

# Supplementary Materials: Detecting disease specific pathway substructures through an integrated systems biology approach

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## 1. Supplementary Tables

**Table S1.** Metrics computed for the subpathways disease-specificity assessment of the two datasets in our case study when microRNAs are removed. The table shows the number of substructures nodes, the number of significant nodes ( $p < 0.01$ ), the number of disease genes, the number of significant disease genes ( $p < 0.01$ ), the number of reachable pairs of disease genes within subpathways, the average distance between a disease gene and a substructure<sup>†</sup>, and the average distance between disease genes contained within each substructure<sup>‡</sup>. The results are compared with a reference computed directly on KEGG pathways.

Dataset	Algorithm	# Nodes		# Disease Genes		Reachable Pairs	†	‡
		$p < 0.01$	All	$p < 0.01$	All			
BRCA	KEGG Pathways	983	6688	30	104	156	-	3
	SPECifIC	247	247	15	15	2	1,83	2
	SubPathway-GM	101	214	9	14	6	2,64	3
	SubPathway-Gmir	135	682	4	8	1	2,76	2
	DESubs	34	34	0	0	0	1,71	-
COAD	KEGG Pathways	995	6688	11	81	88	-	3
	SPECifIC	139	139	9	9	2	1,97	2
	SubPathway-GM	59	173	3	8	4	2,19	3
	SubPathway-Gmir	131	221	4	7	9	2,96	2
	DESubs	6	6	0	0	0	2,4	-

**Table S2.** Enrichment computed on the subpathways extracted by SPECifIC on the two cancer types (BRCA and COAD) using terms coming from the DisGeNET [38,39] database. Only the significant terms ( $p < 0.01$ ) were kept.

COAD		BRCA	
Disease	Adjusted p-value	Disease	Adjusted p-value
Prostatic Neoplasms	0	Prostatic Neoplasms	0
Mammary Neoplasms	0	Mammary Neoplasms	0
Osteosarcoma	0	Osteosarcoma	0
Hepatitis C	0	Hepatitis C	0
Torsades de Pointes	0	Torsades de Pointes	0
Esophageal Neoplasms	0.0001	MICROPHTHALMIA. ISOLATED 8	0
Adenocarcinoma	0.0002	Prostatic Neoplasms. Castration-Resistant	0
Colorectal Neoplasms	0.0005	Neoplasms. Hormone-Dependent	$1.41 \times 10^{-08}$
Hypertensive disease	0.0005	Disorders of Sex Development	$7.05 \times 10^{-08}$
Lung Neoplasms	0.0005	Obesity	$3.38 \times 10^{-06}$
Liver carcinoma	0.0011	Substance-Related Disorders	0.0002
Reperfusion Injury	0.0012	Polycystic Ovary Syndrome	0.0002
		Hypertensive disease	0.0004
		Myocardial Infarction	0.0006
		Stomach Neoplasms	0.0010
		Diabetes Mellitus. Experimental	0.0011
		Colorectal Neoplasms	0.0022

**Table S3.** Results obtained by employing SPECifIC to extract and enrich COAD subpathways using KEGG pathway terms. The terms are sorted by means of p-value. We also reports if the other methods detect the same term as statistically significant ( $p < 0.01$ ). In italics we report the top-20 pathways used for the comparisons.

Pathway	SPECifIC	SubPathway-GM	SubPathway-GMir	DEsubs
<i>metabolism of xenobiotics by cytochrome p450</i>	0		Yes	
<i>steroid hormone biosynthesis</i>	0		Yes	
<i>drug metabolism cytochrome p450</i>	0			
<i>chemical carcinogenesis</i>	0			
<i>drug metabolism other enzymes</i>	0			
<i>linoleic acid metabolism</i>	0			
<i>longevity regulating pathway</i>	$3.27 \times 10^{-08}$			
<i>egfr tyrosine kinase inhibitor resistance</i>	$2.17 \times 10^{-07}$			
<i>endocrine resistance</i>	$2.35 \times 10^{-07}$			
<i>rap1 signaling pathway</i>	$5.32 \times 10^{-07}$			
<i>progesterone mediated oocyte maturation</i>	$5.39 \times 10^{-07}$			
<i>hif 1 signaling pathway</i>	$5.89 \times 10^{-07}$			
<i>melanogenesis</i>	$6.15 \times 10^{-07}$			Yes
<i>apoptosis</i>	$1.27 \times 10^{-06}$	Yes		Yes
<i>platinum drug resistance</i>	$1.27 \times 10^{-06}$			
<i>phospholipase d signaling pathway</i>	$1.30 \times 10^{-06}$			
<i>mtor signaling pathway</i>	$1.55 \times 10^{-06}$			
<i>ras signaling pathway</i>	$1.55 \times 10^{-06}$			
<i>thyroid hormone signaling pathway</i>	$3.13 \times 10^{-06}$			
<i>erbB signaling pathway</i>	$3.32 \times 10^{-06}$			Yes
<i>estrogen signaling pathway</i>	$3.97 \times 10^{-06}$			
<i>inflammatory mediator regulation of trp channels</i>	$4.85 \times 10^{-06}$			
<i>proteoglycans in cancer</i>	$5.00 \times 10^{-06}$			
<i>pathways in cancer</i>	$7.08 \times 10^{-06}$			
<i>platelet activation</i>	$9.18 \times 10^{-06}$			
<i>chemokine signaling pathway</i>	$1.42 \times 10^{-05}$	Yes		
<i>gnrh signaling pathway</i>	$1.50 \times 10^{-05}$			Yes
<i>oxytocin signaling pathway</i>	$1.61 \times 10^{-05}$			
<i>arachidonic acid metabolism</i>	$2.34 \times 10^{-05}$		Yes	
<i>pi3k akt signaling pathway</i>	0.0003			
<i>mapk signaling pathway</i>	0.0017	Yes		Yes
<i>insulin secretion</i>	0.5000			
<i>ovarian steroidogenesis</i>	0.5000			
<i>beta alanine metabolism</i>	0.5000			Yes
<i>long term depression</i>	0.5000			
<i>thyroid hormone synthesis</i>	0.5000			
<i>aldosterone synthesis and secretion</i>	0.5000			
<i>gap junction</i>	0.5000			
<i>vegf signaling pathway</i>	0.5000			Yes
<i>b cell receptor signaling pathway</i>	0.5000			Yes
<i>camp signaling pathway</i>	0.5000			
<i>glucagon signaling pathway</i>	0.5000			
<i>micromas in cancer</i>	0.5000			
<i>regulation of lipolysis in adipocytes</i>	0.5000			
<i>dopaminergic synapse</i>	0.5000			
<i>natural killer cell mediated cytotoxicity</i>	0.5000	Yes		Yes
<i>adrenergic signaling in cardiomyocytes</i>	0.5001			
<i>cgmp pkg signaling pathway</i>	0.5001			
<i>purine metabolism</i>	0.5005		Yes	
<i>fc epsilon ri signaling pathway</i>	1.0000			Yes
<i>cytokine cytokine receptor interaction</i>	1.0000			Yes
<i>inositol phosphate metabolism</i>	1.0000		Yes	Yes
<i>phosphatidylinositol signaling system</i>	1.0000			Yes
<i>leukocyte transendothelial migration</i>	1.0000			Yes
<i>focal adhesion</i>	1.0000	Yes		Yes
<i>toll like receptor signaling pathway</i>	1.0000			Yes
<i>jak stat signaling pathway</i>	1.0000			Yes
<i>regulation of actin cytoskeleton</i>	1.0000			Yes
<i>adipocytokine signaling pathway</i>	1.0000			Yes
<i>starch and sucrose metabolism</i>	1.0000	Yes	Yes	
<i>fatty acid degradation</i>	1.0000	Yes	Yes	
<i>pyrimidine metabolism</i>	1.0000		Yes	
<i>pentose and glucuronate interconversions</i>	1.0000	Yes	Yes	
<i>porphyrin and chlorophyll metabolism</i>	1.0000		Yes	

ascorbate and aldarate metabolism	1.0000		Yes
glutathione metabolism	1.0000	Yes	Yes
galactose metabolism	1.0000		Yes
glycerolipid metabolism	1.0000		Yes
tyrosine metabolism	1.0000	Yes	Yes
glycerophospholipid metabolism	1.0000		Yes
amino sugar and nucleotide sugar metabolism	1.0000	Yes	Yes
fructose and mannose metabolism	1.0000		Yes
citrate cycle tca cycle	1.0000		Yes
pentose phosphate pathway	1.0000		Yes
cysteine and methionine metabolism	1.0000		Yes
ether lipid metabolism	1.0000		Yes
phenylalanine metabolism	1.0000		Yes
arginine and proline metabolism	1.0000	Yes	Yes
pyruvate metabolism	1.0000	Yes	Yes
glycolysis gluconeogenesis	1.0000		Yes
ppar signaling pathway	1.0000	Yes	
tight junction	1.0000	Yes	
calcium signaling pathway	1.0000	Yes	
aldosterone regulated sodium reabsorption	1.0000	Yes	
wnt signaling pathway	1.0000	Yes	
alanine aspartate and glutamate metabolism	1.0000	Yes	
butanoate metabolism	1.0000	Yes	
oocyte meiosis	1.0000	Yes	
cell adhesion molecules cams	1.0000	Yes	
cell cycle	1.0000	Yes	
tgf beta signaling pathway	1.0000	Yes	
fc gamma r mediated phagocytosis	1.0000		
lysine degradation	1.0000		
olfactory transduction	1.0000		
long term potentiation	1.0000		
neurotrophin signaling pathway	1.0000		
nod like receptor signaling pathway	1.0000		
vascular smooth muscle contraction	1.0000		
phenylalanine tyrosine and tryptophan biosynthesis	1.0000		
axon guidance	1.0000		
salivary secretion	1.0000		
insulin signaling pathway	1.0000		
central carbon metabolism in cancer	1.0000		
ampk signaling pathway	1.0000		
sphingolipid signaling pathway	1.0000		
carbohydrate digestion and absorption	1.0000		
viral carcinogenesis	1.0000		
foxo signaling pathway	1.0000		
choline metabolism in cancer	1.0000		
p53 signaling pathway	1.0000		
mrna surveillance pathway	1.0000		
nf kappa b signaling pathway	1.0000		
protein processing in endoplasmic reticulum	1.0000		
apoptosis multiple species	1.0000		
hedgehog signaling pathway	1.0000		
transcriptional misregulation in cancer	1.0000		
circadian entrainment	1.0000		
retrograde endocannabinoid signaling	1.0000		
glutamatergic synapse	1.0000		
gabaergic synapse	1.0000		
renin secretion	1.0000		
gastric acid secretion	1.0000		
pancreatic secretion	1.0000		
abc transporters	1.0000		
dorso ventral axis formation	1.0000		
signaling pathways regulating pluripotency of stem cells	1.0000		
t cell receptor signaling pathway	1.0000		
prolactin signaling pathway	1.0000		
osteoclast differentiation	1.0000		
tnf signaling pathway	1.0000		
th17 cell differentiation	1.0000		
endocrine and other factor regulated calcium reabsorption	1.0000		
vasopressin regulated water reabsorption	1.0000		
autophagy	1.0000		
endocytosis	1.0000		
adherens junction	1.0000		
fatty acid metabolism	1.0000		
proximal tubule bicarbonate reclamation	1.0000		
neomycin kanamycin and gentamicin biosynthesis	1.0000		

carbon metabolism	1.0000
homologous recombination	1.0000
hippo signaling pathway	1.0000
cardiac muscle contraction	1.0000
other types of o glycan biosynthesis	1.0000
ecm receptor interaction	1.0000
protein digestion and absorption	1.0000
ubiquitin mediated proteolysis	1.0000
rna polymerase	1.0000
cytosolic dna sensing pathway	1.0000
neuroactive ligand receptor interaction	1.0000
taste transduction	1.0000
th1 and th2 cell differentiation	1.0000
selenocompound metabolism	1.0000
mineral absorption	1.0000
biosynthesis of amino acids	1.0000
folate biosynthesis	1.0000
intestinal immune network for iga production	1.0000
antifolate resistance	1.0000
hematopoietic cell lineage	1.0000
phototransduction	1.0000
alpha linolenic acid metabolism	1.0000
primary bile acid biosynthesis	1.0000
nucleotide excision repair	1.0000
taurine and hypotaurine metabolism	1.0000
histidine metabolism	1.0000

**Table S4.** Results obtained by employing SubPathway-GM [1] to extract and enrich COAD subpathways using KEGG pathway terms. The terms are sorted by means of p-value. We also reports if the other methods detect the same term as statistically significant ( $p < 0.01$ ). In italics we report the top-20 pathways used for the comparisons.

Pathway	SPECifIC	SubPathway-GM	SubPathway-GMir	DEsubs
<i>ppar signaling pathway</i>		$1.45 \times 10^{-08}$		
<i>starch and sucrose metabolism</i>		$4.93 \times 10^{-07}$	Yes	
<i>natural killer cell mediated cytotoxicity</i>		$3.86 \times 10^{-06}$		Yes
<i>pentose and glucuronate interconversions</i>		$3.86 \times 10^{-06}$	Yes	
<i>tight junction</i>		$4.53 \times 10^{-06}$		
<i>complement and coagulation cascades</i>		0.0003		
<i>arginine and proline metabolism</i>		0.0004	Yes	
<i>apoptosis</i>	Yes	0.0005		Yes
<i>calcium signaling pathway</i>		0.0006		
<i>aldosterone regulated sodium reabsorption</i>		0.0006		
<i>mapk signaling pathway</i>	Yes	0.0012		Yes
<i>fatty acid degradation</i>		0.0012	Yes	
<i>focal adhesion</i>		0.0013		Yes
<i>wnt signaling pathway</i>		0.0013		
<i>alanine aspartate and glutamate metabolism</i>		0.0014		
<i>butanoate metabolism</i>		0.0014		
<i>pyruvate metabolism</i>		0.0020	Yes	
<i>oocyte meiosis</i>		0.0026		
<i>glycosphingolipid biosynthesis lacto and neolacto series</i>		0.0026	Yes	
<i>tyrosine metabolism</i>		0.0029	Yes	
<i>chemokine signaling pathway</i>	Yes	0.0030		
<i>glutathione metabolism</i>		0.0044	Yes	
<i>cell adhesion molecules cams</i>		0.0049		
<i>cell cycle</i>		0.0050		
<i>amino sugar and nucleotide sugar metabolism</i>		0.0065	Yes	
<i>tgf beta signaling pathway</i>		0.0065		
<i>one carbon pool by folate</i>		0.0089	Yes	
<i>phosphatidylinositol signaling system</i>		0.0101		Yes
<i>galactose metabolism</i>		0.0131	Yes	
<i>toll like receptor signaling pathway</i>		0.0147		Yes
<i>phenylalanine metabolism</i>		0.0147	Yes	
<i>inositol phosphate metabolism</i>		0.0148	Yes	Yes
<i>fc gamma r mediated phagocytosis</i>		0.0176		
<i>lysine degradation</i>		0.0176		
<i>glycosphingolipid biosynthesis globo and isoglobo series</i>		0.0195		
<i>vegf signaling pathway</i>		0.0218		Yes
<i>fructose and mannose metabolism</i>		0.0230	Yes	

valine leucine and isoleucine degradation		0.0230	Yes	
adipocytokine signaling pathway		0.0253		Yes
glycerophospholipid metabolism		0.0253	Yes	
olfactory transduction		0.0253		
jak stat signaling pathway		0.0282		Yes
citrate cycle tca cycle		0.0282	Yes	
pentose phosphate pathway		0.0282	Yes	
sulfur metabolism		0.0282	Yes	
long term potentiation		0.0286		
glycosphingolipid biosynthesis ganglio series		0.0294	Yes	
progesterone mediated oocyte maturation	Yes	0.0338		
pathways in cancer	Yes	0.0358		
porphyrin and chlorophyll metabolism		0.0437	Yes	
neurotrophin signaling pathway		0.0437		
arachidonic acid metabolism	Yes	0.0467	Yes	
glycerolipid metabolism		0.0467	Yes	
cysteine and methionine metabolism		0.0471	Yes	
drug metabolism cytochrome p450	Yes	0.0482		
long term depression		0.0546		Yes
propanoate metabolism		0.0581		
mtor signaling pathway	Yes	0.0678		
glycolysis gluconeogenesis		0.0700	Yes	
nod like receptor signaling pathway		0.0700		
vascular smooth muscle contraction		0.0700		
phenylalanine tyrosine and tryptophan biosynthesis		0.0700		
glycine serine and threonine metabolism		0.0700	Yes	
tryptophan metabolism		0.0700		
regulation of actin cytoskeleton		0.0812		Yes
purine metabolism		0.0831	Yes	
sphingolipid metabolism		0.0831	Yes	
fatty acid elongation		0.0831		
synthesis and degradation of ketone bodies		0.0831		
circadian rhythm		0.0831		
melanogenesis	Yes	0.0982		Yes
axon guidance		0.0982		
gnrh signaling pathway	Yes	0.1498		Yes
gap junction		0.1558		
pyrimidine metabolism		0.1713	Yes	
steroid hormone biosynthesis	Yes	0.1858	Yes	
salivary secretion		0.1923		
phagosome		0.2123		
ether lipid metabolism		0.2859	Yes	
fc epsilon ri signaling pathway		0.2921		Yes
insulin signaling pathway		0.3107		
mucin type o glycan biosynthesis		0.3288	Yes	
nicotinate and nicotinamide metabolism		0.4014		

**Table S5.** Results obtained by employing SubPathway-GMir [2] to extract and enrich COAD subpathways using KEGG pathway terms. The terms are sorted by means of p-value. We also reports if the other methods detect the same term as statistically significant ( $p < 0.01$ ). In italics we report the top-20 pathways used for the comparisons.

Pathway	SPECifIC	SubPathway-GM	SubPathway-GMir	DEsubs
<i>metabolism of xenobiotics by cytochrome p450</i>	Yes		0	
<i>purine metabolism</i>			0	
<i>starch and sucrose metabolism</i>		Yes	0	
<i>fatty acid degradation</i>		Yes	0	
<i>steroid hormone biosynthesis</i>	Yes		$1.09 \times 10^{-14}$	
<i>pyrimidine metabolism</i>			$2.40 \times 10^{-14}$	
<i>pentose and glucuronate interconversions</i>		Yes	$2.68 \times 10^{-14}$	
<i>inositol phosphate metabolism</i>			$2.90 \times 10^{-14}$	Yes
<i>porphyrin and chlorophyll metabolism</i>			$2.48 \times 10^{-13}$	
<i>ascorbate and aldarate metabolism</i>			$3.93 \times 10^{-13}$	
<i>glutathione metabolism</i>		Yes	$8.26 \times 10^{-11}$	
<i>galactose metabolism</i>			$8.26 \times 10^{-11}$	
<i>arachidonic acid metabolism</i>	Yes		$1.18 \times 10^{-09}$	
<i>aminoacyl trna biosynthesis</i>			$2.28 \times 10^{-09}$	
<i>glycerolipid metabolism</i>			$2.98 \times 10^{-09}$	
<i>valine leucine and isoleucine degradation</i>			$3.01 \times 10^{-09}$	

<i>tyrosine metabolism</i>	Yes	$1.37 \times 10^{-08}$
<i>glycerophospholipid metabolism</i>		$3.75 \times 10^{-08}$
<i>amino sugar and nucleotide sugar metabolism</i>	Yes	$1.71 \times 10^{-07}$
<i>fructose and mannose metabolism</i>		$7.94 \times 10^{-07}$
<i>citrate cycle tca cycle</i>		$9.41 \times 10^{-07}$
<i>one carbon pool by folate</i>	Yes	$2.09 \times 10^{-06}$
<i>pentose phosphate pathway</i>		$2.89 \times 10^{-06}$
<i>cysteine and methionine metabolism</i>		$2.89 \times 10^{-06}$
<i>glycosphingolipid biosynthesis lacto and neolacto series</i>	Yes	$2.89 \times 10^{-06}$
<i>ether lipid metabolism</i>		$4.29 \times 10^{-06}$
<i>phenylalanine metabolism</i>		$8.71 \times 10^{-06}$
<i>mucin type o glycan biosynthesis</i>		$2.15 \times 10^{-05}$
<i>sulfur metabolism</i>		$4.04 \times 10^{-05}$
<i>arginine and proline metabolism</i>	Yes	0.0001
<i>pyruvate metabolism</i>	Yes	0.0001
<i>glycolysis gluconeogenesis</i>		0.0001
<i>sphingolipid metabolism</i>		0.0002
<i>glycosphingolipid biosynthesis ganglio series</i>		0.0013
<i>glycine serine and threonine metabolism</i>		0.0013

**Table S6.** Results obtained by employing DEsubs [3] to extract and enrich COAD subpathways using KEGG pathway terms. The terms are sorted by means of p-value. We also reports if the other methods detect the same term as statistically significant ( $p < 0.01$ ). In italics we report the top-20 pathways used for the comparisons.

Pathway	SPECifIC	SubPathway-GM	SubPathway-GMir	DEsubs
<i>fc epsilon ri signaling pathway</i>				67
<i>cytokine cytokine receptor interaction</i>				58
<i>erbB signaling pathway</i>	Yes			46
<i>b cell receptor signaling pathway</i>				29
<i>natural killer cell mediated cytotoxicity</i>		Yes		29
<i>inositol phosphate metabolism</i>			Yes	29
<i>phosphatidylinositol signaling system</i>				29
<i>leukocyte transendothelial migration</i>				29
<i>gnrh signaling pathway</i>	Yes			28
<i>mapk signaling pathway</i>	Yes	Yes		16
<i>focal adhesion</i>		Yes		16
<i>long term depression</i>				12
<i>toll like receptor signaling pathway</i>				10
<i>jak stat signaling pathway</i>				7
<i>apoptosis</i>	Yes	Yes		6
<i>vegf signaling pathway</i>				6
<i>regulation of actin cytoskeleton</i>				6
<i>adipocytokine signaling pathway</i>				2
<i>melanogenesis</i>	Yes			1

**Table S7.** Results obtained by employing SPECifIC to extract and enrich BRCA subpathways using KEGG pathway terms. The terms are sorted by means of p-value. We also reports if the other methods detect the same term as statistically significant ( $p < 0.01$ ). In italics we report the top-20 pathways used for the comparisons.

Pathway	SPECifIC	SubPathway-GM	SubPathway-GMir	DEsubs
<i>metabolism of xenobiotics by cytochrome p450</i>	0		Yes	
<i>drug metabolism cytochrome p450</i>	0		Yes	

<i>chemical carcinogenesis</i>	0		
<i>steroid hormone biosynthesis</i>	0		Yes
<i>drug metabolism other enzymes</i>	0		Yes
<i>linoleic acid metabolism</i>	0		Yes
<i>ppar signaling pathway</i>	0	Yes	Yes
<i>phenylalanine metabolism</i>	0		Yes
<i>estrogen signaling pathway</i>	$1.09 \times 10^{-30}$		
<i>chemokine signaling pathway</i>	$1.28 \times 10^{-30}$	Yes	
<i>erbB signaling pathway</i>	$8.64 \times 10^{-29}$		
<i>phospholipase d signaling pathway</i>	$1.11 \times 10^{-27}$		
<i>neurotrophin signaling pathway</i>	$4.63 \times 10^{-27}$	Yes	
<i>insulin signaling pathway</i>	$7.95 \times 10^{-26}$	Yes	
<i>egfr tyrosine kinase inhibitor resistance</i>	$2.76 \times 10^{-25}$		
<i>prolactin signaling pathway</i>	$1.20 \times 10^{-24}$		
<i>oxytocin signaling pathway</i>	$5.67 \times 10^{-24}$		
<i>platelet activation</i>	$5.67 \times 10^{-24}$		
<i>endocrine resistance</i>	$5.87 \times 10^{-24}$		
<i>focal adhesion</i>	$6.00 \times 10^{-24}$	Yes	Yes
<i>inflammatory mediator regulation of trp channels</i>	$1.98 \times 10^{-23}$		
<i>cholinergic synapse</i>	$5.56 \times 10^{-21}$		
<i>adrenergic signaling in cardiomyocytes</i>	$1.53 \times 10^{-20}$		
<i>rap1 signaling pathway</i>	$2.43 \times 10^{-20}$		
<i>vegf signaling pathway</i>	$2.53 \times 10^{-20}$		Yes
<i>sphingolipid signaling pathway</i>	$2.68 \times 10^{-20}$		
<i>natural killer cell mediated cytotoxicity</i>	$3.34 \times 10^{-20}$		Yes
<i>thyroid hormone signaling pathway</i>	$9.45 \times 10^{-19}$		
<i>ras signaling pathway</i>	$2.83 \times 10^{-18}$		
<i>pathways in cancer</i>	$5.11 \times 10^{-18}$		
<i>fc epsilon ri signaling pathway</i>	$1.36 \times 10^{-17}$		Yes
<i>b cell receptor signaling pathway</i>	$7.78 \times 10^{-17}$	Yes	
<i>cgmp pkg signaling pathway</i>	$2.27 \times 10^{-16}$		
<i>phosphatidylinositol signaling system</i>	$7.35 \times 10^{-16}$		
<i>choline metabolism in cancer</i>	$1.56 \times 10^{-15}$		
<i>mtor signaling pathway</i>	$2.78 \times 10^{-15}$		
<i>foxo signaling pathway</i>	$3.66 \times 10^{-15}$		
<i>regulation of actin cytoskeleton</i>	$4.17 \times 10^{-15}$	Yes	Yes
<i>t cell receptor signaling pathway</i>	$6.31 \times 10^{-15}$	Yes	
<i>aldosterone regulated sodium reabsorption</i>	$1.20 \times 10^{-14}$		
<i>central carbon metabolism in cancer</i>	$2.24 \times 10^{-14}$		
<i>longevity regulating pathway multiple species</i>	$3.08 \times 10^{-14}$		
<i>carbohydrate digestion and absorption</i>	$3.96 \times 10^{-14}$		
<i>gnrh signaling pathway</i>	$4.00 \times 10^{-14}$		Yes
<i>proteoglycans in cancer</i>	$1.87 \times 10^{-13}$		
<i>serotonergic synapse</i>	$3.38 \times 10^{-13}$		
<i>regulation of lipolysis in adipocytes</i>	$4.07 \times 10^{-13}$		
<i>leukocyte transendothelial migration</i>	$4.29 \times 10^{-13}$		
<i>fc gamma r mediated phagocytosis</i>	$8.62 \times 10^{-13}$	Yes	
<i>signaling pathways regulating pluripotency of stem cells</i>	$8.89 \times 10^{-13}$		
<i>micrornas in cancer</i>	$1.29 \times 10^{-12}$		
<i>longevity regulating pathway</i>	$1.56 \times 10^{-12}$		
<i>progesterone mediated oocyte maturation</i>	$1.86 \times 10^{-12}$		
<i>long term depression</i>	$2.97 \times 10^{-12}$		Yes
<i>camp signaling pathway</i>	$3.76 \times 10^{-12}$		
<i>axon guidance</i>	$6.84 \times 10^{-12}$		
<i>inositol phosphate metabolism</i>	$1.03 \times 10^{-11}$		Yes
<i>viral carcinogenesis</i>	$2.21 \times 10^{-11}$		
<i>pi3k akt signaling pathway</i>	$2.70 \times 10^{-11}$		
<i>jak stat signaling pathway</i>	$3.09 \times 10^{-11}$	Yes	Yes
<i>dopaminergic synapse</i>	$3.84 \times 10^{-11}$		
<i>toll like receptor signaling pathway</i>	$1.18 \times 10^{-10}$	Yes	Yes
<i>tnf signaling pathway</i>	$1.50 \times 10^{-10}$		
<i>glutamatergic synapse</i>	$1.67 \times 10^{-10}$		
<i>ampk signaling pathway</i>	$4.93 \times 10^{-10}$		
<i>osteoclast differentiation</i>	$6.68 \times 10^{-10}$		
<i>apoptosis</i>	$1.13 \times 10^{-9}$	Yes	Yes
<i>gap junction</i>	$1.32 \times 10^{-7}$	Yes	Yes
<i>cell cycle</i>	$2.99 \times 10^{-7}$	Yes	Yes
<i>oocyte meiosis</i>	$4.41 \times 10^{-7}$		
<i>circadian entrainment</i>	$1.18 \times 10^{-5}$		
<i>long term potentiation</i>	$1.63 \times 10^{-5}$		

vascular smooth muscle contraction	$5.50 \times 10^{-05}$			
wnt signaling pathway	$7.60 \times 10^{-05}$			
glycolysis gluconeogenesis	0.5000		Yes	
tyrosine metabolism	0.5000		Yes	
beta alanine metabolism	0.5000		Yes	
histidine metabolism	0.5000		Yes	
arginine and proline metabolism	0.5000		Yes	
glycine serine and threonine metabolism	0.5000		Yes	
platinum drug resistance	0.5000			
hif 1 signaling pathway	0.5000			
tryptophan metabolism	0.5000		Yes	
hippo signaling pathway	0.5000			
tight junction	0.5000	Yes		
retrograde endocannabinoid signaling	0.5000			
pyrimidine metabolism	0.5001		Yes	
purine metabolism	0.5002		Yes	
calcium signaling pathway	0.5004	Yes		Yes
mapk signaling pathway	0.5010	Yes		Yes
starch and sucrose metabolism	1		Yes	
insulin secretion	1			
melanogenesis	1			Yes
ovarian steroidogenesis	1			
thyroid hormone synthesis	1			
aldosterone synthesis and secretion	1			
glucagon signaling pathway	1			
arachidonic acid metabolism	1		Yes	
p53 signaling pathway	1	Yes		
mrna surveillance pathway	1			
protein processing in endoplasmic reticulum	1			
apoptosis multiple species	1			
nod like receptor signaling pathway	1			
transcriptional misregulation in cancer	1			
glutathione metabolism	1		Yes	
gabaergic synapse	1			
renin secretion	1			
salivary secretion	1			
gastric acid secretion	1			
pancreatic secretion	1			
dorso ventral axis formation	1			
th17 cell differentiation	1			
adipocytokine signaling pathway	1	Yes		Yes
endocrine and other factor regulated calcium reabsorption	1			
vasopressin regulated water reabsorption	1			
cytokine cytokine receptor interaction	1			Yes
endocytosis	1			
adherens junction	1	Yes		Yes
fatty acid degradation	1		Yes	
fatty acid metabolism	1			
citrate cycle tca cycle	1		Yes	
pyruvate metabolism	1		Yes	
proximal tubule bicarbonate reclamation	1			
carbon metabolism	1			
tgf beta signaling pathway	1			
cardiac muscle contraction	1			
lysine degradation	1		Yes	
ecm receptor interaction	1			Yes
pentose and glucuronate interconversions	1		Yes	
ascorbate and aldarate metabolism	1		Yes	
porphyrin and chlorophyll metabolism	1			
cytosolic dna sensing pathway	1			
neuroactive ligand receptor interaction	1			
taste transduction	1			
th1 and th2 cell differentiation	1			
olfactory transduction	1			
intestinal immune network for iga production	1			
antifolate resistance	1			
hematopoietic cell lineage	1			
cell adhesion molecules cams	1			
phototransduction	1			
glycerophospholipid metabolism	1		Yes	
ether lipid metabolism	1		Yes	
alpha linolenic acid metabolism	1			
glycerolipid metabolism	1		Yes	
primary bile acid biosynthesis	1			
alanine aspartate and glutamate metabolism	1		Yes	

butanoate metabolism	1		Yes
fatty acid biosynthesis	1		
peroxisome	1		
fat digestion and absorption	1		
rig i like receptor signaling pathway	1	Yes	
synthesis and degradation of ketone bodies	1		Yes
valine leucine and isoleucine degradation	1		Yes
terpenoid backbone biosynthesis	1		Yes
biosynthesis of unsaturated fatty acids	1		
phagosome	1	Yes	
propanoate metabolism	1		Yes
vitamin b6 metabolism	1		
nicotinate and nicotinamide metabolism	1		Yes
hippo signaling pathway multiple species	1		
thiamine metabolism	1		
one carbon pool by folate	1		Yes

**Table S8.** Results obtained by employing SubPathway-GM [1] to extract and enrich BRCA subpathways using KEGG pathway terms. The terms are sorted by means of p-value. We also reports if the other methods detect the same term as statistically significant ( $p < 0.01$ ). In italics we report the top-20 pathways used for the comparisons.

Pathway	SPECifIC	SubPathway-GM	SubPathway-GMir	DEsubs
<i>cell cycle</i>	Yes	$7.08 \times 10^{-11}$		Yes
<i>focal adhesion</i>	Yes	$2.25 \times 10^{-10}$		Yes
<i>complement and coagulation cascades</i>		$2.00 \times 10^{-08}$		
<i>ppar signaling pathway</i>	Yes	$5.00 \times 10^{-08}$		Yes
<i>tight junction</i>		$8.74 \times 10^{-08}$		
<i>mapk signaling pathway</i>		$1.07 \times 10^{-06}$		Yes
<i>p53 signaling pathway</i>		$1.07 \times 10^{-06}$		
<i>neurotrophin signaling pathway</i>	Yes	$2.71 \times 10^{-06}$		
<i>jak stat signaling pathway</i>	Yes	$1.69 \times 10^{-05}$		Yes
<i>chemokine signaling pathway</i>	Yes	$6.46 \times 10^{-05}$		
<i>regulation of actin cytoskeleton</i>	Yes	$7.65 \times 10^{-05}$		Yes
<i>insulin signaling pathway</i>	Yes	0.0002		
<i>t cell receptor signaling pathway</i>	Yes	0.0004		
<i>fc gamma r mediated phagocytosis</i>	Yes	0.0007		
<i>calcium signaling pathway</i>		0.0008		Yes
<i>notch signaling pathway</i>		0.0016		Yes
<i>phagosome</i>		0.0041		
<i>glycosaminoglycan biosynthesis chondroitin sulfate dermatan sulfate</i>		0.0072		
<i>b cell receptor signaling pathway</i>	Yes	0.0078		
<i>gap junction</i>	Yes	0.0078		Yes
<i>adherens junction</i>		0.0078		Yes
<i>apoptosis</i>	Yes	0.0096		Yes
<i>toll like receptor signaling pathway</i>	Yes	0.0099		Yes
<i>adipocytokine signaling pathway</i>		0.0099		Yes
<i>rig i like receptor signaling pathway</i>		0.0099		
<i>vegf signaling pathway</i>	Yes	0.0104		Yes
<i>dorso ventral axis formation</i>		0.0133		
<i>gnrh signaling pathway</i>	Yes	0.0185		Yes
<i>phenylalanine metabolism</i>	Yes	0.0207	Yes	
<i>hedgehog signaling pathway</i>		0.0407		Yes
<i>glycerolipid metabolism</i>		0.0408	Yes	
<i>leukocyte transendothelial migration</i>	Yes	0.0443		
<i>ecm receptor interaction</i>		0.0450		Yes
<i>mtor signaling pathway</i>	Yes	0.0458		
<i>progesterone mediated oocyte maturation</i>	Yes	0.0458		
<i>tgf beta signaling pathway</i>		0.0458		
<i>glycosylphosphatidylinositol gpi anchor biosynthesis</i>		0.0458		
<i>vascular smooth muscle contraction</i>	Yes	0.0506		
<i>nod like receptor signaling pathway</i>		0.0511		
<i>natural killer cell mediated cytotoxicity</i>	Yes	0.0540		Yes
<i>axon guidance</i>	Yes	0.0560		
<i>n glycan biosynthesis</i>		0.0560	Yes	
<i>drug metabolism cytochrome p450</i>	Yes	0.0619	Yes	
<i>long term potentiation</i>	Yes	0.0780		
<i>tyrosine metabolism</i>		0.0780	Yes	
<i>circadian rhythm</i>		0.0812		

pathways in cancer	Yes	0.0868		
pyruvate metabolism		0.0887	Yes	
wnt signaling pathway	Yes	0.1024		
aldosterone regulated sodium reabsorption	Yes	0.1028		
phosphatidylinositol signaling system	Yes	0.1162		
cell adhesion molecules cams		0.1162		
erbb signaling pathway	Yes	0.1454		
glycolysis gluconeogenesis		0.1572	Yes	
cysteine and methionine metabolism		0.1593	Yes	
butanoate metabolism		0.1615	Yes	
pancreatic secretion		0.1630		
pyrimidine metabolism		0.1671	Yes	
arginine and proline metabolism		0.1747	Yes	
mucin type o glycan biosynthesis		0.1870	Yes	
inositol phosphate metabolism	Yes	0.2146	Yes	
histidine metabolism		0.2146	Yes	
vasopressin regulated water reabsorption		0.2146		
long term depression	Yes	0.2267		Yes
beta alanine metabolism		0.2440	Yes	
glycerophospholipid metabolism		0.2440	Yes	
ether lipid metabolism		0.2440	Yes	
sphingolipid metabolism		0.2593	Yes	
galactose metabolism		0.2717	Yes	
amino sugar and nucleotide sugar metabolism		0.2721	Yes	
gastric acid secretion		0.2761		
glycine serine and threonine metabolism		0.2797	Yes	
glycosphingolipid biosynthesis globo and isoglobo series		0.2864		
salivary secretion		0.2947		
valine leucine and isoleucine degradation		0.2947	Yes	
fructose and mannose metabolism		0.3022	Yes	
taste transduction		0.3127		
purine metabolism		0.3660	Yes	
endocytosis		0.3660		
pantothenate and coa biosynthesis		0.4057		
drug metabolism other enzymes	Yes	0.4292	Yes	
caffeine metabolism		0.4307		
glycosphingolipid biosynthesis ganglio series		0.4307		
nitrogen metabolism		0.4307	Yes	
oocyte meiosis	Yes	0.4833		
melanogenesis		0.4870		Yes
fc epsilon ri signaling pathway	Yes	0.4894		Yes
propanoate metabolism		0.5207	Yes	
tryptophan metabolism		0.5248	Yes	
synthesis and degradation of ketone bodies		0.5248	Yes	
phenylalanine tyrosine and tryptophan biosynthesis		0.5248		
riboflavin metabolism		0.5248	Yes	
one carbon pool by folate		0.5316	Yes	
terpenoid backbone biosynthesis		0.5957	Yes	
cytosolic dna sensing pathway		0.6002		
alanine aspartate and glutamate metabolism		0.6023	Yes	
arachidonic acid metabolism		0.6041	Yes	
glycosaminoglycan degradation		0.6041	Yes	
citrate cycle tca cycle		0.6053	Yes	
glycosaminoglycan biosynthesis heparan sulfate heparin		0.6053		
glycosphingolipid biosynthesis lacto and neolacto series		0.6231	Yes	
selenocompound metabolism		0.6296	Yes	
protein processing in endoplasmic reticulum		0.6463		
pentose phosphate pathway		0.6463	Yes	
fatty acid biosynthesis		0.6569		
lysine degradation		0.6803	Yes	
glyoxylate and dicarboxylate metabolism		0.6936		
lysine biosynthesis		0.6936		
steroid biosynthesis		0.7141	Yes	
folate biosynthesis		0.7141	Yes	
primary bile acid biosynthesis		0.7374		
cytokine cytokine receptor interaction		0.7499		Yes
sulfur metabolism		0.8436		
fatty acid degradation		0.8545	Yes	
glutathione metabolism		0.8911	Yes	
nicotinate and nicotinamide metabolism		0.9075	Yes	
steroid hormone biosynthesis	Yes	0.9227	Yes	
vitamin b6 metabolism		0.9464		
starch and sucrose metabolism		0.9551	Yes	
antigen processing and presentation		0.9874		
pentose and glucuronate interconversions		1	Yes	

porphyrin and chlorophyll metabolism	1	
olfactory transduction	1	
fatty acid elongation	1	Yes

**Table S9.** Results obtained by employing SubPathway-GMir [2] to extract and enrich BRCA subpathways using KEGG pathway terms. The terms are sorted by means of p-value. We also reports if the other methods detect the same term as statistically significant ( $p < 0.01$ ). In italics we report the top-20 pathways used for the comparisons.

Pathway	SPECifIC	SubPathway-GM	SubPathway-GMir	DEsubs
<i>glycolysis gluconeogenesis</i>			0	
<i>pyrimidine metabolism</i>			0	
<i>purine metabolism</i>			0	
<i>glycerophospholipid metabolism</i>			0	
<i>fatty acid degradation</i>			$1.49 \times 10^{-14}$	
<i>inositol phosphate metabolism</i>	Yes		$1.13 \times 10^{-13}$	
<i>lysine degradation</i>			$3.73 \times 10^{-13}$	
<i>pyruvate metabolism</i>			$1.93 \times 10^{-12}$	
<i>valine leucine and isoleucine degradation</i>			$5.51 \times 10^{-12}$	
<i>glycerolipid metabolism</i>			$6.46 \times 10^{-12}$	
<i>tyrosine metabolism</i>			$2.42 \times 10^{-11}$	
<i>n glycan biosynthesis</i>			$3.51 \times 10^{-11}$	
<i>arachidonic acid metabolism</i>			$5.60 \times 10^{-11}$	
<i>ether lipid metabolism</i>			$6.38 \times 10^{-11}$	
<i>arginine and proline metabolism</i>			$9.10 \times 10^{-10}$	
<i>amino sugar and nucleotide sugar metabolism</i>			$2.21 \times 10^{-09}$	
<i>glutathione metabolism</i>			$2.41 \times 10^{-09}$	
<i>sphingolipid metabolism</i>			$2.61 \times 10^{-09}$	
<i>propanoate metabolism</i>			$1.15 \times 10^{-08}$	
<i>glycosphingolipid biosynthesis lacto and neolacto series</i>			$1.15 \times 10^{-08}$	
<i>galactose metabolism</i>			$1.40 \times 10^{-08}$	
<i>fructose and mannose metabolism</i>			$1.40 \times 10^{-08}$	
<i>phenylalanine metabolism</i>	Yes		$4.24 \times 10^{-08}$	
<i>cysteine and methionine metabolism</i>			$5.24 \times 10^{-08}$	
<i>drug metabolism other enzymes</i>	Yes		$1.01 \times 10^{-07}$	
<i>alanine aspartate and glutamate metabolism</i>			$1.01 \times 10^{-07}$	
<i>fatty acid elongation</i>			$1.21 \times 10^{-07}$	
<i>starch and sucrose metabolism</i>			$1.37 \times 10^{-07}$	
<i>butanoate metabolism</i>			$2.19 \times 10^{-07}$	
<i>tryptophan metabolism</i>			$2.84 \times 10^{-07}$	
<i>aminoacyl trna biosynthesis</i>			$5.87 \times 10^{-07}$	
<i>metabolism of xenobiotics by cytochrome p450</i>	Yes		$1.02 \times 10^{-06}$	
<i>steroid hormone biosynthesis</i>	Yes		$1.03 \times 10^{-06}$	
<i>drug metabolism cytochrome p450</i>	Yes		$2.04 \times 10^{-06}$	
<i>citrate cycle tca cycle</i>			$2.04 \times 10^{-06}$	
<i>mucin type o glycan biosynthesis</i>			$2.04 \times 10^{-06}$	
<i>pentose phosphate pathway</i>			$2.82 \times 10^{-06}$	
<i>linoleic acid metabolism</i>	Yes		$7.36 \times 10^{-06}$	
<i>glycine serine and threonine metabolism</i>			$7.49 \times 10^{-06}$	
<i>histidine metabolism</i>			$2.10 \times 10^{-05}$	
<i>pentose and glucuronate interconversions</i>			0.0002	
<i>steroid biosynthesis</i>			0.0002	
<i>terpenoid backbone biosynthesis</i>			0.0002	
<i>one carbon pool by folate</i>			0.0002	
<i>folate biosynthesis</i>			0.0014	
<i>ascorbate and aldarate metabolism</i>			0.0019	
<i>synthesis and degradation of ketone bodies</i>			0.0019	
<i>riboflavin metabolism</i>			0.0019	
<i>nicotinate and nicotinamide metabolism</i>			0.0024	
<i>glycosaminoglycan degradation</i>			0.0057	
<i>beta alanine metabolism</i>			0.0058	
<i>nitrogen metabolism</i>			0.0058	
<i>selenocompound metabolism</i>			0.0058	
<i>glycosphingolipid biosynthesis ganglio series</i>			0.0188	

**Table S10.** Results obtained by employing DESubs [3] to extract and enrich BRCA subpathways using KEGG pathway terms. The terms are sorted by means of p-value. We also reports if the other methods detect the same term as statistically significant ( $p < 0.01$ ). In italics we report the top-20 pathways used for the comparisons.

Pathway	SPECifIC	SubPathway-GM	SubPathway-GMir	DESubs
<i>focal adhesion</i>	Yes	Yes		76
<i>cytokine cytokine receptor interaction</i>				59
<i>cell cycle</i>	Yes	Yes		56
<i>ecm receptor interaction</i>				30
<i>jak stat signaling pathway</i>	Yes	Yes		24
<i>ppar signaling pathway</i>	Yes	Yes		21
<i>mapk signaling pathway</i>		Yes		18
<i>toll like receptor signaling pathway</i>	Yes	Yes		14
<i>adherens junction</i>		Yes		13
<i>gnrh signaling pathway</i>	Yes			10
<i>long term depression</i>	Yes			10
<i>hedgehog signaling pathway</i>				10
<i>natural killer cell mediated cytotoxicity</i>	Yes			8
<i>regulation of actin cytoskeleton</i>	Yes	Yes		8
<i>notch signaling pathway</i>		Yes		8
<i>apoptosis</i>	Yes	Yes		6
<i>adipocytokine signaling pathway</i>		Yes		6
<i>vegf signaling pathway</i>	Yes			5
<i>fc epsilon ri signaling pathway</i>	Yes			5
<i>gap junction</i>	Yes	Yes		4
<i>calcium signaling pathway</i>		Yes		4
<i>melanogenesis</i>				4

**Table S11.** p-Values, computed by means of Wilcoxon rank-sum test, for the comparison between the four methodologies in terms of distances from a disease node to a subpathway. The values where computed for the BRCA dataset.

	SPECifIC	Subpathay-GM	Subpathway-Gmir	DESubs
<b>SPECifIC</b>	-	0.0062	$1.68 \times 10^{-9}$	$3.98 \times 10^{-5}$
<b>Subpathay-GM</b>		-	$2.98 \times 10^{-6}$	$1.01 \times 10^{-5}$
<b>Subpathway-Gmir</b>			-	0.1794
<b>DESubs</b>				-

**Table S12.** p-Values, computed by means of Wilcoxon rank-sum test, for the comparison between the four methodologies in terms of distances from a disease node to a subpathway. The values where computed for the COAD dataset.

	SPECifIC	Subpathay-GM	Subpathway-Gmir	DESubs
<b>SPECifIC</b>	-	$2.26 \times 10^{-7}$	$8.32 \times 10^{-12}$	$8.41 \times 10^{-19}$
<b>Subpathay-GM</b>		-	$1.03 \times 10^{-6}$	$2.44 \times 10^{-13}$
<b>Subpathway-Gmir</b>			-	$4.08 \times 10^{-07}$
<b>DESubs</b>				-

**Table S13.** p-Values, computed by means of Wilcoxon rank-sum test, for the comparison between the four methodologies in terms of distances between disease nodes in a subpathway. The values were computed for the BRCA dataset. No p-values could be computed for DESubs since no disease nodes were found inside substructures.

	KEGG Pathways	SPECifIC	Subpathay-GM	Subpathway-Gmir	DESubs
KEGG Pathways	-	$7.23 \times 10^{-24}$	0.0118	$5.49 \times 10^{-24}$	-
SPECifIC	-	-	0.7974	$4.56 \times 10^{-11}$	-
Subpathay-GM	-	-	-	$6.50 \times 10^{-6}$	-
Subpathway-Gmir	-	-	-	-	-
DESubs	-	-	-	-	-

**Table S14.** p-Values, computed by means of Wilcoxon rank-sum test, for the comparison between the four methodologies in terms of distances between disease nodes in a subpathway. The values were computed for the COAD dataset. No p-values could be computed for DESubs since no disease nodes were found inside substructures.

	KEGG Pathways	SPECifIC	Subpathay-GM	Subpathway-Gmir	DESubs
KEGG Pathways	-	0.0155	$1.74 \times 10^{-5}$	$6.77 \times 10^{-23}$	-
SPECifIC	-	-	$1.67 \times 10^{-7}$	$6.51 \times 10^{-33}$	-
Subpathay-GM	-	-	-	$4.05 \times 10^{-5}$	-
Subpathway-Gmir	-	-	-	-	-
DESubs	-	-	-	-	-

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