Supplementary material to 'Testing for differentially expressed genetic pathways with single-subject N-of-1 data in the presence of inter-gene correlation'

A. Grant Schissler

Interdisciplinary Program in Statistics,

Center for Biomedical Informatics and Biostatistics (CB2),

BIO5 Institute, and Dept. of Medicine

University of Arizona

grantschissler@email.arizona.edu

Walter W. Piegorsch

Interdisciplinary Program in Statistics

Center for Biomedical Informatics and Biostatistics (CB2),

BIO5 Institute, and Dept. of Mathematics

University of Arizona

piegorsch@math.arizona.edu

Yves A. Lussier

Interdisciplinary Program in Statistics,

Center for Biomedical Informatics and Biostatistics (CB2),

BIO5 Institute, and Dept. of Medicine

University of Arizona

yves@email.arizona.edu

This supplementary document provides supporting material for *Testing for differentially expressed genetic pathways with single-subject N-of-1 data in the presence of inter-gene correlation* by A.G. Schissler, et al., (the 'main document'). The various sections below address a variety of supplemental/supporting topics, and are not intended to flow naturally between each other. They are, however, presented in roughly the same order in which their counterpart topics appeared in the main document. As therein, we denote the number of genes within a pathway as G, the number of determined clusters per pathway as m, the pathway expressions grand mean as $\overline{\overline{D}}$, and the cluster-based statistic for testing differential expression within a pathway as T.

1 Selected Pathways for Simulation Study

The complete list of gene cluster assignments for the six selected pathways in the main paper's simulation study appears in Table S1. Fig. S1 follows with histograms for each of the six sets of $\binom{G}{2}$ correlations.

Table S1: Clustering solution for the pathways selected in the simulation study.

Gene set identifier (G)	Cluster label	Cluster size	Gene members
GO:0060350 (15)	1	7	*EVC, MEF2C, BMPR2, BMP4, CER1, HOXA11, DDR2*
GO:0060350 (15)	2	8	*DLX5, COL13A1, BMPR1B, NPPC, INPPL1, STC1, FGFR3, SOX9*
GO:0016925 (30)	1	5	*TRIM28, UBE2I, PIAS4, TRPM4, MUL1*
GO:0016925 (30)	2	7	*SENP2, PIAS2, EYA1, CAPN3, UBA2, SENP5, HDAC4*
GO:0016925 (30)	3	4	*SUMO2, SUMO3, SUMO1, EGR1*
GO:0016925 (30)	4	6	*TOPORS, PIAS1, PIAS3, SENP1, RANBP2, IFIH1*
GO:0016925 (30)	5	4	*RWDD3, BCL11A, RASD2, CTNNB1*

Continued on next page

Gene set identifier (G)	Cluster label	Cluster size	Gene members
GO:0016925 (30)	6	4	*CDKN2A, SAE1, PARK7, MAGEA2*
GO:0048565 (50)	1	11	*ITGA6, CCDC39, NPHP3, GLI3, KIT, NIPBL, AHI1, BBS7, GATA4, FGFR2, CHD8*
GO:0048565 (50)	2	15	*CCDC103, FOXL1, GLI2, COBL, RARB, PTK6, CCDC40, GATA5, SMO, TNF, EPHB3, STRA6, ITGB4, MIXL1, RET*
GO:0048565 (50)	3	9	*SALL1, FOXE1, TGFB2, DACT1, ID2, GATA6, ZIC3, SOX11, NKX2-6*
GO:0048565 (50)	4	15	*SFRP5, SIX2, PCSK5, FOXF1, RARRES2, TBX2, MEGF8, ED-NRB, TCF21, GLI1, PDGFRA, WNT11, PKD1, PKDCC, SOX17*
GO:0045185 (100)	1	5	*PKD1, TWF2, FAF1, SIRT2, ARL2*
GO:0045185 (100)	2	13	*ZNF207, SORL1, BICD1, MXI1, ANK3, TOPORS, ZNF268, DAG1, FLNB, BBS4, GOPC, TEX14, GCC2*
GO:0045185 (100)	3	7	*SEH1L, TWF1, PSMD10, YWHAB, CDC42, BUB3, GOLPH3*
GO:0045185 (100)	4	18	*SUN1, MORC3, LATS1, VPS13C, SYNE2, CLASP2, ANKRD13C, VPS13D, CLASP1, VPS13A, APC, PKD2, PCM1, SUPT7L, HOOK3, RB1, TAF3, G3BP2*
GO:0045185 (100)	5	9	*HSPA5, JUP, SPAG4, CD27, PDIA3, NFKBIE, EZR, RCC2, BCL3*
GO:0045185 (100)	6	17	*LTBP1, PDIA2, ARL2BP, SPTBN4, EPB41L3, CAV1, CER1, SYNE1, SCIN, TAF8, SUN3, MDFI, GSN, BICD2, TLN1, FLNA, SUN2*
GO:0045185 (100)	7	9	*NFKBIA, FBN1, NLRP12, SRGN, SUN5, TNFSF14, IL10, CD4, PML*
GO:0045185 (100)	8	10	*PEX14, NFKBIL1, BECN1, TRIP6, GPAA1, NBL1, AURKC, CCDC22, CREB3, OS9*
GO:0045185 (100)	9	12	*SGOL1, CCNB1, SPAG5, CENPE, ECT2, NEK2, AURKB, FBN2, RACGAP1, SHANK1, NDC80, CASC5*
GO:0002683 (200)	1	22	*DHX58, TGFB3, NFKBIL1, GAS2L1, MUL1, PRMT1, C1QBP, PCBP2, TARBP2, PAF1, APOA1, SERPINB4, SFTPD, FADD, RPS19, HIST1H4J, HOXA7, WDR61, ZFPM1, HIST2H4A, CIB1, RARA*
GO:0002683 (200)	2	20	*LILRB1, CD300A, MNDA, COL3A1, C4BPB, LST1, TNFAIP8L2, C1QC, LILRB3, MAFB, CR1, HMOX1, LILRB2, TGFB1, IL10, HLA-DRB1, ARRB2, LILRB4, THY1, TNF*
GO:0002683 (200)	3	11	*CCL21, INS, CCL2, CCL3, HIST1H4A, CD55, ZC3H12A, FOXJ1, PTGER4, IRF1, THBS1*
GO:0002683 (200)	4	27	*SLA2, NLRC5, MICB, FOXP3, SERPINB9, PTPN22, PTK2B, LPXN, BTN2A2, CTLA4, JAK3, LYN, INHBA, BPI, TNFAIP3, PTPRC, TLR9, LAX1, TIGIT, KLRK1, HLA-DRB5, HLA-DOA, SAMSN1, CCR2, MIXL1, HIST1H4F, HLA-DOB*
GO:0002683 (200)	5	11	*HIST1H4E, CARTPT, APOD, AMBP, HIST1H4H, ALOX15, HIST1H4I, GREM1, HIST1H4D, HIST1H4K, HIST1H4B*
GO:0002683 (200)	6	14	*BMP4, CDKN2A, IFI16, CXCL12, PDCD1LG2, LRRC17, SERP-ING1, TLR4, SLIT2, A2M, PF4, TNFSF4, TICAM2, LGALS3*
GO:0002683 (200)	7	27	*IFNB1, HES1, THOC1, TSPAN6, MEIS2, BCL10, XCL1, SFRP1, PTPN2, PRNP, TGFB2, F2RL1, TRAF3IP1, PLCB1, CDK6, SOX9, LTF, SUSD4, SOX11, SOCS5, C4BPA, MYC, TRIM27, GLMN, CCL28, RUNX1, N4BP2L2*
GO:0002683 (200)	8	10	*MASP1, CD274, NR1D1, DNAJA3, PHPT1, PPM1B, DUSP3, PADI2, APCS, IL31RA*
GO:0002683 (200)	9	12	*C5, FER, EIF2AK2, HIST1H4L, ATM, LGR4, TLR3, MEIS1, ITCH, RC3H1, WASL, CDC73*
GO:0002683 (200)	10	14	*NOTCH1, NR1H3, APOA2, IFNA2, HOXB8, FSTL3, PPARG, PRDM16, CEBPB, TYRO3, ZBTB16, TNFRSF21, IRAK3, ADIPOQ*
GO:0002683 (200)	11	14	*HLA-G, IHH, HES5, CALCA, HIST1H4C, HLA-E, NBL1, NR1H2, HLA-A, CCL25, IFIT1, BST2, HLA-B, TAPBPL*
GO:0002683 (200)	12	18	*GPR55, MICA, PTPRJ, HOXA5, ZNF675, CTR9, TRAFD1, HOXA9, HIST4H4, BMP5, IL4, DAB2IP, GLI3, INHA, SPINK5, LEO1, ZC3H8, LDB1*
GO:0002520 (400)	1	40	*CEBPG, SNX10, TEK, MECOM, NOTCH1, ARNT, TAL1, JAG1, TGFBR3, PPP2R3C, CSF1, SNRK, RIPK1, HIPK2, SP7, PIR, MEOX1, TGFBR2, SBDS, SCIN, TLR4, NOTCH4, ITGB1, TCF21, THPO, PTGER4, CD34, ANXA2, PRDM16, PDE2A, MAPK14, HOXB4, FSTL3, BMP4, ANXA1, ETS1, KDR, HDAC9, TPO, CDKN2B*
GO:0002520 (400)	2	10	*DHRS2, RET, HIST1H4B, G6PD, FLT3, HIST1H4I, HIST1H4E, HIST1H4D, CTNNBIP1, HIST1H4H*

| Gene set identifier (*G*)	Cluster label	Cluster size	Gene members
GO:0002520 (400)	3	3	*IFNA14, CARTPT, FSHR*
GO:0002520 (400)	4	24	*LEF1, N4BP2L2, MSH2, ZC3H8, RUNX1, MSH6, FOXO3, SFRP1, PAXIP1, THOC1, KIT, FGFR2, TNFRSF11A, PTPN2, MYC, ADAM17, PCID2, F2RL1, PRKX, SOX4, TPD52, FOXC1, CTR9, ZNF675*
GO:0002520 (400)	5	19	*PMS2, LDB1, MYB, TIRAP, EPHB3, IL4, INHA, IFNA5, IL23R, ACIN1, RUNX3, ACVR1B, SUPT6H, FARP2, GLI3, IFNA16, RORC, NBEAL2, HIST4H4*
GO:0002520 (400)	6	4	*AHSP, ALAS2, CLC, PF4*
GO:0002520 (400)	7	19	*HIPK1, LIG4, EIF2AK2, TLR3, CDC73, CD46, JAK2, RAG1, BMI1, ZNF160, RNF168, FNIP1, MSH3, NOTCH2, RC3H1, TRAF6, CD164, KLF6, HIST1H4A*
GO:0002520 (400)	8	5	*HSPA1B, HSPA1A, HIST1H4C, HIST1H4L, IFNA6*
GO:0002520 (400)	9	11	*MLH1, MLF1, SIX1, HDAC4, PITX2, RORA, EFNA2, ARIH2, MEF2C, RNF8, GLO1*
GO:0002520 (400)	10	11	*GLRX5, VPS33A, BGLAP, TBX1, JAGN1, TAZ, HAX1, MKNK2, ATPIF1, SOD1, NKAP*
GO:0002520 (400)	11	15	*CD1D, HLA-B, IRF1, IFNA7, IFI16, BATF2, CBFA2T3, TNF, CD74, CCL19, IL27, VCAM1, IFNW1, SFRP2, PLCG2*
GO:0002520 (400)	12	5	*IFNA8, IFNA2, SHH, FOXJ1, IL31RA*
GO:0002520 (400)	13	20	*IKZF1, PTK2B, ADAM8, CAMK4, MIXL1, LYN, IL23A, BLNK, IFNG, THEMIS, CD3D, LCK, ZAP70, ITK, CD2, PTPN22, IL2, CD27, PIK3CD, UBD*
GO:0002520 (400)	14	10	*RARA, EXOSC6, IL3, EPHA2, IL11, FST, LIF, PNP, CLCF1, DYRK3*
GO:0002520 (400)	15	14	*GAS6, GAS2L1, FADD, HDAC5, IRF7, PRELID1, CTNNBL1, ZFPM1, IHH, SART1, DLL1, MYH9, PAF1, ANKRD54*
GO:0002520 (400)	16	9	*FOXE1, NKX2-5, KLF1, WDR61, TNFSF11, BATF, HIST1H4J, CLPTM1, CIB1*
GO:0002520 (400)	17	19	*MTOR, ATP7A, FLVCR1, FUT10, ZBTB1, FLCN, CHD7, CDK13, CDK6, NCOA6, OGT, TET2, PURB, IFNA17, MED1, VPRBP, ATM, ACVR2A, SPINK5*
GO:0002520 (400)	18	18	*VEGFA, PRDX3, CEBPB, ADIPOQ, GAB2, HOXB8, ASH2L, NHEJ1, ZBTB16, CEBPA, CITED2, PGM3, FGF10, RRAS, PPARG, PDE1B, LRP5, IRAK3*
GO:0002520 (400)	19	14	*RIPK3, ZNF385A, HHEX, CALCA, HES5, BATF3, HLA-G, GATA2, HAND2, FLT3LG, FES, TGFB1, LYL1, CDKN2A*
GO:0002520 (400)	20	27	*HES1, CASP9, RPS19, IFNE, GATA3, LEO1, IL34, EFNA4, IFNA13, PRMT1, TNFSF13, LRRC8A, EXOSC3, ZNF16, PDCD2, TCF3, PRTN3, TESC, PRKCZ, GPR55, XBP1, JAG2, ATP6AP1, MT1G, LTF, RHOH, SRC*
GO:0002520 (400)	21	26	*LILRB1, NFAM1, CD4, IL10, IL12RB1, SYK, CSF1R, CCR1, PLEK, TREM2, VNN1, LILRB2, CD28, GPR183, C1QC, IFNA10, BTK, LILRB3, HCLS1, SPI1, MMP9, MAFB, NCKAP1L, RAS-GRP4, CD86, LILRB4*
GO:0002520 (400)	22	12	*ACE, GATA1, TNFSF9, GLI2, AXL, IFNK, TNFSF4, KIRREL3, LRRC17, WNT10B, MFAP5, WNT2B*
GO:0002520 (400)	23	10	*HOXA9, THOC5, HMGB2, POLL, HIST2H4A, SLC25A38, HSPD1, HOXA7, HOXA5, RPS14*
GO:0002520 (400)	24	4	*RSAD2, CSF2, IFNA4, HIST1H4K*
GO:0002520 (400)	25	17	*RUNX2, IL7, MEIS1, FOXP1, PRKCA, TGFB2, CDC42, IFNB1, ZFP36L2, WNT5A, TGFBR1, MEIS2, HIST1H4F, HMGB1, KITLG, HIF1A, SOCS5*
GO:0002520 (400)	26	5	*SH3PXD2A, CASP3, ITGA4, MELK, POLQ*
GO:0002520 (400)	27	24	*JAK3, CD40LG, IFNA21, FOXP3, IL12B, AICDA, TXK, CD79A, EOMES, INHBA, RAG2, TNFAIP3, CASP8, IFNA1, PARP1, PT-PRC, IRF4, CTLA4, APCS, CR2, IKZF3, BLK, CD80, CCR7*
GO:0002520 (400)	28	5	*IL17A, KLF4, CCL3, CSF3, IL6*
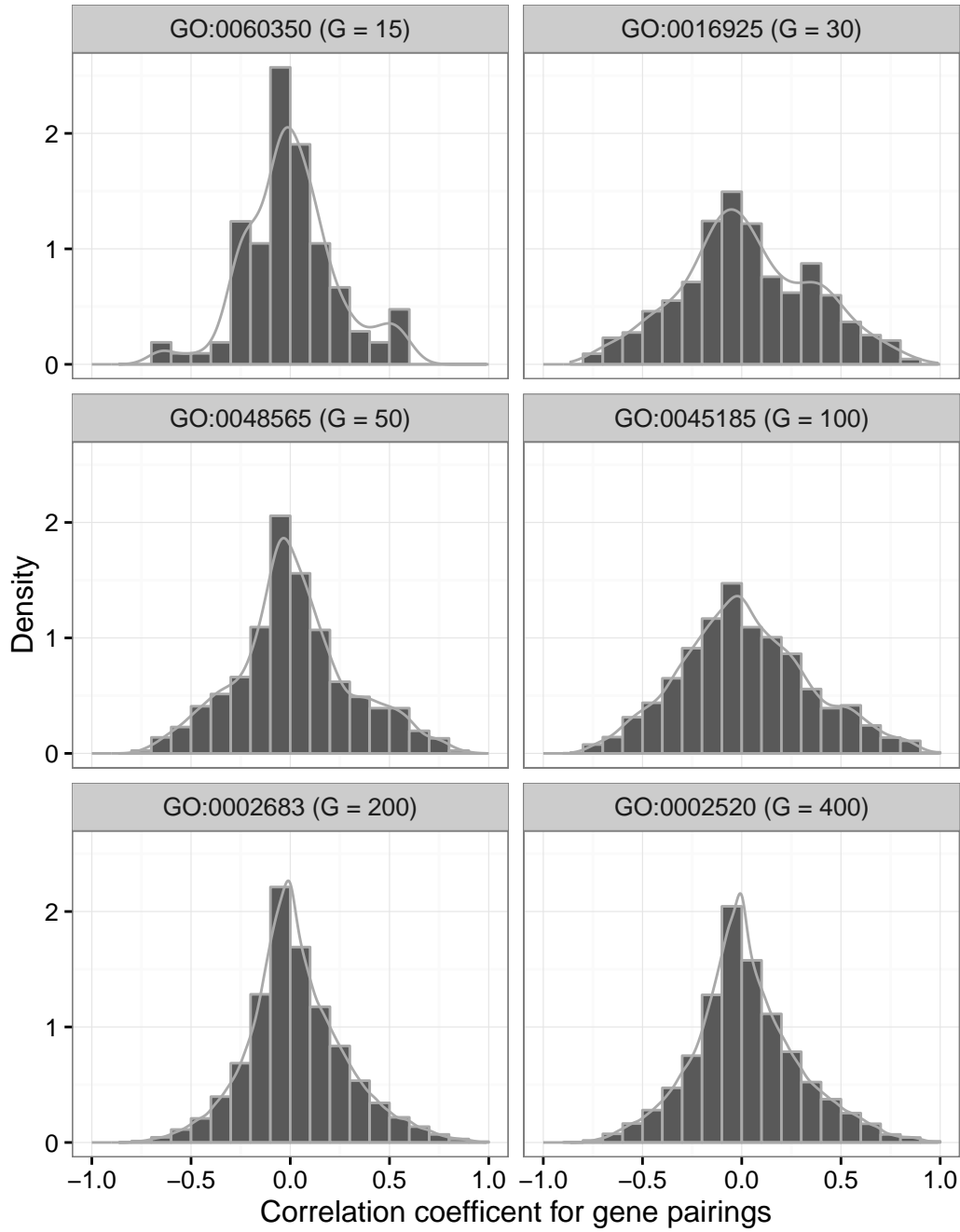
Figure S1: Histograms and overlaid kernel density estimates (gray curves) for each set of $\binom{G}{2}$ correlations associated with the six selected pathways in the simulation. See the main document for details. (Histogram bin widths created manually with uniform breakpoints from -1 to 1.)

2 Rejection Rates from Simulation Study

Table S2 reports the specific numerical rejection rates from the main paper's false-positive simulations with the cluster-based T-statistic, the naïve t-test, and the Wilcoxon signed-rank test. Similarly, Table S3 reports the specific numerical rejection rates from the main paper's power simulations with the cluster-based T-statistic. Recall that 2000 simulated data sets were generated at each parameter configuration. Thus the approximate standard error of the empirical Monte Carlo rejection rates at the nominal 5% level is $\sqrt{(0.05)(0.95)/2000} = 0.005$ and it never exceeds $\sqrt{(0.5)(0.5)/2000} = 0.011$.

Table S2: Empirical false-positive rates (dots) based on 2000 simulated N-of-1-*pathways* data sets for three competing testing procedures (Clust-T = proposed test, t = standard t test, Wil. = Wilcoxon signed-rank test), cross-classified by correlation structure (top: Independent = uncorrelated mRNA expression, Block = cluster-correlated expression, All = unconstrained inter-gene correlation) and pathway size G (left). Fold-change parameter is ψ (see main document; results at $\psi = 1.5$ correspond to Figure 1). Nominal significance level is set to $\alpha = 0.05$.

	Independent			Block			All		
G	Clust-T	t	Wil.	Clust-T	t	Wil.	Clust-T	t	Wil.
					$\psi = 4$				
15	0.059	0.048	0.046	0.046	0.13	0.13	0.034	0.04	0.05
30	0.029	0.032	0.044	0.042	0.17	0.22	0.013	0.07	0.13
50	0.042	0.046	0.045	0.036	0.34	0.35	0.012	0.10	0.11
100	0.041	0.051	0.057	0.032	0.42	0.43	0.003	0.34	0.27
200	0.041	0.040	0.040	0.031	0.44	0.48	0.009	0.46	0.52
400	0.050	0.049	0.045	0.045	0.49	0.52	0.067	0.60	0.63
					$\psi = 2$				
15	0.050	0.041	0.042	0.051	0.12	0.12	0.030	0.04	0.04
30	0.040	0.038	0.048	0.043	0.16	0.23	0.024	0.07	0.13
50	0.041	0.048	0.047	0.036	0.34	0.36	0.011	0.09	0.10
100	0.039	0.049	0.052	0.037	0.43	0.46	0.002	0.34	0.28
200	0.051	0.060	0.066	0.041	0.45	0.50	0.010	0.47	0.53
400	0.046	0.051	0.049	0.044	0.50	0.54	0.067	0.61	0.63
					$\psi = 1.5$				
15	0.057	0.043	0.043	0.049	0.13	0.13	0.039	0.04	0.04
30	0.033	0.029	0.051	0.033	0.17	0.24	0.013	0.06	0.12
50	0.038	0.047	0.051	0.031	0.34	0.35	0.008	0.10	0.11
100	0.036	0.043	0.052	0.032	0.42	0.42	0.004	0.35	0.28
200	0.050	0.051	0.045	0.044	0.44	0.45	0.009	0.43	0.50
400	0.051	0.050	0.044	0.039	0.52	0.55	0.059	0.62	0.63

Table S3: Empirical rejection probabilities ('power') for the cluster-based approach, based on 2000 simulated N-of-1-*pathways* data sets. Results are presented as a function of DEG proportion p. Displays are cross-classified by correlation structure (top: Independent = uncorrelated mRNA expression, Block = cluster-correlated expression, All = unconstrained inter-gene correlation) and pathway size G (left). Simulated fold change is labeled as: $\psi = 4$, $\psi = 2$, and $\psi = 1.5$. Nominal significance level is set to $\alpha = 0.05$.

	Independent			Block			All		
$(G,\ \psi)$	$p{=}0.3$	$p{=}0.6$	$p{=}0.9$	$p{=}0.3$	$p{=}0.6$	$p{=}0.9$	$p{=}0.3$	$p{=}0.6$	$p{=}0.9$
(15, 4)	0.05	0.11	0.18	0.06	0.10	0.14	0.04	0.09	0.11
(15, 2)	0.06	0.06	0.09	0.06	0.06	0.08	0.04	0.04	0.07
(15, 1.5)	0.05	0.05	0.06	0.04	0.05	0.05	0.03	0.04	0.05
(30, 4)	0.16	0.79	0.98	0.14	0.67	0.95	0.13	0.66	0.95
(30, 2)	0.17	0.54	0.82	0.12	0.38	0.65	0.11	0.38	0.63
(30, 1.5)	0.10	0.20	0.49	0.07	0.12	0.31	0.06	0.11	0.29

$(G,\ \psi)$	Independent			Block			All		
	$p=0.3$	$p=0.6$	$p=0.9$	$p=0.3$	$p=0.6$	$p=0.9$	$p=0.3$	$p=0.6$	$p=0.9$
(50, 4)	0.17	0.51	0.85	0.09	0.29	0.54	0.09	0.28	0.52
(50, 2)	0.12	0.35	0.53	0.06	0.15	0.20	0.03	0.11	0.18
(50, 1.5)	0.06	0.13	0.23	0.05	0.06	0.09	0.02	0.04	0.07
(100, 4)	0.87	1.00	1.00	0.45	0.91	0.98	0.47	0.90	0.98
(100, 2)	0.44	0.91	0.99	0.17	0.48	0.70	0.15	0.49	0.70
(100, 1.5)	0.19	0.58	0.86	0.08	0.21	0.34	0.04	0.21	0.35
(200, 4)	0.88	1.00	1.00	0.40	0.91	0.99	0.45	0.91	0.98
(200, 2)	0.50	0.94	1.00	0.15	0.45	0.68	0.15	0.50	0.70
(200, 1.5)	0.22	0.54	0.87	0.06	0.17	0.30	0.04	0.16	0.34
(400, 4)	1.00	1.00	1.00	0.61	1.00	1.00	0.64	0.97	1.00
(400, 2)	0.82	1.00	1.00	0.23	0.67	0.89	0.34	0.69	0.84
(400, 1.5)	0.41	0.91	1.00	0.11	0.29	0.49	0.19	0.41	0.57

3 Differentially Expressed Pathways for Breast Cancer Example

Table S4 displays the 80 dysregulated pathways for patient TCGA-A7-A0CE identified by the cluster-based T-statistic after Benjamini-Hochberg (1995) false-discovery adjustment, ordered by original P-values. Assorted summary statistics are also included. False discovery rate (FDR) is set to less than 15%.

Table S4: The 80 differentially expressed pathways (DEPs) at FDR < 15% for TNBC patient TCGA-A7-A0CE, after application of the cluster-based test procedure. Selected summary statistics are also displayed; see main document for details.

Gene set identifier	Description	$\overline{\overline{D}}$	T-statistic	P-value	G	m
GO:0045785	positive regulation of cell adhesion	-0.75	-4.92	0.0001	226	19
GO:0032101	regulation of response to external stimulus	-0.47	-4.42	0.0001	458	28
GO:0070124	mitochondrial translational initiation	0.28	7.55	0.0003	84	7
GO:0010769	regulation of cell morphogenesis involved in differentiation	-0.51	-4.80	0.0003	168	15
GO:0030155	regulation of cell adhesion	-0.51	-4.24	0.0004	384	22
GO:1902532	negative regulation of intracellular signal transduction	-0.42	-4.37	0.0004	283	18
GO:0009306	protein secretion	-0.65	-4.68	0.0004	272	14
GO:0034142	toll-like receptor 4 signaling pathway	-0.33	-5.35	0.0005	105	10
GO:0051223	regulation of protein transport	-0.56	-3.94	0.0005	452	30
GO:0051092	positive regulation of NF-kappaB transcription factor activity	-0.54	-5.06	0.0005	111	11
GO:0006805	xenobiotic metabolic process	-1.13	-4.77	0.0006	163	12
GO:1901615	organic hydroxy compound metabolic process	-0.65	-4.19	0.0007	367	17
GO:0043408	regulation of MAPK cascade	-0.49	-3.90	0.0008	438	23
GO:0009582	detection of abiotic stimulus	-0.42	-4.33	0.0008	132	14
GO:0070125	mitochondrial translational elongation	0.28	5.58	0.0008	84	8
GO:0071466	cellular response to xenobiotic stimulus	-1.12	-4.55	0.0008	164	12
GO:1903530	regulation of secretion by cell	-0.60	-3.74	0.0009	366	28
GO:0046660	female sex differentiation	-0.25	-13.15	0.0010	29	4
GO:0032368	regulation of lipid transport	-0.48	-6.89	0.0010	62	6
GO:0051145	smooth muscle cell differentiation	-0.64	-28.55	0.0012	18	3
GO:0051222	positive regulation of protein transport	-0.64	-4.02	0.0013	255	15
GO:0034109	homotypic cell-cell adhesion	-0.54	-3.88	0.0013	307	17
GO:0050708	regulation of protein secretion	-0.73	-3.98	0.0014	221	15

Gene set identifier	Description	$\overline{\overline{D}}$	T-statistic	P-value	G	m
GO:0006887	exocytosis	-0.56	-3.98	0.0014	268	15
GO:0044089	positive regulation of cellular component biogenesis	-0.48	-3.82	0.0014	217	18
GO:0007249	I-kappaB kinase/NF-kappaB signaling	-0.39	-4.05	0.0014	209	14
GO:0022407	regulation of cell-cell adhesion	-0.52	-4.03	0.0014	237	14
GO:0007131	reciprocal meiotic recombination	0.55	436.10	0.0015	26	2
GO:0035825	reciprocal DNA recombination	0.55	436.10	0.0015	26	2
GO:0007015	actin filament organization	-0.47	-3.79	0.0015	205	18
GO:0006066	alcohol metabolic process	-0.57	-3.77	0.0015	278	18
GO:0016337	single organismal cell-cell adhesion	-0.49	-3.73	0.0015	450	19
GO:0098771	inorganic ion homeostasis	-0.47	-3.53	0.0016	361	27
GO:0009725	response to hormone	-0.54	-3.44	0.0016	456	34
GO:0006369	termination of RNA polymerase II transcription	0.40	7.60	0.0016	37	5
GO:0032543	mitochondrial translation	0.35	4.96	0.0016	103	8
GO:0009410	response to xenobiotic stimulus	-1.11	-4.13	0.0017	165	12
GO:0051270	regulation of cellular component movement	-0.44	-3.45	0.0017	474	31
GO:0010517	regulation of phospholipase activity	-0.88	-4.21	0.0018	85	11
GO:0050996	positive regulation of lipid catabolic process	-1.37	-351.66	0.0018	18	2
GO:0043409	negative regulation of MAPK cascade	-0.50	-4.55	0.0019	93	9
GO:0098543	detection of other organism	-0.69	-23.07	0.0019	17	3
GO:0043123	positive regulation of I-kappaB kinase/NF-kappaB signaling	-0.34	-3.87	0.0019	155	14
GO:0098660	inorganic ion transmembrane transport	-0.52	-3.44	0.0020	425	27
GO:0055080	cation homeostasis	-0.45	-3.42	0.0021	353	27
GO:0051271	negative regulation of cellular component movement	-0.57	-4.26	0.0021	143	10
GO:0007610	behavior	-0.65	-3.51	0.0022	256	21
GO:0050848	regulation of calcium-mediated signaling	-0.81	-9.77	0.0023	28	4
GO:0040012	regulation of locomotion	-0.44	-3.32	0.0023	457	32
GO:0050801	ion homeostasis	-0.52	-3.52	0.0023	406	20
GO:1903034	regulation of response to wounding	-0.56	-3.48	0.0024	237	21
GO:0043122	regulation of I-kappaB kinase/NF-kappaB signaling	-0.41	-3.82	0.0024	192	13
GO:0043407	negative regulation of MAP kinase activity	-0.57	-6.79	0.0025	54	5
GO:0050778	positive regulation of immune response	-0.46	-3.48	0.0025	428	20
GO:0030336	negative regulation of cell migration	-0.54	-4.33	0.0025	133	9
GO:0006954	inflammatory response	-0.61	-3.43	0.0025	309	22
GO:0031349	positive regulation of defense response	-0.35	-3.57	0.0025	242	17
GO:0034440	lipid oxidation	-0.58	-6.65	0.0026	64	5
GO:0006418	tRNA aminoacylation for protein translation	0.61	4.92	0.0027	42	7
GO:0030278	regulation of ossification	-0.79	-3.96	0.0027	93	11
GO:0002764	immune response-regulating signaling pathway	-0.47	-3.36	0.0027	413	24
GO:0030168	platelet activation	-0.73	-3.83	0.0028	224	12
GO:0032273	positive regulation of protein polymerization	-0.52	-4.48	0.0029	64	8
GO:0043038	amino acid activation	0.63	4.84	0.0029	44	7
GO:0043039	tRNA aminoacylation	0.63	4.84	0.0029	44	7
GO:0022612	gland morphogenesis	-0.89	-8.98	0.0029	24	4
GO:0061180	mammary gland epithelium development	-0.67	-18.46	0.0029	24	3
GO:0090559	regulation of membrane permeability	0.20	6.46	0.0030	57	5
GO:0003071	renal system process involved in regulation of systemic arterial blood pressure	-0.98	-209.23	0.0030	15	2
GO:0051051	negative regulation of transport	-0.52	-3.53	0.0031	261	16
GO:0007009	plasma membrane organization	-0.45	-3.77	0.0031	179	12
GO:0045669	positive regulation of osteoblast differentiation	-0.84	-6.37	0.0031	31	5
GO:2000145	regulation of cell motility	-0.42	-3.19	0.0032	419	33
GO:0032602	chemokine production	-1.03	-6.33	0.0032	48	5
GO:0044708	single-organism behavior	-0.67	-3.97	0.0033	107	10

Table S4 – *Continued from previous page*

Gene set identifier	Description	$\overline{\overline{D}}$	T-statistic	P-value	G	m
GO:0086010	membrane depolarization during action potential	-1.26	-17.44	0.0033	42	3
GO:0050714	positive regulation of protein secretion	-0.88	-3.81	0.0034	102	11
GO:0051046	regulation of secretion	-0.64	-3.34	0.0034	396	20
GO:0055065	metal ion homeostasis	-0.42	-3.51	0.0034	323	15
GO:0042991	transcription factor import into nucleus	-0.44	-4.65	0.0035	64	7

References

Benjamini, Y. and Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society, Series B (Methodological)* **57**, 289–300.