E-03	0.15
Hypertrophic cardiomyopathy (HCM) (KEGG)	1.60E-03	4.21E-03	0.15
Control of skeletal myogenesis by HDAC and calcium/calmodulin-dependent kinase (CaMK) (BIOCARTA)	1.63E-03	4.27E-03	0.15
Cytokines and Inflammatory Response (BIOCARTA)	1.65E-03	4.31E-03	0.15
Neuropeptides VIP and PACAP inhibit the apoptosis of activated T cells (BIOCARTA)	1.69E-03	4.39E-03	0.15
Alpha6 beta4 integrin-ligand interactions (PID)	1.73E-03	4.46E-03	0.15
mTOR signaling pathway (PID)	1.84E-03	4.73E-03	0.15

Adhesion and Diapedesis of Lymphocytes (BIOCARTA)	1.94E-03	4.95E-03	0.15
Lysosome (KEGG)	1.94E-03	4.95E-03	0.15
Regulation of CDC42 activity (PID)	2.16E-03	5.48E-03	0.15
Protein Kinase A at the Centrosome (BIOCARTA)	2.18E-03	5.49E-03	0.15
Pertussis toxin-insensitive CCR5 Signaling in Macrophage (BIOCARTA)	2.18E-03	5.49E-03	0.15
Vitamin C in the Brain (BIOCARTA)	2.20E-03	5.51E-03	0.15
Ribosome (KEGG)	2.26E-03	5.63E-03	0.14
Glycosaminoglycan biosynthesis - chondroitin sulfate (KEGG)	2.35E-03	5.83E-03	0.14
IGF-1 Signaling Pathway (BIOCARTA)	2.45E-03	6.02E-03	0.14
Huntington's disease (KEGG)	2.58E-03	6.30E-03	0.14
ErbB4 signaling events (PID)	2.60E-03	6.30E-03	0.14
Riboflavin metabolism (KEGG)	2.65E-03	6.41E-03	0.14
EPHA2 forward signaling (PID)	2.67E-03	6.41E-03	0.14
HIV Induced T Cell Apoptosis (BIOCARTA)	2.73E-03	6.53E-03	0.14
Integrin-linked kinase signaling (PID)	2.87E-03	6.84E-03	0.14
IL3-mediated signaling events (PID)	2.89E-03	6.84E-03	0.14
Amyotrophic lateral sclerosis (ALS) (KEGG)	2.89E-03	6.84E-03	0.14
Erythropoietin mediated neuroprotection through NF-kB (BIOCARTA)	2.98E-03	7.00E-03	0.14
Glycosaminoglycan degradation (KEGG)	2.99E-03	7.00E-03	0.14
Glucocorticoid receptor regulatory network (PID)	3.10E-03	7.22E-03	0.14
Amino sugar and nucleotide sugar metabolism (KEGG)	3.13E-03	7.28E-03	0.14
FOXA1 transcription factor network (PID)	3.48E-03	8.01E-03	0.14
Complement and coagulation cascades (KEGG)	3.62E-03	8.30E-03	0.14
Reelin signaling pathway (PID)	3.96E-03	9.05E-03	0.14
Ephrin B reverse signaling (PID)	4.36E-03	9.90E-03	0.14
GMCSF-mediated signaling events (PID)	4.41E-03	9.99E-03	0.14
Signaling of Hepatocyte Growth Factor Receptor (BIOCARTA)	3.18E-03	7.36E-03	-0.14
BMP receptor signaling (PID)	2.48E-03	6.07E-03	-0.14
RIG-I-like receptor signaling pathway (KEGG)	2.37E-03	5.86E-03	-0.14
Glycine, serine and threonine metabolism (KEGG)	3.46E-04	1.08E-03	-0.17
Inhibition of Cellular Proliferation by Gleevec (BIOCARTA)	3.04E-04	9.69E-04	-0.17
Presenilin action in Notch and Wnt signaling (BIOCARTA)	1.73E-04	6.04E-04	-0.18
Notch signaling pathway (KEGG)	2.96E-06	1.98E-05	-0.22
Induction of apoptosis through DR3 and DR4/5 Death Receptors (BIOCARTA)	1.43E-07	1.31E-06	-0.25

Supplementary Table 3 - **Pathways predicting survival in both glioblastoma datasets**. We found significant agreement between the pathways that predict survival. Pathways were identified by logrank p-value, with FDR < 10% for each dataset.

	TCGA		REMBRANDT	
Pathway	p-value	FDR	p-value	FDR
BIOCARTA: Agrin in Postsynaptic Differentiation	9.25E-03	0.083	2.45E-02	0.084
BIOCARTA: ALK pathway	1.79E-03	0.074	1.42E-03	0.015
BIOCARTA: Fibrinolysis Pathway	1.47E-03	0.074	6.71E-03	0.039
BIOCARTA: Growth Hormone Signaling Pathway	7.47E-03	0.083	4.35E-03	0.029
BIOCARTA: Regulation of hematopoiesis by cytokines	1.00E-03	0.074	3.05E-02	0.094
KEGG: Alpha linolenic acid metabolism	8.89E-03	0.083	2.26E-04	0.007
KEGG: ARVC	1.06E-02	0.09	1.90E-03	0.018
KEGG: Basal cell carcinoma	9.17E-03	0.083	7.78E-04	0.01
KEGG: ERBB signaling pathway	6.37E-03	0.077	1.94E-02	0.074
KEGG: FcεRI signaling pathway	9.38E-03	0.083	2.73E-05	0.004
KEGG: Focal adhesion	9.38E-03	0.083	3.35E-04	0.008
KEGG: GnRH signaling pathway	6.60E-03	0.077	8.39E-05	0.004
KEGG: Inositol phosphate metabolism	5.33E-03	0.077	1.86E-02	0.072
KEGG: Insulin signaling pathway	3.07E-03	0.074	6.55E-03	0.039
KEGG: Long-term depression	4.77E-03	0.077	5.21E-04	0.009
KEGG: MAPK signaling pathway	1.37E-02	0.099	1.14E-02	0.051
KEGG: Prostate cancer	1.07E-02	0.09	3.79E-04	0.008
KEGG: Vibrio cholerae infection	3.54E-03	0.074	7.84E-05	0.004
KEGG: WNT signaling pathway	3.91E-03	0.074	1.14E-02	0.051
PID: E-cadherin stabilization pathway	4.94E-03	0.077	2.96E-03	0.024
PID: Glypican 1 network	9.14E-03	0.083	8.70E-05	0.004
PID: HIF2α (EPAS1) transcription factor network	1.15E-02	0.092	1.99E-02	0.074
PID: HIV1NEF- Negative effector of Fas and TNF-alpha	2.61E-03	0.074	5.52E-03	0.035
PID: Insulin-mediated glucose transport	1.20E-02	0.094	1.40E-02	0.06
PID: α4β1 integrin signaling events	1.08E-02	0.09	1.84E-02	0.072
PID: β2 integrin cell surface interactions	2.26E-03	0.074	2.72E-03	0.024
PID: α6β4 integrin-ligand interactions	5.60E-03	0.077	3.41E-03	0.026
PID: Direct p53 effectors	6.42E-03	0.077	1.82E-02	0.072
PID: PDGFRβ signaling pathway	3.83E-03	0.074	2.92E-03	0.024
PID: Signaling events mediated by PTP1B	1.18E-02	0.094	1.25E-03	0.015
PID: Reelin signaling pathway	4.19E-03	0.077	1.59E-02	0.065
PID: RET tyrosine kinase signaling	3.69E-03	0.074	8.40E-05	0.004
PID: Syndecan-4-mediated signaling events	6.48E-03	0.077	2.99E-02	0.093
PID: Validated transcriptional targets of TAp63 isoforms	5.79E-04	0.074	1.03E-02	0.048
PID: Signaling events mediated by VEGFR1 and VEGFR2	3.78E-03	0.074	1.65E-04	0.006

Supplementary Table 4 - **Pathways whose deregulation scores significantly differentiate between all subsequent stages of progression (normal->polyp->primary tumor->metastasis) in the Sheffer dataset.**

	Normal vs. polyp		Polyp vs. primary		Primary vs. metastasis	
Pathway	p-value	FDR	p-value	FDR	p-value	FDR
Citrate cycle (TCA cycle) (KEGG)	1.78E-10	2.56E-10	9.51E-09	3.37E-08	7.23E-04	2.53E-03
Pentose phosphate pathway (KEGG)	2.00E-06	2.42E-06	4.48E-11	2.41E-10	1.03E-03	3.32E-03
Galactose metabolism (KEGG)	1.26E-15	4.32E-15	1.92E-03	2.96E-03	9.65E-04	3.17E-03
Ascorbate and aldarate metabolism (KEGG)	2.32E-10	3.30E-10	1.12E-13	1.07E-12	2.03E-03	5.68E-03
Fatty acid metabolism (KEGG)	2.80E-09	3.83E-09	3.24E-17	1.07E-15	1.96E-06	2.83E-05
Oxidative phosphorylation (KEGG)	2.76E-11	4.16E-11	2.45E-11	1.42E-10	4.37E-08	1.72E-06
Pyrimidine metabolism (KEGG)	2.37E-15	6.94E-15	1.91E-04	3.41E-04	2.55E-03	6.76E-03
Valine, leucine and isoleucine degradation (KEGG)	1.56E-13	2.97E-13	1.75E-14	2.15E-13	3.48E-06	3.89E-05
Lysine degradation (KEGG)	1.65E-11	2.55E-11	1.75E-10	7.95E-10	8.38E-06	8.13E-05
beta-Alanine metabolism (KEGG)	2.29E-15	6.94E-15	7.07E-12	4.23E-11	9.76E-04	3.19E-03
Glutathione metabolism (KEGG)	3.87E-15	1.03E-14	2.03E-05	4.15E-05	1.06E-05	9.76E-05
Starch and sucrose metabolism (KEGG)	7.83E-16	3.29E-15	1.90E-12	1.31E-11	3.08E-03	7.75E-03
N-Glycan biosynthesis (KEGG)	2.40E-16	2.25E-15	6.74E-10	2.79E-09	4.99E-03	1.18E-02
Amino sugar and nucleotide sugar metabolism (KEGG)	8.71E-15	2.07E-14	3.39E-15	5.28E-14	2.98E-03	7.54E-03
Inositol phosphate metabolism (KEGG)	6.74E-11	9.97E-11	9.53E-07	2.37E-06	4.70E-05	3.03E-04
Glycerophospholipid metabolism (KEGG)	2.53E-15	7.31E-15	4.03E-05	7.93E-05	2.24E-04	1.00E-03
Sphingolipid metabolism (KEGG)	4.35E-16	2.80E-15	5.25E-08	1.57E-07	1.87E-05	1.49E-04
Propanoate metabolism (KEGG)	1.41E-14	3.25E-14	2.54E-11	1.46E-10	4.28E-04	1.65E-03
Butanoate metabolism (KEGG)	5.50E-11	8.19E-11	1.30E-15	2.20E-14	2.25E-04	1.00E-03
Porphyrin and chlorophyll metabolism (KEGG)	1.58E-11	2.44E-11	3.79E-08	1.19E-07	2.24E-03	6.11E-03
Terpenoid backbone biosynthesis (KEGG)	1.83E-11	2.81E-11	3.22E-02	4.13E-02	1.12E-04	6.01E-04
Drug metabolism - other enzymes (KEGG)	9.37E-12	1.48E-11	9.48E-16	1.65E-14	7.70E-04	2.65E-03
MAPK signaling pathway (KEGG)	1.65E-16	2.25E-15	2.97E-15	4.76E-14	1.71E-05	1.43E-04
Calcium signaling pathway (KEGG)	7.39E-17	2.25E-15	6.29E-13	4.71E-12	2.47E-06	3.04E-05
p53 signaling pathway (KEGG)	2.69E-16	2.25E-15	1.26E-06	2.98E-06	1.62E-03	4.76E-03
SNARE interactions in vesicular transport (KEGG)	2.33E-02	2.47E-02	2.40E-08	7.85E-08	4.33E-06	4.66E-05
Endocytosis (KEGG)	1.03E-15	3.80E-15	3.16E-02	4.07E-02	1.55E-05	1.31E-04
Peroxisome (KEGG)	1.65E-12	2.75E-12	3.97E-17	1.24E-15	3.04E-04	1.29E-03
Apoptosis (KEGG)	6.26E-16	3.01E-15	2.40E-13	2.16E-12	2.25E-06	2.94E-05
Vascular smooth muscle contraction (KEGG)	2.61E-16	2.25E-15	3.50E-11	1.94E-10	6.12E-07	1.25E-05
Notch signaling pathway (KEGG)	7.41E-15	1.78E-14	4.44E-12	2.76E-11	5.07E-05	3.20E-04
VEGF signaling pathway (KEGG)	2.02E-16	2.25E-15	1.38E-10	6.42E-10	3.91E-10	5.08E-08
Adherens junction (KEGG)	4.45E-16	2.80E-15	2.00E-02	2.65E-02	2.14E-04	9.66E-04
Tight junction (KEGG)	1.23E-16	2.25E-15	2.68E-06	6.11E-06	3.09E-03	7.75E-03
Neurotrophin signaling pathway (KEGG)	3.43E-15	9.33E-15	4.27E-04	7.23E-04	1.81E-03	5.21E-03
Olfactory transduction (KEGG)	7.82E-15	1.87E-14	2.76E-14	3.20E-13	2.61E-02	4.67E-02
GnRH signaling pathway (KEGG)	9.76E-04	1.07E-03	1.15E-10	5.62E-10	2.80E-03	7.20E-03
Type II diabetes mellitus (KEGG)	9.83E-14	1.93E-13	4.01E-03	5.85E-03	1.85E-02	3.60E-02
Alzheimer's disease (KEGG)	7.39E-16	3.20E-15	7.78E-12	4.61E-11	8.19E-08	2.85E-06
Parkinson's disease (KEGG)	1.04E-14	2.43E-14	7.29E-08	2.10E-07	2.06E-08	1.11E-06
Huntington's disease (KEGG)	1.34E-15	4.50E-15	3.49E-09	1.32E-08	3.68E-08	1.55E-06
Prion diseases (KEGG)	6.24E-16	3.01E-15	1.10E-05	2.37E-05	1.18E-03	3.77E-03
Pathways in cancer (KEGG)	1.96E-16	2.25E-15	6.21E-17	1.75E-15	1.72E-02	3.39E-02
Pancreatic cancer (KEGG)	2.94E-15	8.22E-15	1.28E-12	9.13E-12	8.65E-11	4.28E-08
Glioma (KEGG)	1.40E-16	2.25E-15	5.05E-14	5.34E-13	2.07E-02	3.91E-02
Dilated cardiomyopathy (KEGG)	1.63E-16	2.25E-15	6.36E-09	2.36E-08	1.01E-03	3.29E-03
Actions of Nitric Oxide in the Heart (BIOCARTA)	2.85E-16	2.25E-15	6.21E-08	1.82E-07	5.47E-05	3.34E-04
Activation of Csk by cAMP-dependent Protein Kinase Inhibits Signaling through the T Cell Receptor (BIOCARTA)	1.49E-14	3.41E-14	2.63E-04	4.53E-04	1.43E-05	1.22E-04
Attenuation of GPCR Signaling (BIOCARTA)	9.25E-16	3.58E-15	5.79E-08	1.72E-07	2.00E-02	3.80E-02
Bioactive Peptide Induced Signaling Pathway (BIOCARTA)	7.00E-16	3.14E-15	4.92E-03	7.06E-03	5.74E-05	3.43E-04
Effects of calcineurin in Keratinocyte Differentiation (BIOCARTA)	2.50E-15	7.25E-15	1.99E-05	4.13E-05	1.71E-03	4.96E-03
EGF Signaling Pathway (BIOCARTA)	8.57E-09	1.14E-08	2.37E-07	6.38E-07	5.35E-03	1.26E-02
Electron Transport Reaction in Mitochondria (BIOCARTA)	1.43E-09	1.97E-09	3.18E-07	8.40E-07	4.80E-05	3.06E-04
Erk1/Erk2 Mapk Signaling pathway (BIOCARTA)	6.89E-16	3.14E-15	1.78E-03	2.76E-03	1.61E-02	3.25E-02
FAS signaling pathway (CD95) (BIOCARTA)	1.17E-12	1.99E-12	6.16E-11	3.23E-10	2.22E-02	4.08E-02
Feeder Pathways for Glycolysis (BIOCARTA)	1.14E-10	1.66E-10	9.48E-08	2.70E-07	1.47E-02	3.01E-02
GATA3 participate in activating the Th2 cytokine genes expression (BIOCARTA)	8.75E-16	3.48E-15	4.72E-08	1.44E-07	9.76E-03	2.12E-02
Growth Hormone Signaling Pathway (BIOCARTA)	1.22E-15	4.20E-15	8.72E-07	2.18E-06	8.60E-04	2.89E-03
Hemoglobin's Chaperone (BIOCARTA)	5.93E-03	6.32E-03	1.03E-02	1.42E-02	5.69E-07	1.25E-05
HIV Induced T Cell Apoptosis (BIOCARTA)	2.68E-04	2.99E-04	3.43E-08	1.10E-07	1.58E-06	2.53E-05
HIV-I Nef: negative effector of Fas and TNF (BIOCARTA)	1.38E-10	2.00E-10	2.06E-04	3.62E-04	1.24E-02	2.57E-02
Keratinocyte Differentiation (BIOCARTA)	1.48E-15	4.84E-15	1.18E-03	1.87E-03	1.40E-04	7.08E-04
mCalpain and friends in Cell motility (BIOCARTA)	6.81E-16	3.14E-15	1.24E-07	3.48E-07	1.05E-02	2.25E-02
Multiple antiapoptotic pathways from IGF-1R signaling lead to BAD	9.78E-16	3.74E-15	6.47E-09	2.38E-08	1.91E-02	3.69E-02

phosphorylation (BIOCARTA)						
Neuropeptides VIP and PACAP inhibit the apoptosis of activated T cells (BIOCARTA)	4.23E-16	2.78E-15	1.33E-09	5.34E-09	5.57E-04	2.05E-03
Nitric Oxide Signaling Pathway (BIOCARTA)	8.28E-16	3.38E-15	5.03E-08	1.52E-07	2.17E-02	4.03E-02
Phosphoinositides and their downstream targets (BIOCARTA)	3.26E-03	3.49E-03	1.30E-08	4.49E-08	1.68E-02	3.32E-02
Phospholipase C-epsilon pathway (BIOCARTA)	5.60E-16	2.91E-15	8.26E-09	2.97E-08	1.85E-02	3.60E-02
Protein Kinase A at the Centrosome (BIOCARTA)	1.29E-15	4.37E-15	3.51E-08	1.12E-07	1.96E-02	3.77E-02
Regulation of BAD phosphorylation (BIOCARTA)	4.73E-16	2.80E-15	1.03E-06	2.53E-06	9.54E-04	3.15E-03
Rho-Selective Guanine Exchange Factor AKAP13 Mediates Stress Fiber Formation (BIOCARTA)	5.60E-16	2.91E-15	5.14E-08	1.54E-07	1.66E-02	3.30E-02
Role of Erk5 in Neuronal Survival (BIOCARTA)	5.00E-16	2.85E-15	7.56E-05	1.43E-04	7.04E-03	1.57E-02
Role of Tob in T-cell activation (BIOCARTA)	2.29E-11	3.47E-11	8.79E-08	2.51E-07	3.61E-05	2.46E-04
Stress Induction of HSP Regulation (BIOCARTA)	3.64E-02	3.83E-02	6.76E-12	4.08E-11	1.18E-08	7.73E-07
Transcription factor CREB and its extracellular signals (BIOCARTA)	7.33E-16	3.20E-15	2.42E-09	9.48E-09	1.81E-02	3.54E-02
Trka Receptor Signaling Pathway (BIOCARTA)	2.51E-11	3.80E-11	1.06E-06	2.57E-06	3.46E-04	1.38E-03
VEGF, Hypoxia, and Angiogenesis (BIOCARTA)	5.00E-16	2.85E-15	1.78E-04	3.20E-04	2.39E-03	6.43E-03
Vitamin C in the Brain (BIOCARTA)	6.84E-04	7.54E-04	4.05E-14	4.36E-13	1.94E-03	5.51E-03
WNT Signaling Pathway (BIOCARTA)	1.27E-14	2.95E-14	1.64E-13	1.52E-12	1.50E-03	4.54E-03
Nongenotropic Androgen signaling (PID)	6.44E-13	1.14E-12	1.00E-04	1.85E-04	1.50E-04	7.55E-04
Regulation of CDC42 activity (PID)	4.56E-15	1.18E-14	1.79E-08	5.97E-08	3.07E-05	2.17E-04
Validated transcriptional targets of deltaNp63 isoforms (PID)	4.47E-16	2.80E-15	3.82E-02	4.86E-02	2.71E-06	3.21E-05
E-cadherin signaling in keratinocytes (PID)	1.88E-08	2.46E-08	8.39E-07	2.11E-06	2.01E-04	9.21E-04
Regulation of nuclear estrogen receptor alpha (PID)	9.61E-07	1.18E-06	9.78E-07	2.41E-06	2.44E-03	6.51E-03
EGF receptor (ErbB1) signaling pathway (PID)	5.85E-14	1.18E-13	1.05E-06	2.56E-06	2.58E-03	6.83E-03
FAS (CD95) signaling pathway (PID)	1.54E-11	2.39E-11	4.85E-04	8.11E-04	8.31E-06	8.13E-05
Signaling events mediated by HDAC Class III (PID)	1.48E-16	2.25E-15	2.68E-03	4.03E-03	2.83E-03	7.22E-03
HIF-1-alpha transcription factor network (PID)	2.66E-16	2.25E-15	4.28E-03	6.20E-03	2.26E-02	4.12E-02
HIV-1 Nef: Negative effector of Fas and TNF-alpha (PID)	4.25E-07	5.30E-07	5.58E-04	9.28E-04	2.10E-02	3.93E-02
FOXA1 transcription factor network (PID)	7.12E-15	1.72E-14	1.84E-10	8.33E-10	3.43E-04	1.38E-03
IGF1 pathway (PID)	5.88E-04	6.52E-04	1.97E-02	2.60E-02	1.04E-02	2.22E-02
IL12-mediated signaling events (PID)	3.03E-13	5.59E-13	9.41E-05	1.76E-04	2.67E-03	6.96E-03
Alpha4 beta1 integrin signaling events (PID)	9.22E-14	1.81E-13	6.36E-07	1.62E-06	2.57E-02	4.61E-02
Notch signaling pathway (PID)	5.29E-16	2.91E-15	5.03E-18	2.29E-16	1.59E-04	7.65E-04
Signaling mediated by p38-alpha and p38-beta (PID)	8.11E-17	2.25E-15	5.09E-06	1.13E-05	6.35E-04	2.28E-03
Direct p53 effectors (PID)	2.54E-16	2.25E-15	6.30E-14	6.43E-13	4.23E-04	1.64E-03
PDGFR-alpha signaling pathway (PID)	2.79E-15	7.86E-15	8.88E-04	1.44E-03	4.67E-06	4.94E-05
Trk receptor signaling mediated by PI3K and PLC-gamma (PID)	6.44E-13	1.14E-12	1.06E-09	4.31E-09	7.26E-06	7.29E-05
Presenilin action in Notch and Wnt signaling (PID)	6.77E-13	1.19E-12	1.20E-10	5.83E-10	6.41E-03	1.45E-02
Sphingosine 1-phosphate (S1P) pathway (PID)	2.51E-16	2.25E-15	4.35E-05	8.50E-05	4.24E-07	1.01E-05
S1P4 pathway (PID)	6.46E-15	1.60E-14	1.81E-06	4.22E-06	6.29E-06	6.42E-05
Validated transcriptional targets of TAp63 isoforms (PID)	2.69E-16	2.25E-15	2.23E-02	2.93E-02	2.17E-02	4.03E-02
Signaling events mediated by TCPTP (PID)	4.09E-15	1.08E-14	1.16E-04	2.13E-04	2.12E-06	2.94E-05
Neurotrophic factor-mediated Trk receptor signaling (PID)	1.41E-14	3.25E-14	2.17E-08	7.18E-08	3.45E-03	8.47E-03
VEGF and VEGFR signaling network (PID)	2.71E-15	7.67E-15	7.96E-15	1.10E-13	2.17E-10	4.28E-08
VEGFR1 specific signals (PID)	2.85E-16	2.25E-15	2.30E-08	7.56E-08	4.29E-10	5.08E-08

Supplementary Table 5 - **Pathways whose deregulation scores have significant positive correlation with the CIN index, in all three colorectal datasets (Sheffer, Sveen and Kogo).** Listing the Spearman correlation coefficient (ρ), p-value, and Benjamini-Hochberg false discovery rate (FDR) of each.

	Sheffer et al.			Sveen et al.			Kogo et al.		
Pathway	ρ	p-value	FDR	ρ	p-value	FDR	ρ	p-value	FDR
Y branching of actin filaments (BIOCARTA)	0.48	1.99E-12	7.77E-12	0.28	6.63E-03	2.48E-02	0.32	9.71E-05	4.38E-04
ALK in cardiac myocytes (BIOCARTA)	0.51	9.98E-14	4.34E-13	0.32	2.39E-03	1.09E-02	0.22	6.40E-03	1.74E-02
Regulation of BAD phosphorylation (BIOCARTA)	0.26	1.69E-04	3.60E-04	0.28	7.44E-03	2.71E-02	0.28	5.21E-04	1.94E-03
Effects of calcineurin in Keratinocyte Differentiation (BIOCARTA)	0.79	0	0	0.52	1.19E-06	4.00E-05	0.39	1.75E-06	1.31E-05
CARM1 and Regulation of the Estrogen Receptor (BIOCARTA)	0.35	5.28E-07	1.45E-06	0.36	8.05E-04	5.01E-03	0.44	1.04E-07	9.78E-07
Pertussis toxin-insensitive CCR5 Signaling in Macrophage (BIOCARTA)	0.62	3.25E-21	2.43E-20	0.26	1.13E-02	3.74E-02	0.39	2.83E-06	2.01E-05
CD40L Signaling Pathway (BIOCARTA)	0.43	6.39E-10	2.09E-09	0.37	5.81E-04	4.09E-03	0.19	1.51E-02	3.87E-02
Cadmium induces DNA synthesis and proliferation in macrophages (BIOCARTA)	0.15	2.13E-02	3.55E-02	0.34	1.27E-03	6.88E-03	0.23	4.40E-03	1.26E-02
CTL mediated immune response against target cells (BIOCARTA)	0.50	4.15E-13	1.73E-12	0.46	1.38E-05	2.33E-04	0.49	3.28E-09	5.70E-08
CXCR4 Signaling Pathway (BIOCARTA)	0.20	2.84E-03	5.16E-03	0.32	2.18E-03	1.02E-02	0.47	1.01E-08	1.39E-07
Induction of apoptosis through DR3 and DR4/5 Death Receptors (BIOCARTA)	0.28	5.79E-05	1.30E-04	0.36	6.83E-04	4.54E-03	0.44	7.00E-08	6.90E-07
Phospholipids as signalling intermediaries (BIOCARTA)	0.41	5.89E-09	1.77E-08	0.33	1.96E-03	9.49E-03	0.21	8.95E-03	2.37E-02
Electron Transport Reaction in Mitochondria (BIOCARTA)	0.23	1.10E-03	2.09E-03	0.32	2.63E-03	1.19E-02	0.24	3.32E-03	9.97E-03
Fc Epsilon Receptor I Signaling in Mast Cells (BIOCARTA)	0.75	2.83E-34	7.60E-33	0.30	4.82E-03	1.95E-02	0.42	4.06E-07	3.42E-06
Feeder Pathways for Glycolysis (BIOCARTA)	0.42	2.55E-09	8.01E-09	0.34	1.18E-03	6.61E-03	0.31	1.81E-04	7.68E-04
HIV-I Nef: negative effector of Fas and TNF (BIOCARTA)	0.74	0	0	0.51	1.10E-06	4.00E-05	0.51	3.20E-10	7.01E-09
IL22 Soluble Receptor Signaling Pathway (BIOCARTA)	0.63	1.53E-21	1.18E-20	0.29	5.82E-03	2.26E-02	0.48	3.59E-09	6.07E-08
Keratinocyte Differentiation (BIOCARTA)	0.66	3.01E-24	3.17E-23	0.31	3.65E-03	1.55E-02	0.46	1.65E-08	2.07E-07
Role of Mitochondria in Apoptotic Signaling (BIOCARTA)	0.14	2.55E-02	4.23E-02	0.52	8.75E-07	3.45E-05	0.41	7.01E-07	5.75E-06
Regulation of p27 Phosphorylation during Cell Cycle Progression (BIOCARTA)	0.16	1.45E-02	2.44E-02	0.25	1.47E-02	4.49E-02	0.23	3.58E-03	1.05E-02
p38 MAPK Signaling Pathway (BIOCARTA)	0.48	3.10E-12	1.18E-11	0.37	4.68E-04	3.50E-03	0.37	6.34E-06	3.98E-05
Influence of Ras and Rho proteins on G1 to S Transition (BIOCARTA)	0.29	2.78E-05	6.47E-05	0.40	1.58E-04	1.58E-03	0.20	1.10E-02	2.89E-02
Ras Signaling Pathway (BIOCARTA)	0.24	5.35E-04	1.06E-03	0.27	9.83E-03	3.40E-02	0.37	7.79E-06	4.65E-05
Acetylation and Deacetylation of RelA in The Nucleus (BIOCARTA)	0.28	5.40E-05	1.22E-04	0.54	2.77E-07	1.26E-05	0.19	1.45E-02	3.74E-02
E2F1 Destruction Pathway (BIOCARTA)	0.16	1.45E-02	2.44E-02	0.25	1.47E-02	4.49E-02	0.23	3.58E-03	1.05E-02
Activation of Src by Protein-tyrosine phosphatase alpha (BIOCARTA)	0.29	3.05E-05	7.08E-05	0.25	1.32E-02	4.18E-02	0.31	1.82E-04	7.68E-04
TACI and BCMA stimulation of B cell immune responses (BIOCARTA)	0.22	1.71E-03	3.18E-03	0.30	4.56E-03	1.90E-02	0.29	4.16E-04	1.57E-03
HIV Induced T Cell Apoptosis (BIOCARTA)	0.69	3.89E-27	5.11E-26	0.38	3.02E-04	2.52E-03	0.53	3.55E-11	1.17E-09
VEGF, Hypoxia, and Angiogenesis (BIOCARTA)	0.61	2.34E-20	1.59E-19	0.46	1.49E-05	2.44E-04	0.42	3.82E-07	3.27E-06
WNT Signaling Pathway (BIOCARTA)	0.44	1.66E-10	5.59E-10	0.47	9.22E-06	1.88E-04	0.24	2.98E-03	9.11E-03
Adherens junction (KEGG)	0.47	1.10E-11	4.01E-11	0.33	1.90E-03	9.35E-03	0.23	3.94E-03	1.14E-02
Amino sugar and nucleotide sugar metabolism (KEGG)	0.41	3.24E-09	9.94E-09	0.49	3.52E-06	8.32E-05	0.40	1.17E-06	9.24E-06
Ascorbate and aldarate metabolism (KEGG)	0.27	1.16E-04	2.51E-04	0.40	1.66E-04	1.61E-03	0.23	5.00E-03	1.41E-02
Cysteine and methionine metabolism (KEGG)	0.25	3.61E-04	7.40E-04	0.29	5.73E-03	2.26E-02	0.36	1.56E-05	8.16E-05
Drug metabolism - other enzymes (KEGG)	0.55	2.31E-16	1.17E-15	0.41	9.84E-05	1.04E-03	0.18	2.00E-02	4.94E-02
ErbB signaling pathway (KEGG)	0.63	0	0	0.33	1.86E-03	9.21E-03	0.25	1.87E-03	5.99E-03
Ether lipid metabolism (KEGG)	0.31	1.34E-05	3.18E-05	0.50	2.22E-06	5.57E-05	0.31	1.97E-04	8.20E-04
Galactose metabolism (KEGG)	0.53	3.99E-15	1.83E-14	0.46	1.62E-05	2.58E-04	0.25	1.75E-03	5.69E-03
Glycerophospholipid metabolism (KEGG)	0.22	1.76E-03	3.27E-03	0.51	1.29E-06	4.00E-05	0.32	1.12E-04	4.97E-04
Glycosphingolipid biosynthesis - globo series (KEGG)	0.32	4.94E-06	1.23E-05	0.34	1.38E-03	7.32E-03	0.22	5.42E-03	1.50E-02
Glycosphingolipid biosynthesis - lacto and neolacto series (KEGG)	0.36	3.26E-07	9.12E-07	0.32	2.29E-03	1.06E-02	0.22	5.16E-03	1.44E-02
Glycosylphosphatidylinositol(GPI)-anchor biosynthesis (KEGG)	0.25	2.91E-04	6.01E-04	0.50	2.26E-06	5.57E-05	0.20	1.29E-02	3.37E-02

Hematopoietic cell lineage (KEGG)	0.66	0	0	0.28	6.68E-03	2.48E-02	0.30	2.18E-04	8.95E-04
Inositol phosphate metabolism (KEGG)	0.62	2.25E-21	1.70E-20	0.45	2.64E-05	3.66E-04	0.37	6.90E-06	4.20E-05
Intestinal immune network for IgA production (KEGG)	0.62	0	0	0.34	1.46E-03	7.49E-03	0.30	2.92E-04	1.16E-03
Limonene and pinene degradation (KEGG)	0.26	1.99E-04	4.20E-04	0.43	6.48E-05	7.51E-04	0.22	5.75E-03	1.59E-02
MAPK signaling pathway (KEGG)	0.72	6.59E-31	1.34E-29	0.28	6.55E-03	2.47E-02	0.26	1.52E-03	5.15E-03
Neuroactive ligand-receptor interaction (KEGG)	0.71	7.33E-30	1.35E-28	0.31	2.87E-03	1.28E-02	0.30	2.53E-04	1.02E-03
Notch signaling pathway (KEGG)	0.36	4.55E-07	1.26E-06	0.36	7.78E-04	4.89E-03	0.31	2.03E-04	8.38E-04
Oxidative phosphorylation (KEGG)	0.24	6.02E-04	1.18E-03	0.57	3.97E-08	2.93E-06	0.24	3.55E-03	1.05E-02
O-Glycan biosynthesis (KEGG)	0.47	8.87E-12	3.26E-11	0.28	6.46E-03	2.46E-02	0.35	2.24E-05	1.12E-04
Pathogenic Escherichia coli infection (KEGG)	0.30	1.72E-05	4.04E-05	0.61	1.76E-09	3.47E-07	0.43	1.45E-07	1.34E-06
Pentose and glucuronate interconversions (KEGG)	0.45	9.18E-11	3.12E-10	0.37	4.99E-04	3.69E-03	0.39	1.90E-06	1.41E-05
Phosphatidylinositol signaling system (KEGG)	0.67	0	0	0.56	6.46E-08	3.96E-06	0.32	1.13E-04	4.97E-04
Porphyrin and chlorophyll metabolism (KEGG)	0.47	7.43E-12	2.76E-11	0.47	7.71E-06	1.69E-04	0.37	5.64E-06	3.66E-05
Propanoate metabolism (KEGG)	0.36	3.52E-07	9.82E-07	0.49	4.28E-06	9.72E-05	0.30	2.72E-04	1.09E-03
Renin-angiotensin system (KEGG)	0.42	2.73E-09	8.53E-09	0.28	7.09E-03	2.60E-02	0.37	6.25E-06	3.97E-05
Selenoamino acid metabolism (KEGG)	0.42	2.46E-09	7.79E-09	0.35	1.02E-03	6.01E-03	0.35	1.98E-05	1.01E-04
Sphingolipid metabolism (KEGG)	0.49	1.06E-12	4.27E-12	0.45	1.98E-05	3.00E-04	0.34	3.13E-05	1.52E-04
Starch and sucrose metabolism (KEGG)	0.50	1.92E-13	8.21E-13	0.40	1.93E-04	1.80E-03	0.26	1.59E-03	5.26E-03
Sulfur metabolism (KEGG)	0.33	2.94E-06	7.70E-06	0.38	3.37E-04	2.76E-03	0.35	2.47E-05	1.23E-04
Nongenotropic Androgen signaling (PID)	0.75	4.03E-34	1.03E-32	0.64	2.97E-10	1.76E-07	0.52	1.32E-10	3.40E-09
Regulation of Androgen receptor activity (PID)	0.57	3.55E-17	1.84E-16	0.44	4.21E-05	5.66E-04	0.31	1.83E-04	7.68E-04
Caspase cascade in apoptosis (PID)	0.45	7.54E-11	2.59E-10	0.33	2.00E-03	9.57E-03	0.44	6.82E-08	6.90E-07
E-cadherin signaling in keratinocytes (PID)	0.70	3.46E-28	4.99E-27	0.28	6.50E-03	2.46E-02	0.24	2.79E-03	8.63E-03
E-cadherin signaling in the nascent adherens junction (PID)	0.68	8.05E-27	1.01E-25	0.34	1.45E-03	7.49E-03	0.19	1.61E-02	4.08E-02
EphrinA-EPHA pathway (PID)	0.26	1.85E-04	3.92E-04	0.31	3.26E-03	1.43E-02	0.36	1.29E-05	7.07E-05
Regulation of nuclear estrogen receptor alpha (PID)	0.33	2.50E-06	6.60E-06	0.58	3.26E-08	2.75E-06	0.45	4.02E-08	4.37E-07
FAS (CD95) signaling pathway (PID)	0.69	7.54E-28	1.04E-26	0.43	4.85E-05	6.11E-04	0.53	4.49E-11	1.40E-09
Fc-epsilon receptor I signaling in mast cells (PID)	0.64	5.93E-23	5.62E-22	0.26	1.29E-02	4.11E-02	0.29	3.68E-04	1.42E-03
HIV-1 Nef: Negative effector of Fas and TNF-alpha (PID)	0.65	5.91E-24	6.13E-23	0.58	1.94E-08	1.92E-06	0.53	5.82E-11	1.64E-09
FOXA1 transcription factor network (PID)	0.56	7.04E-17	3.62E-16	0.45	2.29E-05	3.38E-04	0.43	1.68E-07	1.52E-06
FOXA2 and FOXA3 transcription factor networks (PID)	0.58	8.53E-18	4.71E-17	0.27	9.38E-03	3.28E-02	0.45	2.78E-08	3.23E-07
IL2 signaling events mediated by PI3K (PID)	0.60	1.45E-19	9.03E-19	0.47	1.06E-05	2.09E-04	0.53	2.82E-11	1.04E-09
IL4-mediated signaling events (PID)	0.31	1.17E-05	2.79E-05	0.34	1.24E-03	6.83E-03	0.53	1.37E-11	5.38E-10
Insulin-mediated glucose transport (PID)	0.49	1.52E-12	6.03E-12	0.34	1.43E-03	7.47E-03	0.42	2.83E-07	2.49E-06
Integrin family cell surface interactions (PID)	0.24	6.36E-04	1.23E-03	0.26	1.09E-02	3.67E-02	0.19	1.71E-02	4.31E-02
p38 MAPK signaling pathway (PID)	0.49	7.13E-13	2.91E-12	0.32	2.17E-03	1.02E-02	0.26	1.33E-03	4.54E-03
Direct p53 effectors (PID)	0.71	7.69E-30	1.38E-28	0.31	3.35E-03	1.44E-02	0.58	1.93E-13	1.27E-11
Class I PI3K signaling events mediated by Akt (PID)	0.43	7.96E-10	2.56E-09	0.33	2.01E-03	9.57E-03	0.56	2.06E-12	8.69E-11
Retinoic acid receptors-mediated signaling (PID)	0.35	8.34E-07	2.24E-06	0.27	9.22E-03	3.28E-02	0.19	1.68E-02	4.23E-02
Sphingosine 1-phosphate (S1P) pathway (PID)	0.39	3.59E-08	1.04E-07	0.51	2.08E-06	5.57E-05	0.23	3.58E-03	1.05E-02
S1P5 pathway (PID)	0.54	1.54E-15	7.60E-15	0.39	2.17E-04	1.94E-03	0.28	5.31E-04	1.95E-03
Regulation of nuclear SMAD2/3 signaling (PID)	0.70	6.32E-29	9.82E-28	0.56	6.69E-08	3.96E-06	0.58	1.94E-13	1.27E-11

Supplementary Table 6 - **List of pathways that are more deregulated in microsatellite stable (MSS) tumors than in MSI-high tumors in the Sheffer et al. dataset**. Additionally, for those pathways that are significantly differentially deregulated in Sveen the p-value of the significance is listed.

	Sheffer et al.		Sveen et al.	
Pathway	**p-value**	**FDR**	**p-value**	**FDR**
The 4-1BB-dependent immune response (BIOCARTA)	3.34E-02	6.73E-02		
Angiotensin-converting enzyme 2 regulates heart function (BIOCARTA)	4.77E-02	8.95E-02		
Hemoglobin's Chaperone (BIOCARTA)	6.27E-04	3.49E-03	7.10E-06	1.66E-03
ALK in cardiac myocytes (BIOCARTA)	1.89E-02	4.34E-02		
Antigen Dependent B Cell Activation (BIOCARTA)	4.58E-02	8.64E-02		
Angiotensin II mediated activation of JNK Pathway via Pyk2 dependent signaling (BIOCARTA)	8.53E-03	2.32E-02		
Bioactive Peptide Induced Signaling Pathway (BIOCARTA)	3.82E-07	3.34E-05		
B Lymphocyte Cell Surface Molecules (BIOCARTA)	9.46E-03	2.46E-02		
Effects of calcineurin in Keratinocyte Differentiation (BIOCARTA)	2.74E-06	8.09E-05	1.84E-04	5.70E-03
Role of EGF Receptor Transactivation by GPCRs in Cardiac Hypertrophy (BIOCARTA)	3.09E-03	1.06E-02		
Pertussis toxin-insensitive CCR5 Signaling in Macrophage (BIOCARTA)	5.89E-03	1.74E-02		
The Co-Stimulatory Signal During T-cell Activation (BIOCARTA)	8.75E-03	2.36E-02		
CTL mediated immune response against target cells (BIOCARTA)	7.42E-04	3.91E-03	1.88E-03	2.36E-02
CXCR4 Signaling Pathway (BIOCARTA)	4.66E-06	8.89E-05	1.52E-02	7.12E-02
Induction of apoptosis through DR3 and DR4/5 Death Receptors (BIOCARTA)	3.21E-02	6.59E-02	4.91E-03	4.47E-02
EGF Signaling Pathway (BIOCARTA)	3.31E-04	2.11E-03		
Erythropoietin mediated neuroprotection through NF-kB (BIOCARTA)	5.50E-03	1.64E-02		
Role of Erk5 in Neuronal Survival (BIOCARTA)	2.67E-05	3.00E-04		
FAS signaling pathway (CD95) (BIOCARTA)	3.49E-02	6.96E-02		
Fc Epsilon Receptor I Signaling in Mast Cells (BIOCARTA)	1.74E-07	2.57E-05	1.25E-02	6.44E-02
Feeder Pathways for Glycolysis (BIOCARTA)	1.65E-02	3.90E-02		
Growth Hormone Signaling Pathway (BIOCARTA)	3.94E-06	8.89E-05		
Hypoxia-Inducible Factor in the Cardiovascular System (BIOCARTA)	4.23E-02	8.11E-02		
HIV-I Nef: negative effector of Fas and TNF (BIOCARTA)	1.15E-03	5.37E-03	2.28E-03	2.71E-02
Stress Induction of HSP Regulation (BIOCARTA)	2.84E-04	1.85E-03		
IL22 Soluble Receptor Signaling Pathway (BIOCARTA)	1.19E-03	5.45E-03	2.09E-02	8.83E-02
IL-7 Signal Transduction (BIOCARTA)	3.70E-02	7.34E-02		
Keratinocyte Differentiation (BIOCARTA)	1.33E-04	1.09E-03		
Reversal of Insulin Resistance by Leptin (BIOCARTA)	4.16E-02	8.07E-02		
MAPKinase Signaling Pathway (BIOCARTA)	1.68E-05	2.13E-04		
Role of MEF2D in T-cell Apoptosis (BIOCARTA)	2.23E-03	8.66E-03		
Role of Mitochondria in Apoptotic Signaling (BIOCARTA)	9.10E-03	2.40E-02		
p38 MAPK Signaling Pathway (BIOCARTA)	2.77E-03	1.01E-02		
Regulation of transcriptional activity by PML (BIOCARTA)	4.97E-02	9.16E-02		
Phosphoinositides and their downstream targets (BIOCARTA)	1.16E-04	1.02E-03		
Acetylation and Deacetylation of RelA in The Nucleus (BIOCARTA)	3.86E-02	7.63E-02	1.88E-03	2.36E-02
SODD/TNFR1 Signaling Pathway (BIOCARTA)	2.77E-03	1.01E-02		
TNF/Stress Related Signaling (BIOCARTA)	3.32E-02	6.73E-02		
TACI and BCMA stimulation of B cell immune responses (BIOCARTA)	1.07E-02	2.71E-02		
HIV Induced T Cell Apoptosis (BIOCARTA)	2.37E-04	1.59E-03	2.79E-03	3.11E-02
Lck and Fyn tyrosine kinases in initiation of TCR Activation (BIOCARTA)	2.33E-02	5.13E-02		
T Cell Receptor Signaling Pathway (BIOCARTA)	1.73E-04	1.33E-03		
T Cytotoxic Cell Surface Molecules (BIOCARTA)	2.44E-02	5.32E-02		
Th1/Th2 Differentiation (BIOCARTA)	4.70E-03	1.46E-02		
T Helper Cell Surface Molecules (BIOCARTA)	3.93E-02	7.71E-02		
Role of Tob in T-cell activation (BIOCARTA)	3.51E-03	1.16E-02		
Toll-Like Receptor Pathway (BIOCARTA)	5.41E-04	3.11E-03		
Trka Receptor Signaling Pathway (BIOCARTA)	8.90E-07	4.58E-05	5.90E-05	2.90E-03
VEGF, Hypoxia, and Angiogenesis (BIOCARTA)	9.43E-05	8.85E-04	5.32E-04	1.08E-02
WNT Signaling Pathway (BIOCARTA)	3.85E-06	8.89E-05	6.97E-05	2.94E-03
Adherens junction (KEGG)	1.62E-02	3.83E-02		
Adipocytokine signaling pathway (KEGG)	5.52E-05	5.52E-04		
Allograft rejection (KEGG)	2.18E-03	8.64E-03		
Alzheimer's disease (KEGG)	1.70E-05	2.13E-04		
Amino sugar and nucleotide sugar metabolism (KEGG)	1.53E-02	3.70E-02		
Antigen processing and presentation (KEGG)	7.25E-04	3.89E-03		
Apoptosis (KEGG)	2.72E-04	1.79E-03		
Arrhythmogenic right ventricular cardiomyopathy (ARVC) (KEGG)	9.29E-08	2.36E-05		
Ascorbate and aldarate metabolism (KEGG)	5.58E-03	1.66E-02		
Asthma (KEGG)	2.58E-03	9.71E-03		
Autoimmune thyroid disease (KEGG)	2.43E-03	9.27E-03		
Axon guidance (KEGG)	1.62E-02	3.84E-02		
Basal cell carcinoma (KEGG)	1.11E-04	9.94E-04		
Basal transcription factors (KEGG)	3.56E-05	3.76E-04	2.57E-02	9.80E-02
beta-Alanine metabolism (KEGG)	1.67E-03	7.08E-03		

Butanoate metabolism (KEGG)	2.45E-03	9.28E-03		
B cell receptor signaling pathway (KEGG)	1.19E-04	1.03E-03		
Calcium signaling pathway (KEGG)	2.07E-02	4.73E-02		
Cardiac muscle contraction (KEGG)	2.18E-06	7.16E-05		
Cell adhesion molecules (CAMs) (KEGG)	7.31E-04	3.89E-03		
Chronic myeloid leukemia (KEGG)	5.07E-06	9.08E-05		
Cytosolic DNA-sensing pathway (KEGG)	3.23E-04	2.08E-03		
Endocytosis (KEGG)	1.38E-03	6.17E-03		
Epithelial cell signaling in Helicobacter pylori infection (KEGG)	1.44E-06	6.07E-05		
ErbB signaling pathway (KEGG)	2.10E-04	1.46E-03		
Fatty acid metabolism (KEGG)	4.48E-03	1.40E-02		
Fc gamma R-mediated phagocytosis (KEGG)	4.55E-02	8.62E-02		
Folate biosynthesis (KEGG)	4.81E-06	8.89E-05	2.51E-02	9.75E-02
Galactose metabolism (KEGG)	4.41E-02	8.38E-02		
Glutathione metabolism (KEGG)	4.67E-04	2.79E-03	1.03E-02	5.96E-02
Graft-versus-host disease (KEGG)	7.48E-04	3.91E-03		
Hedgehog signaling pathway (KEGG)	3.41E-02	6.83E-02		
Hematopoietic cell lineage (KEGG)	5.21E-03	1.58E-02		
Histidine metabolism (KEGG)	1.36E-02	3.34E-02		
Hypertrophic cardiomyopathy (HCM) (KEGG)	1.51E-04	1.19E-03		
Inositol phosphate metabolism (KEGG)	5.81E-06	9.74E-05		
Intestinal immune network for IgA production (KEGG)	5.29E-03	1.59E-02		
Jak-STAT signaling pathway (KEGG)	1.32E-04	1.09E-03		
Leishmania infection (KEGG)	1.59E-02	3.80E-02		
Limonene and pinene degradation (KEGG)	1.56E-02	3.76E-02		
Long-term potentiation (KEGG)	1.39E-04	1.13E-03		
Lysine degradation (KEGG)	1.01E-02	2.60E-02	2.19E-05	1.94E-03
Lysosome (KEGG)	1.57E-03	6.87E-03		
MAPK signaling pathway (KEGG)	5.78E-07	4.05E-05		
Maturity onset diabetes of the young (KEGG)	2.22E-02	4.92E-02		
Melanogenesis (KEGG)	1.90E-02	4.35E-02		
Natural killer cell mediated cytotoxicity (KEGG)	6.00E-05	5.91E-04		
Neuroactive ligand-receptor interaction (KEGG)	1.07E-04	9.89E-04		
Neurotrophin signaling pathway (KEGG)	6.79E-06	1.00E-04		
Nicotinate and nicotinamide metabolism (KEGG)	8.92E-04	4.47E-03		
Non-small cell lung cancer (KEGG)	2.85E-03	1.01E-02		
Oxidative phosphorylation (KEGG)	1.07E-02	2.71E-02		
O-Glycan biosynthesis (KEGG)	2.95E-06	8.30E-05		
p53 signaling pathway (KEGG)	1.98E-06	6.87E-05		
Parkinson's disease (KEGG)	8.10E-03	2.25E-02		
Pathways in cancer (KEGG)	5.34E-06	9.29E-05		
Peroxisome (KEGG)	1.11E-03	5.25E-03	5.55E-03	4.56E-02
Phenylalanine metabolism (KEGG)	1.84E-02	4.25E-02		
Phosphatidylinositol signaling system (KEGG)	2.77E-05	3.03E-04		
Porphyrin and chlorophyll metabolism (KEGG)	6.65E-06	1.00E-04		
Primary bile acid biosynthesis (KEGG)	2.82E-02	6.01E-02		
Primary immunodeficiency (KEGG)	1.14E-02	2.87E-02		
Propanoate metabolism (KEGG)	1.03E-03	5.06E-03		
Proteasome (KEGG)	3.18E-02	6.56E-02		
Pyruvate metabolism (KEGG)	3.79E-03	1.23E-02		
Regulation of actin cytoskeleton (KEGG)	1.14E-02	2.87E-02		
Renal cell carcinoma (KEGG)	1.68E-06	6.61E-05		
Renin-angiotensin system (KEGG)	3.54E-06	8.89E-05	1.05E-03	1.68E-02
RNA polymerase (KEGG)	3.90E-02	7.69E-02		
SNARE interactions in vesicular transport (KEGG)	6.19E-07	4.05E-05		
Starch and sucrose metabolism (KEGG)	2.60E-03	9.71E-03		
Steroid hormone biosynthesis (KEGG)	6.32E-04	3.49E-03		
Sulfur metabolism (KEGG)	1.36E-03	6.12E-03		
Systemic lupus erythematosus (KEGG)	1.06E-03	5.13E-03		
Thyroid cancer (KEGG)	1.60E-02	3.80E-02		
Tight junction (KEGG)	2.69E-05	3.00E-04		
Type II diabetes mellitus (KEGG)	6.79E-06	1.00E-04		
Type I diabetes mellitus (KEGG)	1.92E-03	7.88E-03		
T cell receptor signaling pathway (KEGG)	1.11E-05	1.49E-04		
Ubiquitin mediated proteolysis (KEGG)	3.13E-07	3.34E-05	7.92E-04	1.38E-02
Valine, leucine and isoleucine degradation (KEGG)	1.69E-03	7.14E-03		
VEGF signaling pathway (KEGG)	7.38E-06	1.06E-04		
Viral myocarditis (KEGG)	1.49E-03	6.56E-03		
Wnt signaling pathway (KEGG)	1.78E-04	1.34E-03		
ALK2 signaling events (PID)	8.84E-04	4.47E-03		
Nongenotropic Androgen signaling (PID)	4.61E-06	8.89E-05	9.71E-03	5.91E-02

BCR signaling pathway (PID)	4.65E-02	8.75E-02		
BMP receptor signaling (PID)	2.22E-02	4.92E-02		
Caspase cascade in apoptosis (PID)	3.41E-03	1.14E-02	2.29E-03	2.71E-02
CD40/CD40L signaling (PID)	1.20E-02	2.99E-02		
TCR signaling in naive CD8+ T cells (PID)	2.33E-03	8.93E-03		
Regulation of CDC42 activity (PID)	3.36E-03	1.13E-02		
C-MYB transcription factor network (PID)	4.01E-03	1.29E-02		
CXCR4-mediated signaling events (PID)	9.16E-03	2.41E-02		
E-cadherin signaling in keratinocytes (PID)	3.73E-06	8.89E-05		
E-cadherin signaling in the nascent adherens junction (PID)	6.48E-04	3.54E-03		
Stabilization and expansion of the E-cadherin adherens junction (PID)	4.14E-02	8.07E-02		
Endothelins (PID)	1.15E-03	5.37E-03		
EPHA2 forward signaling (PID)	2.07E-04	1.45E-03		
EPHA forward signaling (PID)	3.92E-05	4.07E-04		
Ephrin B reverse signaling (PID)	4.80E-02	8.97E-02		
EPO signaling pathway (PID)	7.93E-06	1.12E-04		
Regulation of nuclear estrogen receptor alpha (PID)	2.92E-02	6.17E-02	5.55E-03	4.56E-02
EGF receptor (ErbB1) signaling pathway (PID)	1.93E-03	7.89E-03		
ErbB4 signaling events (PID)	3.77E-06	8.89E-05	4.91E-03	4.47E-02
ErbB receptor signaling network (PID)	2.85E-03	1.01E-02		
EGFR-dependent Endothelin signaling events (PID)	2.44E-02	5.32E-02		
Signaling events mediated by focal adhesion kinase (PID)	1.80E-04	1.34E-03		
FAS (CD95) signaling pathway (PID)	8.37E-05	8.11E-04		
Fc-epsilon receptor I signaling in mast cells (PID)	2.73E-02	5.87E-02	1.32E-02	6.69E-02
Glypican 1 network (PID)	6.74E-04	3.66E-03		
Glypican 3 network (PID)	5.37E-02	9.77E-02	1.52E-02	7.12E-02
Signaling events mediated by HDAC Class III (PID)	1.84E-02	4.25E-02		
Hedgehog signaling events mediated by Gli proteins (PID)	1.01E-02	2.59E-02		
HIV-1 Nef: Negative effector of Fas and TNF-alpha (PID)	4.66E-06	8.89E-05	7.11E-04	1.27E-02
FOXA1 transcription factor network (PID)	4.06E-03	1.30E-02		
IL12 signaling mediated by STAT4 (PID)	6.22E-04	3.49E-03		
IL2-mediated signaling events (PID)	1.08E-03	5.17E-03		
IL2 signaling events mediated by PI3K (PID)	1.07E-03	5.13E-03		
IL2 signaling events mediated by STAT5 (PID)	8.26E-03	2.26E-02		
IL4-mediated signaling events (PID)	4.36E-03	1.39E-02		
IL5-mediated signaling events (PID)	9.95E-03	2.57E-02		
IL6-mediated signaling events (PID)	4.42E-03	1.39E-02		
Insulin-mediated glucose transport (PID)	6.12E-06	9.78E-05	2.32E-02	9.33E-02
AlphaE beta7 integrin cell surface interactions (PID)	3.99E-04	2.45E-03	1.34E-03	1.98E-02
Signaling events mediated by Stem cell factor receptor (c-Kit) (PID)	1.41E-02	3.44E-02		
LKB1 signaling events (PID)	1.44E-04	1.15E-03		
LPA receptor mediated events (PID)	1.80E-05	2.17E-04		
Trk receptor signaling mediated by the MAPK pathway (PID)	9.89E-03	2.56E-02		
N-cadherin signaling events (PID)	3.16E-02	6.56E-02		
Nephrin/Neph1 signaling in the kidney podocyte (PID)	9.39E-03	2.46E-02		
Netrin-mediated signaling events (PID)	1.59E-03	6.87E-03		
Atypical NF-kappaB pathway (PID)	4.18E-02	8.08E-02		
Canonical NF-kappaB pathway (PID)	8.15E-03	2.25E-02		
p38 MAPK signaling pathway (PID)	1.10E-04	9.94E-04		
Direct p53 effectors (PID)	1.79E-06	6.62E-05		
PDGFR-alpha signaling pathway (PID)	4.14E-02	8.07E-02		
PDGFR-beta signaling pathway (PID)	1.87E-05	2.21E-04		
Class I PI3K signaling events mediated by Akt (PID)	1.74E-02	4.05E-02	2.01E-03	2.47E-02
Class I PI3K signaling events (PID)	2.29E-04	1.56E-03		
Trk receptor signaling mediated by PI3K and PLC-gamma (PID)	5.93E-06	9.74E-05		
Presenilin action in Notch and Wnt signaling (PID)	4.32E-02	8.25E-02	2.26E-02	9.22E-02
RAC1 signaling pathway (PID)	7.01E-03	2.01E-02		
Regulation of RAC1 activity (PID)	5.36E-03	1.61E-02		
Retinoic acid receptors-mediated signaling (PID)	9.31E-07	4.58E-05		
S1P4 pathway (PID)	2.05E-05	2.37E-04		
S1P5 pathway (PID)	8.26E-03	2.26E-02		
Regulation of nuclear SMAD2/3 signaling (PID)	5.14E-03	1.57E-02		
Syndecan-4-mediated signaling events (PID)	1.41E-02	3.44E-02		
Proteoglycan syndecan-mediated signaling events (PID)	8.81E-03	2.37E-02		
TCR signaling in naive CD4+ T cells (PID)	6.73E-03	1.95E-02		
JNK signaling in the CD4+ TCR pathway (PID)	4.95E-04	2.87E-03		
Neurotrophic factor-mediated Trk receptor signaling (PID)	2.75E-03	1.01E-02		
Signaling events mediated by VEGFR1 and VEGFR2 (PID)	1.25E-04	1.05E-03		
VEGFR1 specific signals (PID)	1.76E-05	2.17E-04		

Supplementary Table 7 - **List of pathways that are more deregulated in MSI-high than in MSS in the Sheffer et al. dataset**. Additionally, for those pathways that are significantly differentially deregulated in Sveen the p-value of the significance is listed

	Sheffer et al.		Sveen et al.	
Pathway	p-value	FDR	p-value	FDR
Attenuation of GPCR Signaling (BIOCARTA)	2.96E-03	1.04E-02		
Agrin in Postsynaptic Differentiation (BIOCARTA)	1.20E-04	1.03E-03		
Rho-Selective Guanine Exchange Factor AKAP13 Mediates Stress Fiber Formation (BIOCARTA)	3.90E-03	1.26E-02	1.00E-02	5.91E-02
AKAP95 role in mitosis and chromosome dynamics (BIOCARTA)	2.13E-03	8.51E-03		
Protein Kinase A at the Centrosome (BIOCARTA)	3.07E-03	1.06E-02	1.83E-02	8.27E-02
CCR3 signaling in Eosinophils (BIOCARTA)	3.19E-02	6.57E-02	5.55E-03	4.56E-02
Role of PI3K subunit p85 in regulation of Actin Organization and Cell Migration (BIOCARTA)	2.63E-03	9.79E-03		
Cystic Fibrosis Transmembrane Conductance Regulator And Beta 2 Adrenergic Receptor Pathway (BIOCARTA)	4.83E-04	2.85E-03	2.26E-02	9.22E-02
Regulation And Function Of ChREBP in Liver (BIOCARTA)	3.30E-05	3.55E-04		
Regulation of ck1/cdk5 by type 1 glutamate receptors (BIOCARTA)	3.02E-03	1.06E-02		
Transcription factor CREB and its extracellular signals (BIOCARTA)	1.59E-03	6.87E-03		
Cytokine Network (BIOCARTA)	1.60E-04	1.25E-03		
Dendritic cells in regulating TH1 and TH2 Development (BIOCARTA)	9.01E-05	8.59E-04		
Repression of Pain Sensation by the Transcriptional Regulator DREAM (BIOCARTA)	3.74E-03	1.22E-02		
fMLP induced chemokine gene expression in HMC-1 cells (BIOCARTA)	2.86E-02	6.05E-02		
Free Radical Induced Apoptosis (BIOCARTA)	7.67E-04	3.97E-03	1.14E-04	3.74E-03
GATA3 participate in activating the Th2 cytokine genes expression (BIOCARTA)	2.81E-03	1.01E-02		
Signaling Pathway from G-Protein Families (BIOCARTA)	2.23E-03	8.66E-03		
Inactivation of Gsk3 by AKT causes accumulation of b-catenin in Alveolar Macrophages (BIOCARTA)	1.20E-07	2.36E-05		
Multiple antiapoptotic pathways from IGF-1R signaling lead to BAD phosphorylation (BIOCARTA)	4.42E-03	1.39E-02		
IL 3 signaling pathway (BIOCARTA)	3.39E-02	6.82E-02		
Cytokines and Inflammatory Response (BIOCARTA)	2.83E-03	1.01E-02	1.00E-02	5.91E-02
Adhesion and Diapedesis of Lymphocytes (BIOCARTA)	2.15E-02	4.79E-02		
mCalpain and friends in Cell motility (BIOCARTA)	1.88E-03	7.82E-03		
CDK Regulation of DNA Replication (BIOCARTA)	3.82E-04	2.38E-03		
Monocyte and its Surface Molecules (BIOCARTA)	4.16E-02	8.07E-02		
How Progesterone Initiates Oocyte Membrane (BIOCARTA)	4.51E-03	1.40E-02		
mTOR Signaling Pathway (BIOCARTA)	5.02E-02	9.22E-02		
Biosynthesis of neurotransmitters (BIOCARTA)	1.46E-03	6.51E-03		
NFAT and Hypertrophy of the heart (Transcription in the broken heart) (BIOCARTA)	2.23E-03	8.66E-03		
Nerve growth factor pathway (NGF) (BIOCARTA)	4.95E-02	9.16E-02		
Ras-Independent pathway in NK cell-mediated cytotoxicity (BIOCARTA)	6.26E-03	1.83E-02		
Selective expression of chemokine receptors during T-cell polarization (BIOCARTA)	4.41E-02	8.38E-02		
Actions of Nitric Oxide in the Heart (BIOCARTA)	3.26E-02	6.65E-02		
Nitric Oxide Signaling Pathway (BIOCARTA)	3.27E-03	1.11E-02		
NFkB activation by Nontypeable Hemophilus influenzae (BIOCARTA)	2.12E-02	4.75E-02		
Regulation of p27 Phosphorylation during Cell Cycle Progression (BIOCARTA)	2.10E-02	4.75E-02		
Multi-step Regulation of Transcription by Pitx2 (BIOCARTA)	2.64E-02	5.72E-02		
Phospholipase C-epsilon pathway (BIOCARTA)	3.25E-03	1.11E-02		
Mechanism of Gene Regulation by Peroxisome Proliferators via PPARa(alpha) (BIOCARTA)	9.10E-03	2.40E-02	1.18E-02	6.42E-02
The SARS-coronavirus Life Cycle (BIOCARTA)	2.03E-04	1.45E-03		
Sonic Hedgehog (Shh) Pathway (BIOCARTA)	1.89E-03	7.82E-03		
E2F1 Destruction Pathway (BIOCARTA)	2.10E-02	4.75E-02		
TGF beta signaling pathway (BIOCARTA)	1.33E-02	3.29E-02		
TPO Signaling Pathway (BIOCARTA)	3.70E-02	7.34E-02		
ABC transporters (KEGG)	4.59E-04	2.77E-03		
Alanine, aspartate and glutamate metabolism (KEGG)	5.00E-03	1.53E-02	8.81E-04	1.49E-02
Arachidonic acid metabolism (KEGG)	4.19E-06	8.89E-05		
Base excision repair (KEGG)	7.15E-03	2.03E-02		
Bladder cancer (KEGG)	3.04E-02	6.37E-02		
Cell cycle (KEGG)	1.35E-02	3.33E-02		
Chemokine signaling pathway (KEGG)	2.14E-04	1.47E-03	2.45E-03	2.78E-02
Cytokine-cytokine receptor interaction (KEGG)	1.19E-03	5.45E-03		
DNA replication (KEGG)	4.59E-04	2.77E-03		
Gap junction (KEGG)	3.95E-07	3.34E-05		
Glycosaminoglycan biosynthesis - keratan sulfate (KEGG)	2.73E-03	1.01E-02		
GnRH signaling pathway (KEGG)	1.47E-05	1.94E-04		
Homologous recombination (KEGG)	4.77E-03	1.47E-02		
Insulin signaling pathway (KEGG)	4.33E-06	8.89E-05		
Long-term depression (KEGG)	3.04E-02	6.37E-02		
Mismatch repair (KEGG)	9.50E-04	4.72E-03	1.61E-05	1.90E-03
Nitrogen metabolism (KEGG)	1.95E-03	7.89E-03		
Nucleotide excision repair (KEGG)	6.69E-03	1.95E-02		
Olfactory transduction (KEGG)	3.26E-02	6.65E-02		
One carbon pool by folate (KEGG)	2.34E-08	1.38E-05		

Oocyte meiosis (KEGG)	7.15E-03	2.03E-02	9.44E-03	5.81E-02
PPAR signaling pathway (KEGG)	6.86E-07	4.05E-05	2.04E-02	8.73E-02
Progesterone-mediated oocyte maturation (KEGG)	6.02E-04	3.42E-03	1.40E-02	6.78E-02
Proximal tubule bicarbonate reclamation (KEGG)	4.85E-02	9.01E-02		
Purine metabolism (KEGG)	7.58E-03	2.13E-02		
RIG-I-like receptor signaling pathway (KEGG)	2.75E-02	5.88E-02		
Taste transduction (KEGG)	4.91E-04	2.87E-03	2.09E-02	8.83E-02
Taurine and hypotaurine metabolism (KEGG)	3.48E-03	1.16E-02		
TGF-beta signaling pathway (KEGG)	3.29E-03	1.11E-02		
Toll-like receptor signaling pathway (KEGG)	2.52E-04	1.67E-03		
Vascular smooth muscle contraction (KEGG)	3.34E-02	6.73E-02		
Vasopressin-regulated water reabsorption (KEGG)	1.63E-03	6.98E-03		
Vibrio cholerae infection (KEGG)	3.09E-03	1.06E-02	1.25E-02	6.44E-02
a4b7 Integrin signaling (PID)	8.87E-03	2.37E-02		
ALK1 signaling events (PID)	2.03E-04	1.45E-03		
ATM pathway (PID)	2.79E-02	5.96E-02		
ATR signaling pathway (PID)	2.29E-03	8.86E-03		
Aurora B signaling (PID)	6.13E-03	1.80E-02		
Regulation of nuclear beta catenin signaling and target gene transcription (PID)	3.18E-02	6.56E-02		
CDC42 signaling events (PID)	3.11E-02	6.49E-02		
CXCR3-mediated signaling events (PID)	7.99E-03	2.24E-02		
ErbB1 downstream signaling (PID)	9.03E-03	2.40E-02	1.70E-03	2.28E-02
Fanconi anemia pathway (PID)	2.61E-02	5.67E-02		
FGF signaling pathway (PID)	7.79E-04	4.00E-03		
FOXM1 transcription factor network (PID)	2.11E-02	4.75E-02	2.04E-02	8.73E-02
FoxO family signaling (PID)	1.76E-03	7.36E-03		
GMCSF-mediated signaling events (PID)	8.64E-04	4.40E-03	8.91E-03	5.66E-02
Signaling events mediated by HDAC Class II (PID)	3.82E-04	2.38E-03		
Signaling events mediated by the Hedgehog family (PID)	4.21E-02	8.10E-02		
IFN-gamma pathway (PID)	2.36E-02	5.17E-02		
IL1-mediated signaling events (PID)	1.07E-03	5.13E-03		
IL27-mediated signaling events (PID)	1.00E-05	1.38E-04	1.12E-02	6.24E-02
IL8- and CXCR1-mediated signaling events (PID)	7.39E-03	2.09E-02	6.85E-03	4.90E-02
Insulin Pathway (PID)	3.56E-03	1.17E-02		
Alpha4 beta1 integrin signaling events (PID)	2.72E-02	5.86E-02	1.25E-03	1.89E-02
mTOR signaling pathway (PID)	2.45E-06	7.63E-05		
C-MYC pathway (PID)	1.02E-02	2.60E-02		
Validated targets of C-MYC transcriptional repression (PID)	8.15E-03	2.25E-02	1.12E-02	6.24E-02
Calcineurin-regulated NFAT-dependent transcription in lymphocytes (PID)	7.01E-03	2.01E-02	3.15E-04	7.17E-03
p73 transcription factor network (PID)	1.80E-02	4.19E-02		
p75(NTR)-mediated signaling (PID)	8.75E-03	2.36E-02		
PDGF receptor signaling network (PID)	2.12E-02	4.75E-02		
PLK1 signaling events (PID)	1.17E-02	2.91E-02		
PLK3 signaling events (PID)	1.60E-02	3.80E-02		
Polo-like kinase signaling events in the cell cycle (PID)	1.98E-03	7.96E-03	6.26E-03	4.68E-02
Signaling events mediated by PRL (PID)	1.26E-03	5.71E-03		
Regulation of retinoblastoma protein (PID)	5.10E-02	9.31E-02		
Glucocorticoid receptor regulatory network (PID)	2.00E-04	1.45E-03	1.53E-03	2.16E-02
Signaling events regulated by Ret tyrosine kinase (PID)	4.85E-02	9.01E-02	7.05E-03	4.90E-02
Regulation of RhoA activity (PID)	1.91E-04	1.41E-03	2.30E-05	1.94E-03
RXR and RAR heterodimerization with other nuclear receptor (PID)	1.29E-06	5.85E-05	8.41E-03	5.40E-02
Syndecan-3-mediated signaling events (PID)	4.97E-02	9.16E-02	1.12E-02	6.24E-02
TGF-beta receptor signaling (PID)	1.73E-02	4.05E-02		
TRAIL signaling pathway (PID)	5.21E-05	5.31E-04	3.86E-05	2.53E-03
Canonical Wnt signaling pathway (PID)	5.10E-02	9.31E-02		