Supplementary Note

Supplementary Note 1: Database search terms for perturbations

Below, we list experimental evidence that our chosen pathway modulators indeed have the effect we assume in our model (PubMed IDs). We further provide our search term and all the ArrayExpress accessions we used to build our model.

- EGFR
  - Experimental evidence and secondary literature
    EGF[1], TGFα[1], Epiregulin[1], Heregulin[1], Neuregulin[1], Epigen[2], Beta-cellulin[1], Cetuximab[3], Amphiregulin[3], Gefinitib (Iressa)[3,4], Erlotinib (Tarceva)[3,4], Lapatinib[4], Tyrphostin AG1478[5], Trastuzumab (Herceptin)[3]
  - Search term
    (egf* OR "growth factor" OR TGFα OR epiregulin OR heregulin OR neuregulin OR epigen OR betacellulin OR amphiregulin OR iressa OR gefitinib OR cetuximab OR erlotinib OR lapatinib OR AG1478 OR trastuzumab OR herceptin) organism:sapiens samplecount:[4 TO 10000] raw:true exptype:"Transcription profiling"
  - Accessions
    E-GEOD-13168[6], E-GEOD-14256[7], E-GEOD-14987[8], E-GEOD-16179[9], E-GEOD-16659[10], E-GEOD-17948[11], E-GEOD-18232[12], E-GEOD-20854, E-GEOD-21618[13], E-GEOD-22288[14], E-GEOD-26732[15], E-GEOD-30516[16], E-GEOD-32217[17], E-GEOD-32975[18], E-GEOD-33442[19], E-GEOD-34104[20], E-GEOD-34652[21], E-GEOD-42781[22], E-GEOD-51212[23], E-GEOD-55823[24], E-GEOD-57156[25], E-GEOD-60880, E-GEOD-6462, E-MEXP-2065, E-MEXP-256, E-MEXP-440, E-MTAB-2091, E-TABM-440
- Hypoxia
  - Experimental evidence and secondary literature
    HIF-1[26]
  - Search term
    (hypoxia* OR HIF1 OR HIF-1) organism:sapiens samplecount:[4 TO 10000] raw:true exptype:"Transcription profiling"
  - Accessions
    E-GEOD-11904[27], E-GEOD-15583[28], E-GEOD-17353[29], E-GEOD-17714[30], E-GEOD-18494[31], E-GEOD-19197[32], E-GEOD-22282[33], E-GEOD-22469, E-GEOD-25452, E-GEOD-26820[34], E-GEOD-27523[35], E-GEOD-28603, E-GEOD-29406[36], E-GEOD-30979[37], E-GEOD-32100[38], E-GEOD-33115[39], E-GEOD-34112, E-GEOD-35819, E-GEOD-35973, E-GEOD-39042[40], E-GEOD-4086[41], E-GEOD-41999, E-GEOD-43608[42], E-GEOD-47009, E-GEOD-48002[43], E-GEOD-52315[44], E-GEOD-53012[45], E-GEOD-57613[46], E-GEOD-58049[47], E-GEOD-65168[48], E-GEOD-9649[49], E-TABM-948
- JAK-STAT
  - Experimental evidence and secondary literature
    Interferonβ/γ[50], IL-2[51], IL-3[51], IL-6[51,52], IL-10[51], IL-13[51], Prolaktin[50], EPO[51]
  - Search term
    (ifn* OR interferon OR JAK OR STAT OR prolaktin OR EPO OR IL-2 OR IL2 OR IL-3 OR IL3 OR IL-6 OR IL6 OR IL-10 OR IL10 OR IL-13 OR IL13) organism:sapiens samplecount:[4 TO 10000] raw:true exptype:"Transcription profiling"
  - Accessions
    E-GEOD-10685[53], E-GEOD-10943, E-GEOD-15743[54], E-GEOD-16452[55], E-GEOD-16755[56], E-GEOD-17477, E-GEOD-19182[57], E-GEOD-19392[58], E-GEOD-20272[59], E-GEOD-31193[60], E-GEOD-3183, E-GEOD-32387[61], E-GEOD-32407[62], E-GEOD-35601, E-GEOD-36287[63], E-GEOD-38147[64],

E-GEOD-43700[65], E-GEOD-440, E-GEOD-51402[66], E-GEOD-53213[67], E-GEOD-53751[68], E-GEOD-55510[69], E-GEOD-6092, E-GEOD-8515[70], E-GEOD-8687[71], E-GEOD-9481[72], E-MEXP-3746, E-MTAB-2091, E-MTAB-2477

- MAPK
  - Experimental evidence and secondary literature
    BRAF[73], RAF[73], MEK[73,74], ERK[73,74], PD-0325901[75], CI-1040[75], PLX4720[76], AZD6244[75], GSK1120212 (Trametinib)[75], U0126[74]
  - Search term
    (b-raf OR braf OR raf* OR mek* OR erk* OR PD*0325901 OR CI*1040 OR PLX* OR U0126 OR AZD6244 OR GSK1120212 OR *metinib OR PD*325901) organism:sapiens samplecount:[4 TO 10000] raw:true exptype:"Transcription profiling"
  - Accessions
    E-GEOD-10086[77], E-GEOD-12764[78,79], E-GEOD-13487[80], E-GEOD-13827, E-GEOD-14934[81], E-GEOD-15417[82], E-GEOD-17089[83], E-GEOD-18232[12], E-GEOD-20051[84], E-GEOD-24862[85], E-GEOD-29884, E-GEOD-31019[86], E-GEOD-32975[18], E-GEOD-35230[87], E-GEOD-41816[88], E-GEOD-42872[89], E-GEOD-45757[90], E-GEOD-45758[90], E-GEOD-50591[91], E-GEOD-50649[92], E-GEOD-51212[23], E-GEOD-53091, E-GEOD-58869
- NFkB
  - Experimental evidence and secondary literature
    TNFα pathway activation[93], Lipopolysaccharide (LPS)[94], Parthenidolide[95], Zymosan[96], BAY 11-7082[97]
  - Search term
    (LPS OR sa:lps OR sa:lipopolysaccharide OR pam3c* OR zymosan OR parthenolide OR sa:11-7082 OR sa:*salicyl*) organism:sapiens samplecount:[4 TO 10000] raw:true exptype:"Transcription profiling"
  - Accessions
    E-GEOD-10739[98], E-GEOD-14000[99], E-GEOD-14419, E-GEOD-16193[100], E-GEOD-16650, E-GEOD-19315[101], E-GEOD-19625[102], E-GEOD-20114[103], E-GEOD-22103[104], E-GEOD-23371[105], E-GEOD-24897[106], E-GEOD-25146[107], E-GEOD-25147[107], E-GEOD-25148[107], E-GEOD-26567, E-GEOD-29700[108], E-GEOD-32141[109], E-GEOD-40885, E-GEOD-42358[110], E-GEOD-42660[111], E-GEOD-43596[112], E-GEOD-46236[113], E-GEOD-46914[114], E-GEOD-59472[115], E-GEOD-7538[116], E-GEOD-9916, E-MEXP-1103, E-MEXP-2577, E-MEXP-3931, E-MTAB-1393, E-TABM-868
- p53
  - Experimental evidence and secondary literature
    DNA double strand breaks[117], Ionizing radiation[118], Nutlin-3a (MDM2 inhibition)[119,120], RITA (MDM2 inhibition)[121], Doxorubicin[120], Cisplatin[122,123], Carboplatin[123], Oxaliplatin[123]
  - Search term
    (sa:*p53 OR sa:mdm2 OR sa:nutlin* OR sa:*radiation OR sa:*radiated OR sa:"dna damage" OR sa:ddr OR sa:*rubicin OR sa:*platin OR sa:docetaxel OR sa:gamma) organism:sapiens samplecount:[4 TO 10000] raw:true exptype:"Transcription profiling"
  - Accessions
    E-GEOD-11578[124], E-GEOD-15658, E-GEOD-18552[125], E-GEOD-30137[126], E-GEOD-30174[127], E-GEOD-30753, E-GEOD-30988[128], E-GEOD-35006[129], E-GEOD-46642[130], E-GEOD-56640[131], E-MEXP-2623, E-MEXP-390, E-MTAB-1403
- PI3K
  - Experimental evidence and secondary literature
    PIK3CA H1047R[132], Ras G12V/Y40C[81], PTEN[133], BKM120[134], LY294002[135,136], GSK1059615[134], PI-103[136], GDC941[134], BEZ235[134],

  - Search term
    (SF1126 OR LY294002 OR TGR*1202 OR SAR2454* OR GSK1059615 OR 80*6946 OR Perifosine OR Idelalisib OR PI3K OR PIK3* OR PTEN OR BEZ235 OR RP6530 OR GDC*941 OR INK1117) organism:sapiens samplecount:[4 TO 10000] raw:true exptype:"Transcription profiling"
  - Accessions
    E-GEOD-14934[81], E-GEOD-17785, E-GEOD-32975[18], E-GEOD-33643[137], E-GEOD-38255, E-GEOD-40564[138], E-GEOD-42762[139], E-GEOD-45276[140], E-GEOD-51212[23], E-GEOD-53309[141], E-GEOD-6263[142], E-GEOD-9601[143], E-MEXP-3640

- TGFb
  - Experimental evidence and secondary literature
    TGFβ ligand[144,145], BMP ligands (BMP2, BMP4, BMP6)[146],
  - Search term
    (tgf OR "tgf-*" OR "bmp*" OR "SMAD*" "transforming growth factor" OR "A 83-01" OR "A-83-01" OR "A83-01" OR "D 4476" OR "D4476" OR "D-4476" OR "GW 788388" OR "GW788388" OR "GW-788388" OR "LY 364947" OR "LY-364947" OR "LY364947" OR "R 268712" OR "R-268712" OR "R268712" OR RepSox OR "SB 431542" OR "SB-431542" OR "SB431542" OR "SB 505124" OR "SB-505124" OR "SB505124" OR "SB 525334" OR "SB-525334" OR "SB525334" OR "SD 208" OR "SD208" OR "SD-208") organism:sapiens samplecount:[4 TO 10000] raw:true exptype:"Transcription profiling"
  - Accessions
    E-GEOD-10311[147], E-GEOD-16111, E-GEOD-20671[148], E-GEOD-26241[149], E-GEOD-26351[150], E-GEOD-27526[151], E-GEOD-28074[152], E-GEOD-40266[153], E-GEOD-46019[154], E-GEOD-5457, E-GEOD-54756, E-GEOD-60135[155], E-GEOD-63383[156], E-GEOD-7144, E-MEXP-2645

- TNFa
  - Experimental evidence and secondary literature
    TNFα[157,158]
  - Search term
    (tnf* OR "necrosis factor") organism:sapiens samplecount:[4 TO 10000] raw:true exptype:"Transcription profiling"
  - Accessions
    E-GEOD-11115, E-GEOD-11467[159], E-GEOD-12161[160], E-GEOD-12548[161], E-GEOD-13837[162], E-GEOD-16650, E-GEOD-24422[163], E-GEOD-2638[164], E-GEOD-2639, E-GEOD-26868[165], E-GEOD-28548, E-GEOD-32975[18], E-GEOD-36287[63], E-GEOD-37139[166], E-GEOD-38351[167], E-GEOD-40413[168], E-GEOD-43685[169], E-GEOD-43738[170], E-GEOD-59237[171], E-GEOD-59472[115], E-GEOD-65707[172], E-GEOD-8166[173], E-MEXP-3540, E-MTAB-1027, E-MTAB-1312, E-MTAB-2091, E-SGRP-3

- Trail
  - Experimental evidence and secondary literature
    Recombinant Trail[174], FasL[174], Caspase 8[174], ABT-737[175], ABT-199[176], GX15-070 (Obatoclax)[175]
  - Search term
    (rtrail OR trail* OR fas OR fasl) organism:sapiens samplecount:[4 TO 10000] raw:true exptype:"Transcription profiling" array:(A-AFFY-33 OR A-AFFY-44 OR A-AFFY-37 OR A-AFFY-141) OR (ABT-737 OR ABT-199 OR obatoclax OR GX15-070 OR casp8 OR caspase) organism:sapiens samplecount:[4 TO 10000] raw:true exptype:"Transcription profiling"
  - Accessions
    E-GEOD-29955[177], E-GEOD-36149[178], E-GEOD-36572, E-GEOD-62533[179], E-GEOD-8346

- VEGF

– Experimental evidence and secondary literature
VEGF[180], PGF/PDGF[181], FGF[182,183], Sunitinib (Sutent)[184], Pazopanib (Votrient)[184], Everolimus (Afinitor)[185], Bevacizumab (Avastin)[184], Sorafenib (Nexavar)[184], Withaferin[186],

– Search term
(VEGF* OR sunitinib OR nexavar OR sutent OR pazopanib OR OR afinitor OR votrient OR Bevacizumab OR sorafenib OR PDGF* OR PGF OR FGF OR Withaferin) organism:sapiens samplecount:[4 TO 10000] raw:true exptype:"Transcription profiling"

– Accessions
E-GEOD-14256[7], E-GEOD-18913[187], E-GEOD-19098[188], E-GEOD-1923[189], E-GEOD-29368[190], E-GEOD-42001, E-GEOD-48841[191], E-GEOD-52488[192], E-GEOD-53633[193], E-GEOD-58203[194], E-GEOD-7403[195], E-MTAB-2091

Supplementary Tables

Supplementary Table 1: Area under the ROC curve for perturbation experiments. Pathway scores derived by different pathway methods, known pathway perturbations are True Positives.

inferred	PROGENy	Z-score	SPEED (our data)	SPEED (web)	EPSA (our data)	GSEA (our genes)
EGFR	0.81	0.50	0.71	0.59	0.78	0.37
Hypoxia	0.96	0.51	0.95	NA	0.92	0.94
JAK-STAT	0.87	0.51	0.95	0.76	0.80	0.90
MAPK	0.81	0.50	0.17	0.13	0.38	0.88
NFkB	0.82	0.50	0.94	NA	0.87	0.87
p53	0.93	0.52	0.82	NA	0.87	0.92
PI3K	0.79	0.52	0.20	0.72	0.22	0.14
TGFb	0.92	0.49	0.85	0.48	0.85	0.88
TNFa	0.93	0.50	0.98	0.78	0.88	0.98
Trail	0.60	0.52	0.98	NA	0.88	0.71
VEGF	0.78	0.49	0.83	0.36	0.70	0.25

Supplementary Table 2: Pathway mapping for different methods

(a) Gene Ontology. GO categories (ID and name) shown for the 11 pathways we investigate.

2*Pathway	Gene Ontology	
	ID	Name
EGFR	GO:0007259	ERBB signaling pathway
Hypoxia	GO:0071456	cellular response to hypoxia
JAK-STAT	GO:0007259	JAK-STAT signal transduction
MAPK	GO:0000165	MAPK cascade
NFkB	GO:0038061	NIK/NF-kappaB signaling
p53	GO:0030330	DNA damage response, signal transduction by p53 class mediator
PI3K	GO:0014065	phosphatidylinositol 3-kinase signaling
TNFa	GO:0033209	tumor necrosis factor-mediated signaling pathway
TGFb	GO:0007179	transforming growth factor beta receptor signaling pathway
Trail	GO:0036462	TRAIL-activated apoptotic signaling pathway
VEGF	GO:0038084	vascular endothelial growth factor signaling pathway

(b) Reactome and Pathifier. Listed are reactome pathway names that were used either for GSVA pathway scores or Pathifier scores using the respective R packages. If more than one pathway is listed all of them were used in the gene set.

Pathway	Name
2*EGFR	Signaling by EGFR
	Signaling by EGFR in Cancer
Hypoxia	Cellular response to hypoxia
3*JAK-STAT	Signaling by Interleukins
	Interferon Signaling
	Signalling to STAT3
MAPK	Signalling to ERKs
2*NFkB	TAK1 activates NFkB:w: by phosphorylation and activation of IKKs complex
	RIP-mediated NFkB activation via ZBP1
p53	Transcriptional Regulation by TP53
4*PI3K	PI3K Cascade
	Constitutive Signaling by Aberrant PI3K in Cancer
	PI3K/AKT Signaling in Cancer
	PI3K/AKT activation
TNFa	TNF signaling
TGFb	Signaling by TGF-beta Receptor Complex
Trail	TRAIL signaling
VEGF	Signaling by VEGF

(c) Signaling Pathway Impact Analysis. KEGG pathway IDs and names that SPIA relies on are listed (this is part of the SPIA R package).

2*Pathway	SPIA	
	ID	Name
EGFR	04012	ErbB signaling pathway
Hypoxia	-	-
JAK-STAT	04630	Jak-STAT signaling pathway
MAPK	04010	MAPK signaling pathway
NFkB	04064	NF-kappa B signaling pathway
p53	-	-
PI3K	04150	mTOR signaling pathway
TNFa	-	-
TGFb	04350	TGF-beta signaling pathway
Trail	04210	Apoptosis
VEGF	04370	VEGF signaling pathway

(d) PARADIGM. This method is different as it performs inference on a signaling network instead of providing pathways itself. We used the network the TCGA is using in their analyses[1]. This network has activity nodes for pathways and important processes that we used here, as listed.

Pathway	PARADIGM
EGFR	epidermal growth factor receptor activity (abstract)
Hypoxia	response to hypoxia (abstract)
JAK-STAT	STAT-1-3-5-active
MAPK	MEK-1-2-active
NFkB	NFkB Complex (complex)
p53	response to DNA damage stimulus (abstract)
PI3K	PIK3CA
TNFa	tumor necrosis factor receptor activity (abstract)
TGFb	SMAD1-5-8-active
Trail	induction of apoptosis (abstract)
VEGF	platelet-derived growth factor receptor activity (abstract)

(e) Signatures published and validated in Gatza et al. (2009)

Pathway	Gatza (2009)
EGFR	EGFR
Hypoxia	HYPOXIA
JAK-STAT	STAT1, STAT3, IFNA, IFNG
MAPK	PROLIFERATION, PROLIFERATION (PAM50)
p53	P53, P53 MUT/P53 WT CORR
PI3K	PI3K, PIK3CA
TNFa	TNFA
TGFb	TGFB
VEGF	VEGF/HYPOXIA

Supplementary Table 3: FDR-adjusted p-values for mutation/copy number associations with pathway scores obtained by PROGENy. Associations using TCGA data corrected for cancer type. Mutated genes included in table if any method has FDR $< 10^{-7}$, copy number alterations for related genes (e.g. ERBB2_amp for EGFR).

Method	Subset	EGFR	Hypoxia	JAK.STAT	MAPK	NFkB	p53	PI3K	TGFb	TNFa	Trail	VEGF
Gene Ontology	ARID1A	n.s.	n.s.	n.s.	n.s.	n.s.	1.6e-07	n.s.	n.s.	n.s.	n.s.	n.s.
Pathifier	ARID1A	n.s.	n.s.	2.7e-09	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Iorio (2016)	ARID1A	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	3.0e-04	n.s.	n.s.	n.s.	n.s.
PROGENy	ASH1L	n.s.	7.3e-04	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Reactome	ASH1L	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	4.4e-04	n.s.	n.s.	n.s.
Iorio (2016)	ASH1L	9.6e-08	n.s.	n.s.	4.4e-06	n.s.	n.s.	1.6e-05	n.s.	n.s.	n.s.	n.s.
Gatza (2009)	ASH1L	n.s.	1.5e-04	n.s.	n.s.	n.s.	n.s.	5.2e-08	n.s.	n.s.	n.s.	5.1e-04
PROGENy	BRAF	1.3e-11	n.s.	7.3e-04	1.1e-18	4.8e-16	n.s.	n.s.	n.s.	2.1e-17	n.s.	n.s.
Gene Ontology	BRAF	3.8e-04	n.s.	1.6e-13	3.3e-07	n.s.	3.2e-08	1.9e-08	n.s.	1.2e-04	1.3e-10	n.s.
Reactome	BRAF	n.s.	n.s.	6.2e-18	1.3e-09	1.4e-13	n.s.	n.s.	n.s.	n.s.	1.8e-10	4.5e-04
SPIA	BRAF	n.s.	n.s.	3.0e-04	3.0e-04	1.5e-05	n.s.	n.s.	n.s.	n.s.	2.6e-04	n.s.
Pathifier	BRAF	1.3e-07	5.1e-04	n.s.	n.s.	1.7e-07	n.s.	1.7e-07	n.s.	8.3e-04	1.0e-08	1.6e-15
PARADIGM	BRAF	n.s.	n.s.	n.s.	3.0e-06	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Iorio (2016)	BRAF	9.7e-05	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	6.1e-09	n.s.	n.s.
Gatza (2009)	BRAF	2.5e-12	n.s.	8.6e-20	3.0e-04	n.s.	n.s.	1.4e-07	n.s.	3.0e-18	n.s.	n.s.
Gatza (2009)	BRAF_amp	n.s.	n.s.	n.s.	1.8e-04	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
PROGENy	CDH1	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	1.3e-09	n.s.	n.s.	n.s.	n.s.
Gene Ontology	CDH1	n.s.	n.s.	n.s.	n.s.	1.0e-08	n.s.	2.3e-04	n.s.	n.s.	n.s.	n.s.
Reactome	CDH1	n.s.	n.s.	n.s.	n.s.	n.s.	3.3e-07	n.s.	1.0e-07	n.s.	n.s.	n.s.
SPIA	CDH1	n.s.	n.s.	9.4e-06	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Pathifier	CDH1	n.s.	4.5e-04	n.s.	n.s.	n.s.	3.8e-07	n.s.	n.s.	n.s.	n.s.	n.s.
Iorio (2016)	CDH1	n.s.	n.s.	n.s.	1.7e-06	n.s.	n.s.	1.6e-06	n.s.	n.s.	n.s.	6.4e-08
Gatza (2009)	CDH1	n.s.	n.s.	n.s.	6.9e-13	n.s.	n.s.	2.0e-11	n.s.	n.s.	n.s.	1.9e-05
SPIA	CTNNB1	n.s.	n.s.	n.s.	1.5e-05	n.s.	n.s.	n.s.	3.8e-06	n.s.	n.s.	n.s.
Pathifier	CTNNB1	3.9e-13	n.s.	n.s.	n.s.	n.s.	n.s.	2.4e-28	n.s.	n.s.	n.s.	n.s.
PROGENy	EGFR_amp	2.6e-10	2.3e-04	n.s.	4.4e-20	2.3e-04	n.s.	n.s.	n.s.	9.4e-05	n.s.	3.6e-06
Gene Ontology	EGFR_amp	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	9.4e-05	n.s.
Reactome	EGFR_amp	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	8.9e-05	n.s.	n.s.
SPIA	EGFR_amp	4.7e-12	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Gatza (2009)	EGFR_amp	n.s.	n.s.	n.s.	1.7e-06	n.s.	4.2e-06	3.9e-04	n.s.	n.s.	n.s.	8.2e-09
PROGENy	ERBB2_amp	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	6.0e-05	n.s.
Gene Ontology	ERBB2_amp	n.s.	n.s.	2.5e-05	n.s.	1.8e-04	n.s.	n.s.	n.s.	n.s.	2.9e-05	n.s.
Reactome	ERBB2_amp	n.s.	n.s.	n.s.	n.s.	n.s.	6.1e-04	n.s.	n.s.	n.s.	n.s.	n.s.
SPIA	ERBB2_amp	n.s.	n.s.	n.s.	1.1e-10	5.1e-11	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Iorio (2016)	ERBB2_amp	n.s.	n.s.	1.4e-05	2.6e-13	n.s.	n.s.	8.1e-06	2.0e-05	n.s.	n.s.	n.s.
Gatza (2009)	ERBB2_amp	n.s.	n.s.	n.s.	5.3e-16	n.s.	1.4e-07	1.1e-06	n.s.	n.s.	n.s.	n.s.
Reactome	GATA3	n.s.	n.s.	n.s.	n.s.	n.s.	4.4e-04	n.s.	n.s.	n.s.	n.s.	n.s.
SPIA	GATA3	n.s.	n.s.	n.s.	1.3e-06	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Iorio (2016)	GATA3	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	4.7e-05	n.s.	n.s.	n.s.	n.s.
Gatza (2009)	GATA3	n.s.	n.s.	n.s.	n.s.	n.s.	3.3e-13	n.s.	n.s.	n.s.	n.s.	n.s.
Reactome	KEAP1	n.s.	n.s.	n.s.	n.s.	n.s.	3.2e-05	n.s.	n.s.	n.s.	n.s.	n.s.
Pathifier	KEAP1	n.s.	n.s.	n.s.	n.s.	n.s.	6.1e-19	n.s.	n.s.	n.s.	n.s.	n.s.
Iorio (2016)	KEAP1	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	1.7e-06	n.s.	n.s.	n.s.	n.s.
PROGENy	KRAS	1.3e-09	n.s.	n.s.	5.4e-11	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Reactome	KRAS	n.s.	5.5e-04	n.s.	n.s.	n.s.	n.s.	n.s.	1.3e-04	n.s.	n.s.	n.s.
Gatza (2009)	KRAS	4.6e-04	5.3e-04	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
PROGENy	KRAS_amp	2.4e-06	n.s.	n.s.	1.3e-08	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Reactome	KRAS_amp	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	4.3e-04	n.s.	n.s.	n.s.
SPIA	KRAS_amp	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	1.3e-07
Pathifier	KRAS_amp	n.s.	n.s.	n.s.	7.5e-05	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Gatza (2009)	KRAS_amp	n.s.	n.s.	n.s.	3.1e-06	n.s.	8.7e-05	7.5e-04	n.s.	n.s.	n.s.	n.s.
PROGENy	NFE2L2	n.s.	n.s.	n.s.	n.s.	n.s.	1.1e-09	n.s.	n.s.	n.s.	n.s.	n.s.
Reactome	NFE2L2	n.s.	n.s.	n.s.	n.s.	n.s.	4.8e-11	n.s.	n.s.	n.s.	n.s.	n.s.
PROGENy	NRAS	2.2e-04	n.s.	n.s.	n.s.	2.8e-05	n.s.	n.s.	n.s.	3.6e-07	n.s.	n.s.
Gene Ontology	NRAS	n.s.	n.s.	1.2e-08	2.8e-05	n.s.	n.s.	9.4e-05	n.s.	n.s.	7.7e-06	n.s.
Reactome	NRAS	n.s.	n.s.	8.4e-10	n.s.	5.5e-05	n.s.	7.2e-04	n.s.	n.s.	2.1e-04	n.s.
SPIA	NRAS	n.s.	n.s.	6.2e-04	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Pathifier	NRAS	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	1.3e-05
Gatza (2009)	NRAS	2.4e-06	n.s.	1.7e-11	n.s.	n.s.	n.s.	n.s.	n.s.	1.4e-08	n.s.	n.s.
PROGENy	PIK3CA	n.s.	n.s.	n.s.	4.3e-05	n.s.	1.8e-07	n.s.	n.s.	n.s.	n.s.	n.s.
Gene Ontology	PIK3CA	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	6.0e-04	n.s.	n.s.	n.s.	n.s.
Gatza (2009)	PIK3CA	n.s.	n.s.	n.s.	1.5e-04	n.s.	3.7e-10	n.s.	n.s.	n.s.	n.s.	3.3e-06
PROGENy	PIK3CA_amp	6.9e-04	2.3e-07	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Gene Ontology	PIK3CA_amp	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	7.5e-07
SPIA	PIK3CA_amp	n.s.	n.s.	n.s.	2.7e-06	3.3e-05	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
PARADIGM	PIK3CA_amp	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	1.2e-142	n.s.	n.s.	n.s.	n.s.
Iorio (2016)	PIK3CA_amp	n.s.	n.s.	2.3e-07	8.7e-12	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Gatza (2009)	PIK3CA_amp	n.s.	n.s.	n.s.	2.2e-28	n.s.	2.3e-21	3.1e-20	n.s.	n.s.	n.s.	7.0e-07
PROGENy	PTEN_del	n.s.	3.4e-07	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Gene Ontology	PTEN_del	n.s.	n.s.	n.s.	n.s.	n.s.	1.6e-05	4.7e-05	n.s.	2.8e-05	n.s.	n.s.
Reactome	PTEN_del	1.4e-06	n.s.	n.s.	n.s.	n.s.	n.s.	6.6e-15	n.s.	n.s.	n.s.	n.s.
Iorio (2016)	PTEN_del	n.s.	n.s.	n.s.	8.5e-07	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Gatza (2009)	PTEN_del	n.s.	n.s.	n.s.	7.9e-16	n.s.	n.s.	8.4e-15	2.2e-04	n.s.	n.s.	2.0e-09
Gatza (2009)	RB1	n.s.	n.s.	n.s.	5.4e-10	n.s.	n.s.	2.8e-11	n.s.	n.s.	n.s.	n.s.
PROGENy	TP53	n.s.	2.1e-17	2.7e-05	1.5e-07	3.9e-04	5.2e-65	2.4e-21	n.s.	3.7e-04	n.s.	n.s.
Gene Ontology	TP53	n.s.	7.7e-04	n.s.	6.6e-05	6.2e-13	n.s.	1.1e-11	n.s.	4.6e-07	n.s.	n.s.
Reactome	TP53	9.3e-04	n.s.	n.s.	n.s.	n.s.	n.s.	1.4e-13	2.5e-08	n.s.	n.s.	n.s.
Pathifier	TP53	8.5e-18	9.4e-13	n.s.	7.5e-05	1.7e-13	n.s.	3.7e-07	n.s.	n.s.	n.s.	3.7e-04
PARADIGM	TP53	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	6.6e-08	n.s.	n.s.	n.s.	n.s.
Iorio (2016)	TP53	n.s.	n.s.	n.s.	2.9e-16	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	6.1e-09
Gatza (2009)	TP53	n.s.	n.s.	n.s.	5.6e-58	n.s.	4.3e-105	1.1e-32	n.s.	n.s.	n.s.	1.3e-56
PROGENy	TP53_del	n.s.	n.s.	n.s.	n.s.	n.s.	3.2e-05	n.s.	n.s.	n.s.	n.s.	n.s.
Iorio (2016)	TP53_del	n.s.	n.s.	n.s.	1.9e-04	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Gatza (2009)	TP53_del	n.s.	n.s.	n.s.	n.s.	n.s.	9.8e-07	n.s.	n.s.	n.s.	n.s.	n.s.

Supplementary Table 4: Stratification statistics: subsets and numbers for figure 4c. Shown is the combination between a mutation/pathway, the number of cell lines, and median drug response in each subset. Subsets are defined by: (1) Whether a mutation is present (mut) or not (wt), or disregarding mutational status (blank). (2) Whether the pathway score is in the top (active) or bottom quartile (inactive), or neither (blank) of the subset defined by mutations.

Treatment	Mutation	Pathway	Number of cell lines	Median DR [log uM]
BRAF + Dabrafenib			756	3.78
BRAF + Dabrafenib		active	189	3.03
BRAF + Dabrafenib		average	378	3.86
BRAF + Dabrafenib		inactive	189	4.18
BRAF + Dabrafenib	mut		75	-1.57
BRAF + Dabrafenib	mut	active	19	-2.55
BRAF + Dabrafenib	mut	inactive	19	2.18
BRAF + Dabrafenib	wt		681	3.93
BRAF + Dabrafenib	wt	active	170	3.70
BRAF + Dabrafenib	wt	inactive	170	4.25
MAPK + AZ628			756	1.97
MAPK + AZ628		active	189	-0.59
MAPK + AZ628		average	378	1.75
MAPK + AZ628		inactive	189	2.75
MAPK + AZ628	mut		222	0.41
MAPK + AZ628	mut	active	56	-0.83
MAPK + AZ628	mut	inactive	56	0.99
MAPK + AZ628	wt		534	2.42
MAPK + AZ628	wt	active	134	1.63
MAPK + AZ628	wt	inactive	134	2.93
MAPK + Trametinib			756	-0.97
MAPK + Trametinib		active	189	-3.11
MAPK + Trametinib		average	378	-0.78
MAPK + Trametinib		inactive	189	1.14
MAPK + Trametinib	mut		222	-3.26
MAPK + Trametinib	mut	active	56	-4.38
MAPK + Trametinib	mut	inactive	56	-0.42
MAPK + Trametinib	wt		534	-0.28
MAPK + Trametinib	wt	active	134	-1.59
MAPK + Trametinib	wt	inactive	134	1.61

Supplementary Table 5: Stratification statistics: significance tests for figure 4c. For the same subsets, results of the Mann-Whitney U test between different quartiles of the pathway score within different subsets defined by mutational status with p-value as indicated. Difference in mutations indicated by wt (wild-type), mut (mutated), or blank (any). Inferred pathway activity is indicated by + (top quartile) − (bottom quartile) or blank (any). Distance reported as a fold change of medians where positive numbers mean more, negative numbers less sensitive.

Treatment	Reference	Comparison	p-value	FC (medians)
MAPK + Trametinib	MAPK_wt	MAPK_mut	4.65e-29	950
MAPK + Trametinib	MAPK-	MAPK+	8.91e-37	17930
MAPK + Trametinib	MAPK-_wt	MAPK+_wt	7.11e-22	1580
MAPK + Trametinib	MAPK-_mut	MAPK+_mut	7.13e-07	9130
MAPK + Trametinib	MAPK-_mut	MAPK+_wt	2.40e-02	15
MAPK + AZ628	MAPK_wt	MAPK_mut	1.03e-14	102
MAPK + AZ628	MAPK-	MAPK+	1.51e-11	2199
MAPK + AZ628	MAPK-_wt	MAPK+_wt	1.84e-04	20
MAPK + AZ628	MAPK-_mut	MAPK+_mut	1.41e-02	65
MAPK + AZ628	MAPK-_mut	MAPK+_wt	2.34e-02	-4
BRAF + Dabrafenib	BRAF_wt	BRAF_mut	1.88e-24	314085
BRAF + Dabrafenib	MAPK-	MAPK+	2.52e-09	14
BRAF + Dabrafenib	MAPK-_wt	MAPK+_wt	9.73e-04	4
BRAF + Dabrafenib	MAPK-_mut	MAPK+_mut	1.40e-01	54026
BRAF + Dabrafenib	MAPK-_mut	MAPK+_wt	3.64e-04	-33

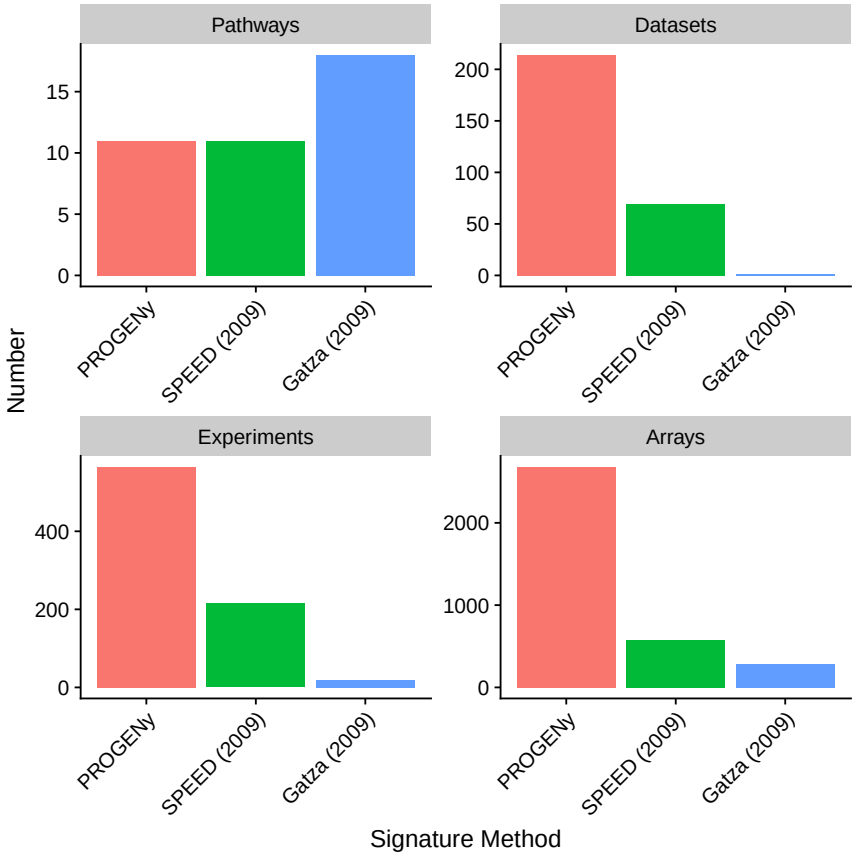
Supplementary Table 6: Validation of significant GDSC associations in the CCLE with overlapping drugs (PD-0325901, AZD6244, and 17-AAG). Effect size is 10-fold drug response per pathway score standard deviation.

Dataset	Drug	Pathway	Effect size	FDR
CCLE	PD-0325901	MAPK	-1.16	1.6e-08
CCLE	PD-0325901	EGFR	-1.16	2.1e-07
CCLE	AZD6244	MAPK	-0.80	3.2e-05
CCLE	17-AAG	EGFR	-0.33	0.033
GDSC	PD-0325901	MAPK	-0.40	8e-05
GDSC	PD-0325901	EGFR	-0.35	0.0017
GDSC	17-AAG	EGFR	-0.29	0.026
GDSC	AZD6244	MAPK	-0.25	0.036

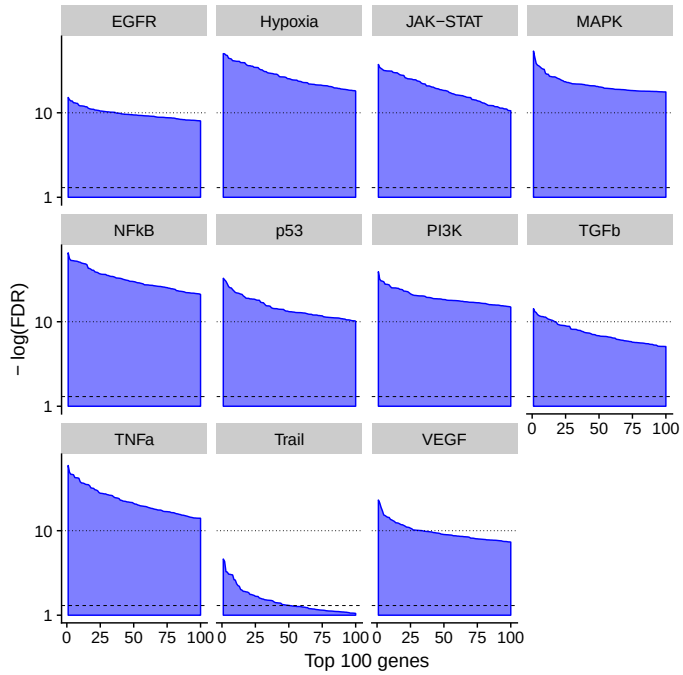
Supplementary Table 7: Stability of the highlighted survival associations across 100 bootstraps (resampling patients within each cohort with replacement). The associations are significant for 93 or more bootstraps and the median p-value is highliy significant.

Cohort	Pathway	Median p-value	# of significance (5% FDR)
ACC	p53	0.00012	98
KIRC	TNFa	6.1e-05	97
LGG	JAK-STAT	0.00029	93

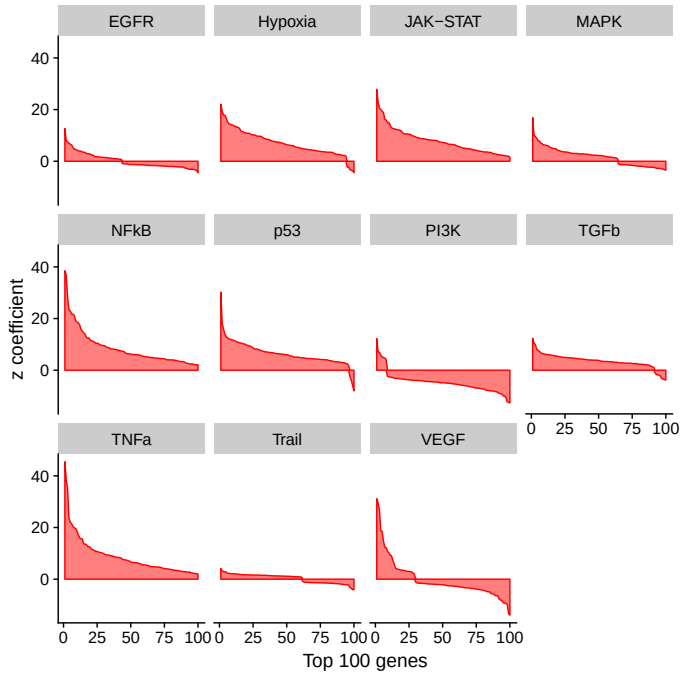
Supplementary Figures



Supplementary Figure 1: Comparison of dataset size between SPEED (data source for Iorio 2016), Gatza (2009), and PROGENy. Gatza et al. derived 18 pathway signatures using only the MCF-10A cell line (thus also 18 experiments), and a total of 287 arrays. In 2014, they included additional signatures from other sources to a total of 53, but some are redundant, others not pathways, and all still limited to breast cancer. SPEED (Parikh et al. 2009) assembled consensus signatures for for 11 pathways using 69 GEO submissions, 215 different conditions and 572 arrays. Our data set consists of 11 pathways, 217 GEO submissions, 568 different experiments and a total of 2687 arrays. This means we use more evidence per pathway and cover a broader set of experimental conditions, but also reflects the imposed limitation of only considering experiments if there are at least two unperturbed arrays available in order to estimate the basal variability. In addition, all our expression values are derived from raw data and not preprocessed data that we can not reproduce.

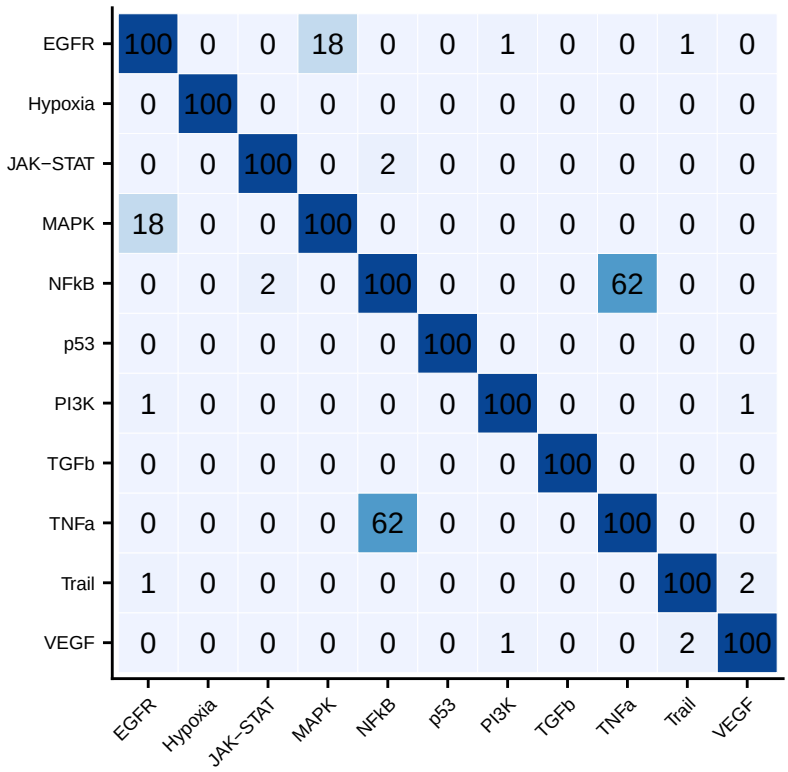


(a) Distribution of FDR-correctd p-values for signature genes (double log). Genes (horizonal axis) are ordered by significance. Dashed line at 5% FDR, dotted line at 10^{-10}

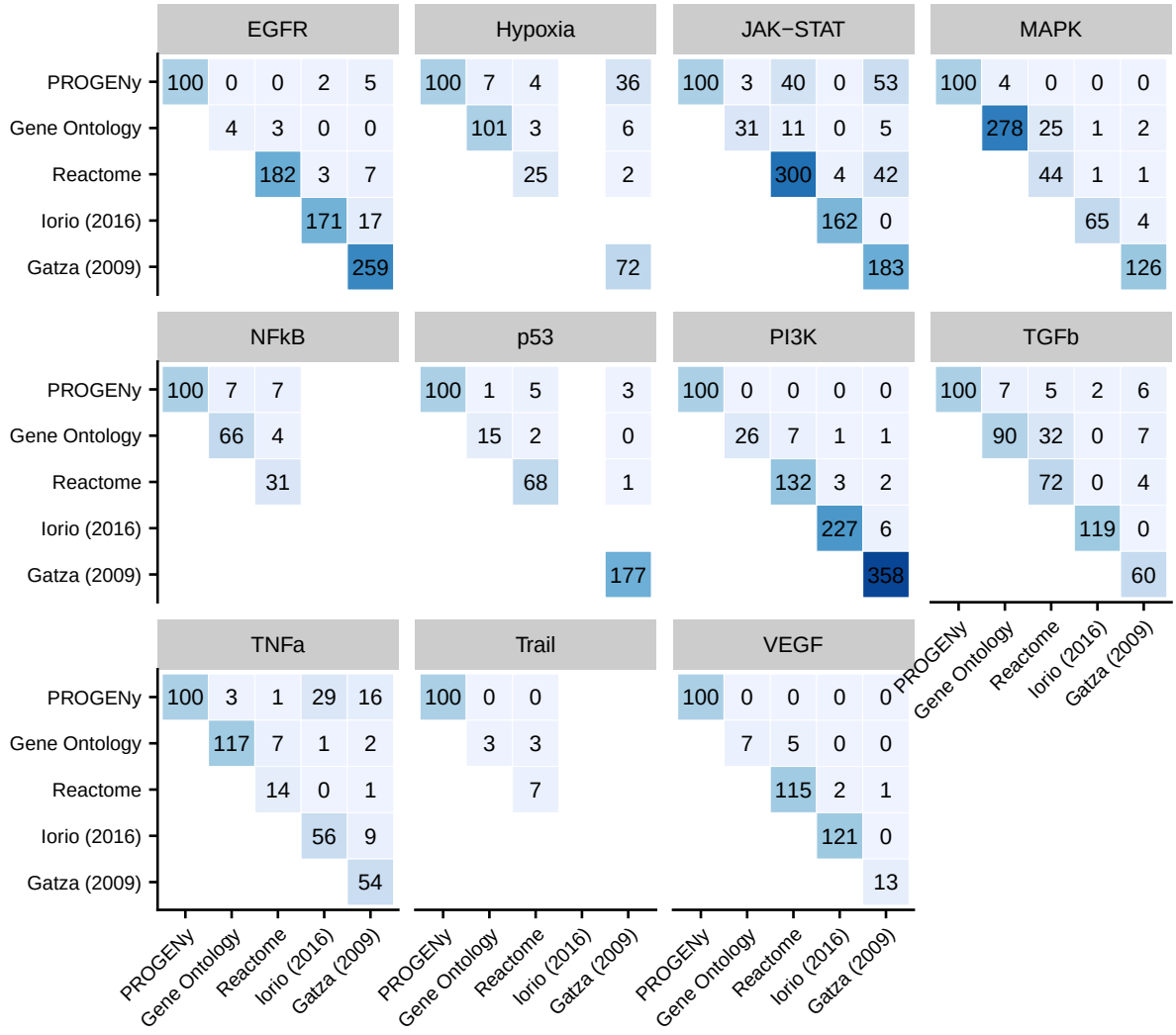


(b) Distribution of z-scores of the top 100 significant genes (different order compared to a). Signature genes are comprised of both up- and downregulated genes for most of the pathways. In no pathway there a single or a few z-scores are high enough to overshadow the rest of the signature, indicating that the model is numerically stable.

Supplementary Figure 2: Distribution of the top 100 genes used in the model, as outcome for the multiple regression of all pathways



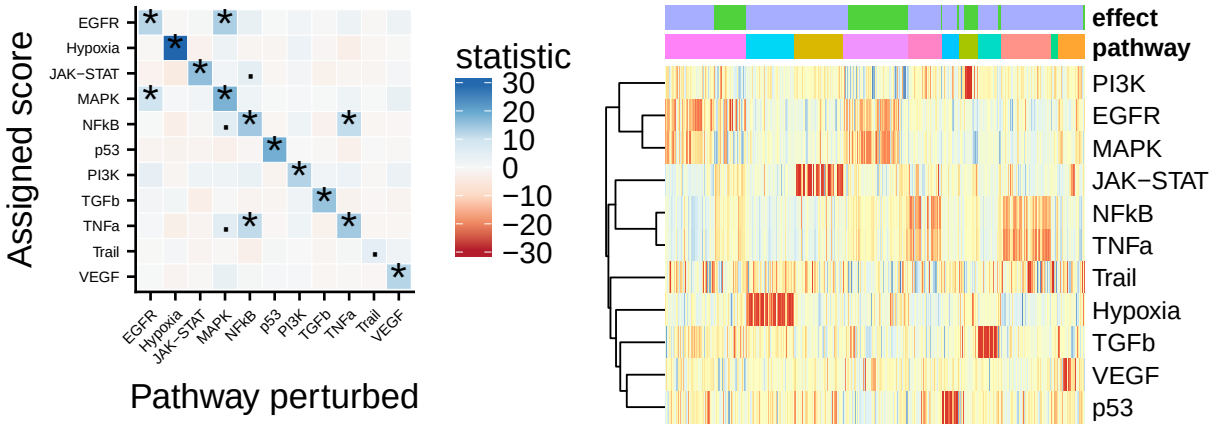
(a) Overlap of signature genes for different pathways. For the 100 genes we selected for each individual pathway, this shows how many of those signature genes are present in another pathway as well. The overlap is generally low, with the highest numbers between TNFa and NFkB (62) and EGFR and MAPK (18). As both of these pathway pairs have one component that is directly upstream of the other, this is to be exptected. This also shows that the response genes are specific to their perturbation and not a common phenotype like stress response because of any perturbation.



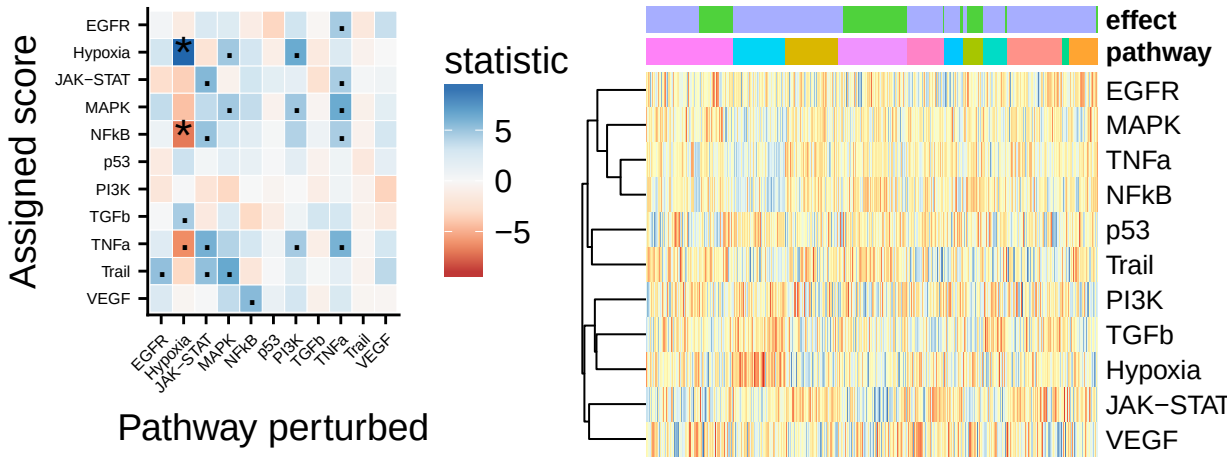
(b) Difference in gene sets between PROGENy genes and Gene Ontology, Reactome (incl. Pathifier), SPEED-derived Iorio (2016) and Gatza (2009). PROGENy genes are different to pathway members and gene annotations, with between 0 and 7 genes in common. Overlap with other signatures is higher, but still a minor fraction of the total number of signature genes.

Supplementary Figure 3: Overlap between different gene sets

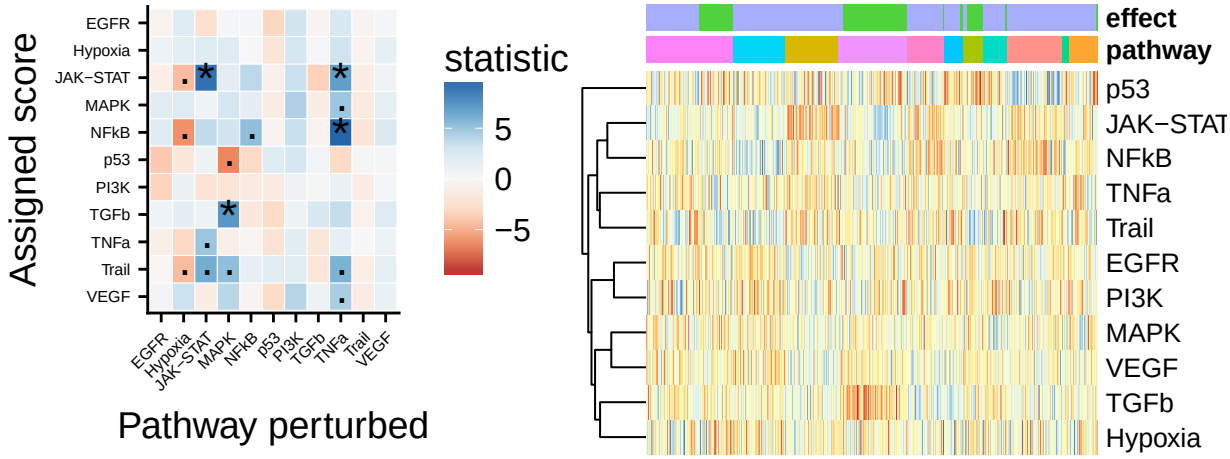
Supplementary Figure 4: Results of a hypergeometric test for enrichment in the overlap between the gene set derived in PROGENy and Gene Ontology categories between 5 and 200 genes in size. Each panel corresponds to one pathway, length of the bars to the negative log10 of the FDR. Top 10 categories are shown for each pathway. Dotted vertical line represents 10% FDR.



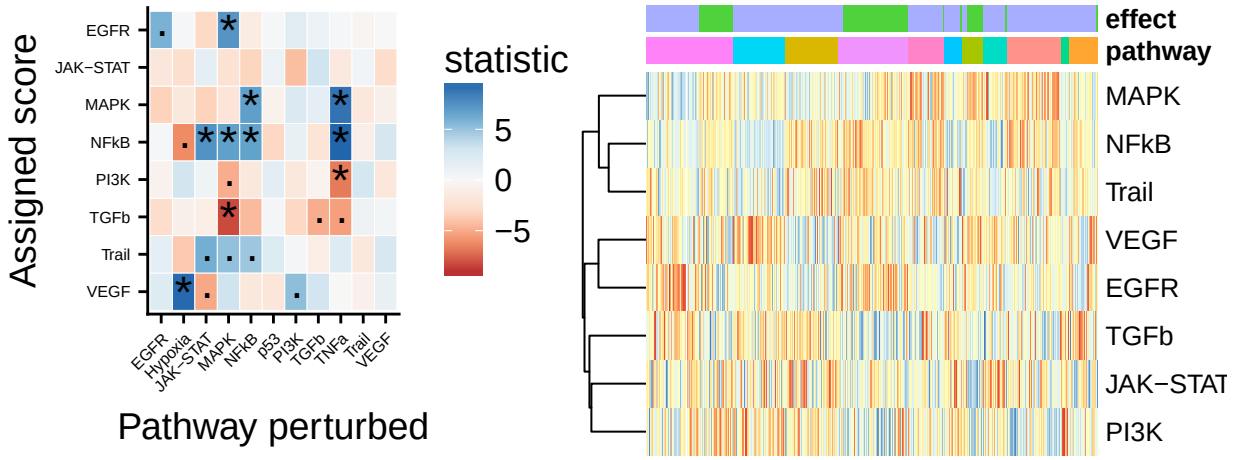
(a) Perturbation-response genes



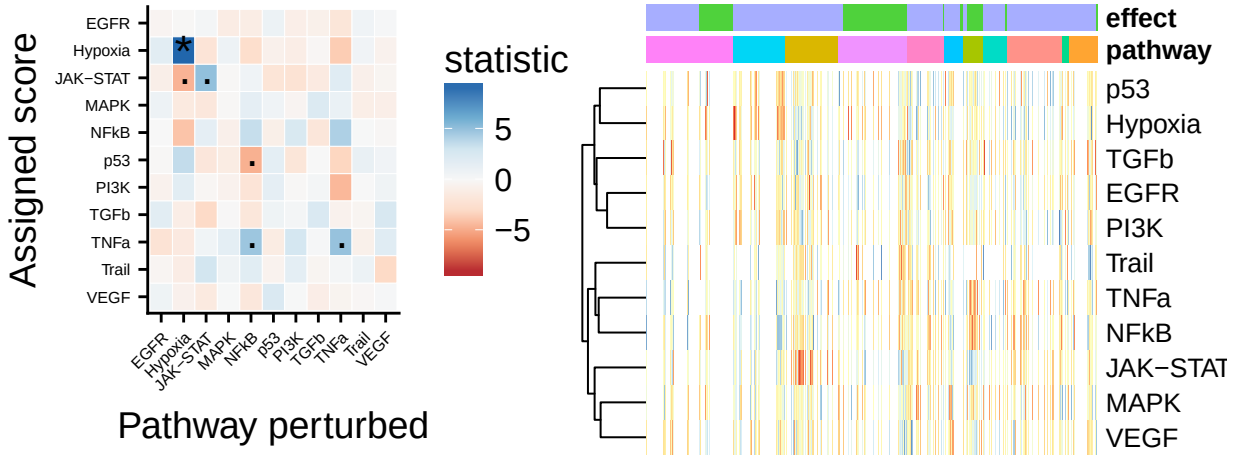
(b) Gene Ontology



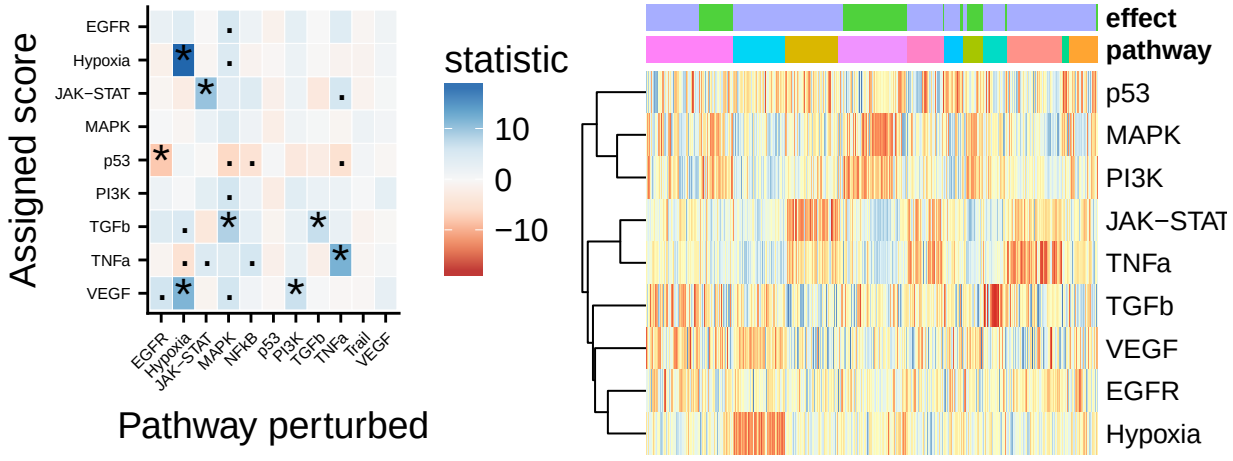
(c) Reactome



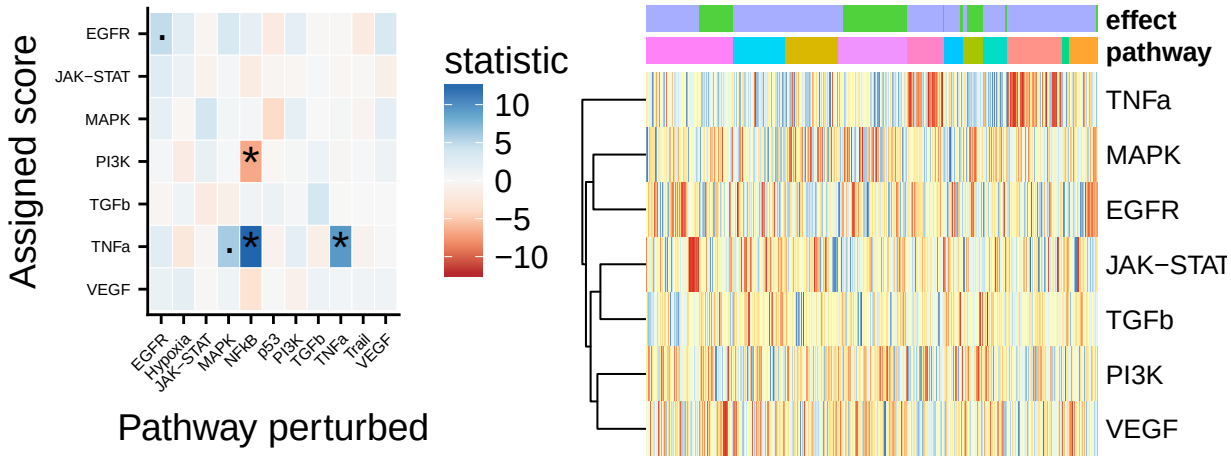
(d) SPIA



(e) Pathifier

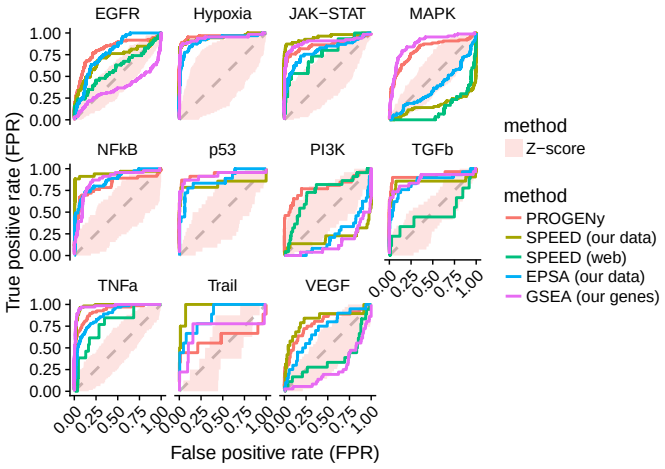


(f) Gatza (2009)

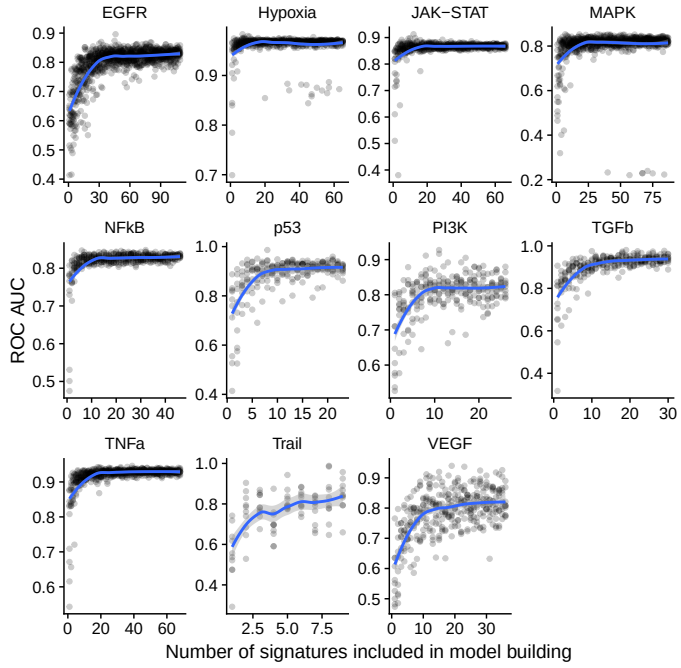


(g) SPEED-derived (Iorio et al., 2016)

Supplementary Figure 5: Distribution of pathway scores for individual experiments (right) and their statistics (left). Right: perturbation experiments on horizontal axis, ordered alphabetically as indicated by color bar for pathways. Effect of a perturbatin on the corresponding pathway is activating (teal) or inhibiting (orange). Cells in the heatmap correspond to relative pathway activation according to pathway scores for different methods. Pathway inhibitions shown in the activating direction (negative inhibition). White cells indicate experiments where we could not derive pathway scores (Pathifier). Left: statistical associations between perturbed pathway and change in scores for all pathway scores given any perturbation. Significance indicated with a dot for $FDR < 10^{-5}$ and a star for $FDR < 10^{-10}$, color grading by Wald statistic. For perturbation-response genes, pathway scores (rows in heatmap) cluster for EGFR/MAPK and to a lesser extent PI3K, as well as TNFa/NFkB, supported by statistical associations. As this was performed on the same set of experiments as was used to create the model, these associations only quantify the amount of cross-activation and heterogeneity in the response, the significance of the model itself is shown in figure 2. It does, however, show that competing pathway methods are for the most part unable to recover perturbed pathways or associate with a different perturbation than the one applied. This highlights that methods based on pathway mapping should only interpreted as either only expression level instead of activity, or potential signal flow as opposed to actual signal flow.



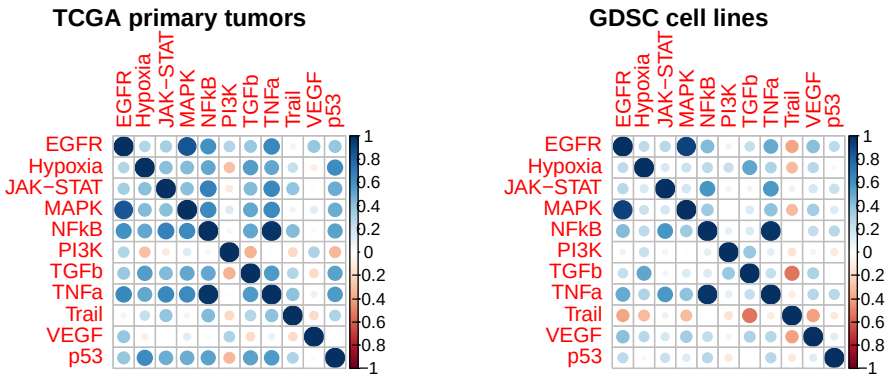
(a) Comparison between PROGENy (linear model of z-scores), SPEED (Fisher's Exact Test for z-scores, where web refers to the web tool at http://speed.sys-bio.net and our data to using an FET on our curated experiments), and EPSA (Spearman correlation between significant median fold changes of the model and the fold changes of each perturbation experiment). Additionally, GSEA (KS-test) using the PROGENy gene list and the highest z-scores of individual experiments (red shade) are shown.



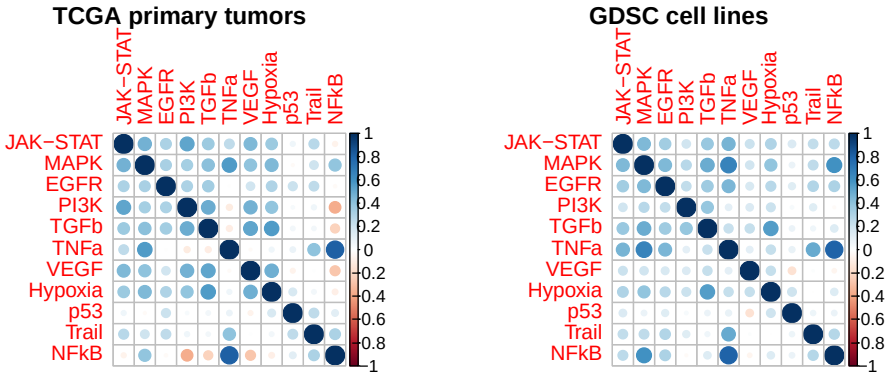
(b) AUC with different number of signatures. The PROGENy model is build limiting each pathway to n signatures. The obtained AUC first increases quickly with few signatures and then levels off between 10 and 40 signatures.

Supplementary Figure 6: ROC curves for different ways to compute consensus models (a) and smaller sets of signatures (b). For each signature, we test if perturbed pathways are ordered before non-perturbed pathways (negative fold changes taken for inhibitions)

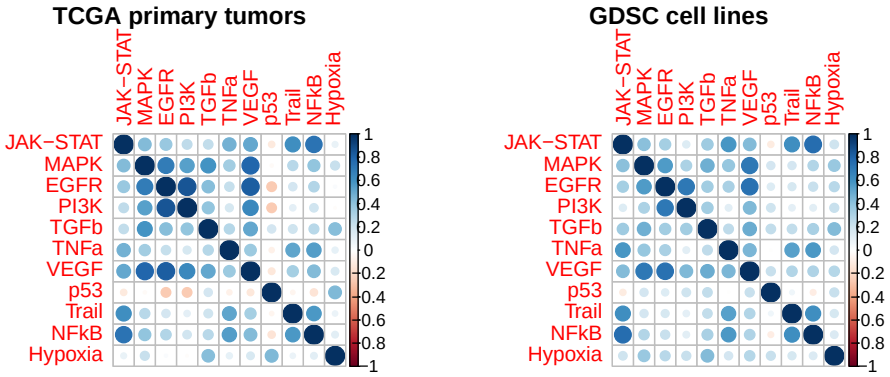
Supplementary Figure 7: Relative pathway activation patterns for activity measurement vs. inference by PROGENy. Data sources (publication DOI in panel title) are experiments where PTMs (mostly Western Blots of pathway drivers) and gene expression were measured in at least duplicate and that were not previously included in model building. Each panel shows a pathway with activity measurement on the left and inferred pathway score on the right. The Y-axis is scaled to a normal distribution and should be used only to compare basal vs. perturbed experiments of the same kind. Difference quantified using a one-tailed t-test. Hinges represent quartiles, whiskers 1.5*IQR.



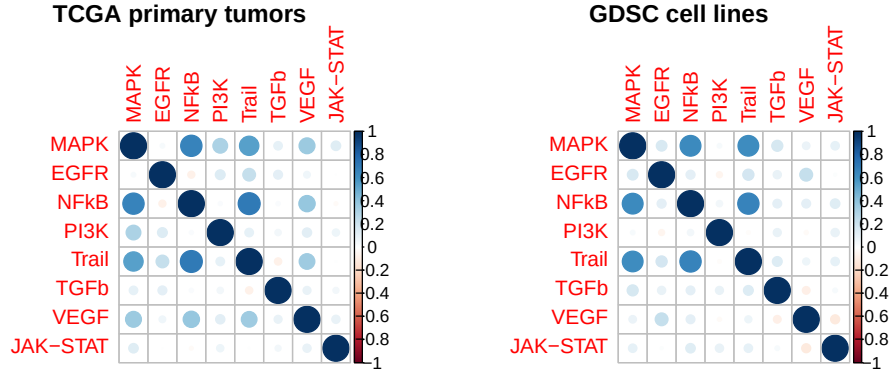
(a) Perturbation-response genes



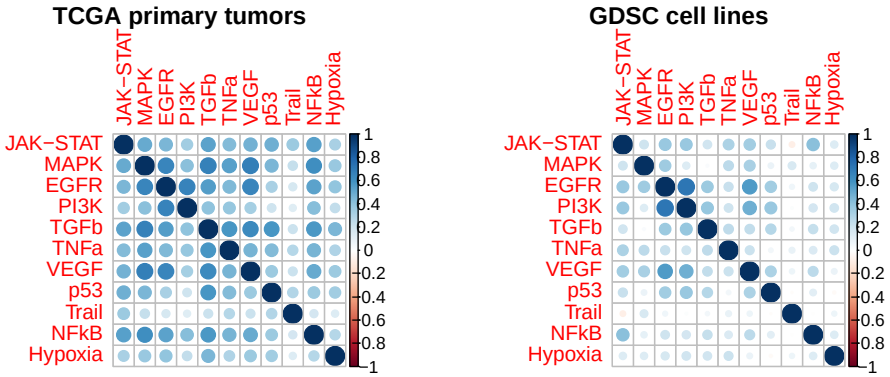
(b) Gene Ontology



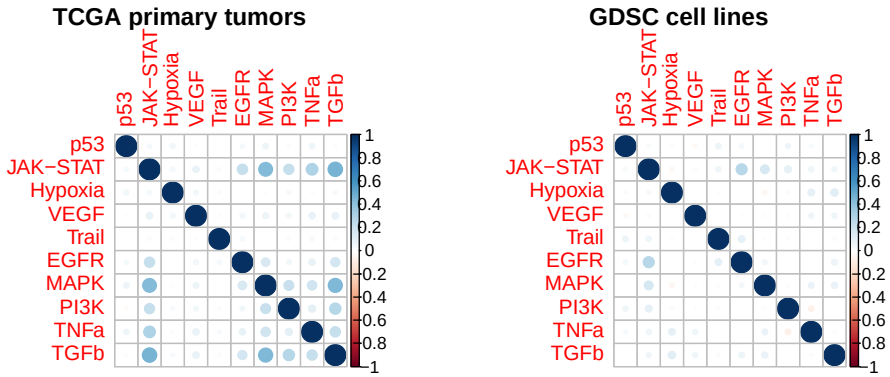
(c) Reactome



(d) SPIA

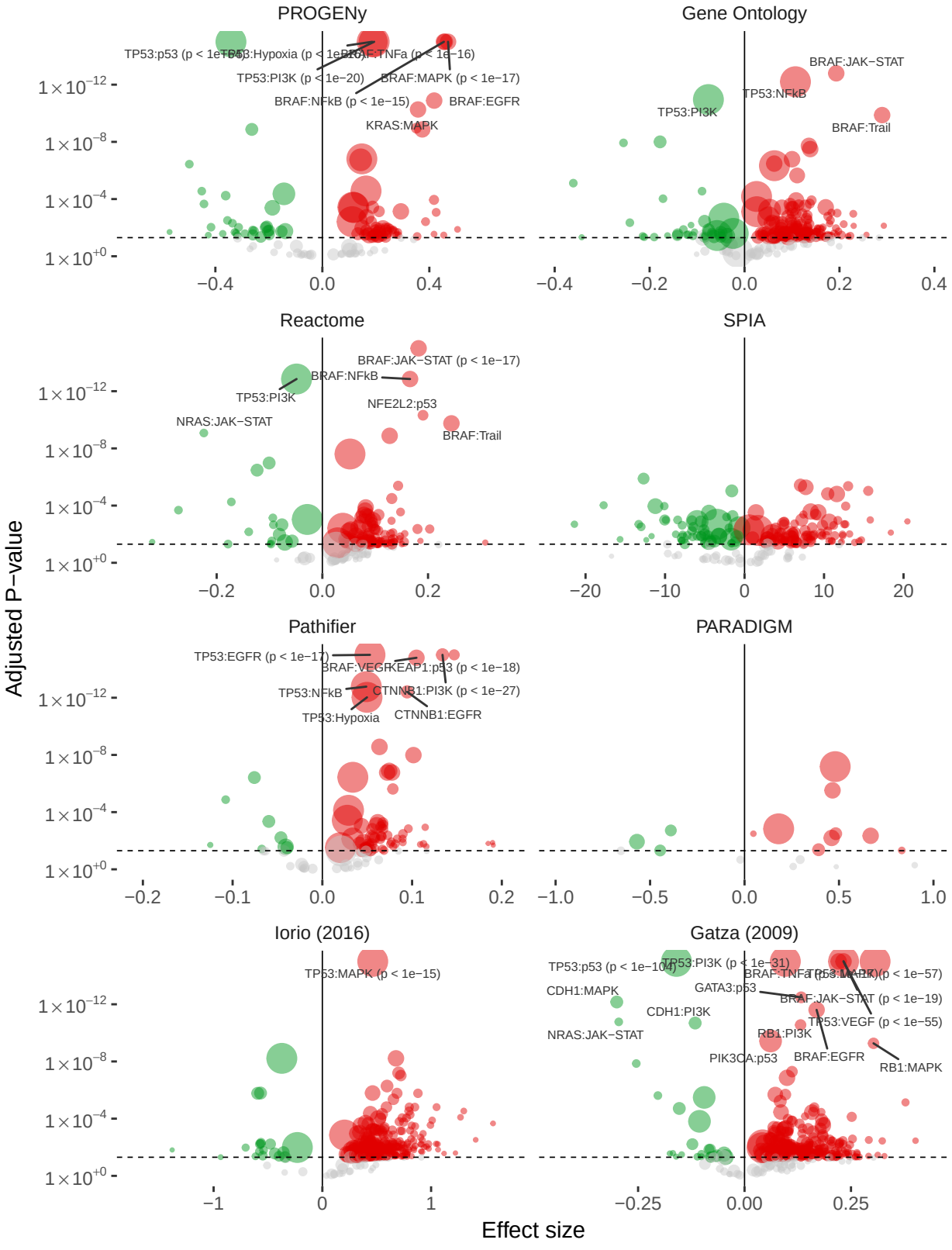


(e) Pathifier

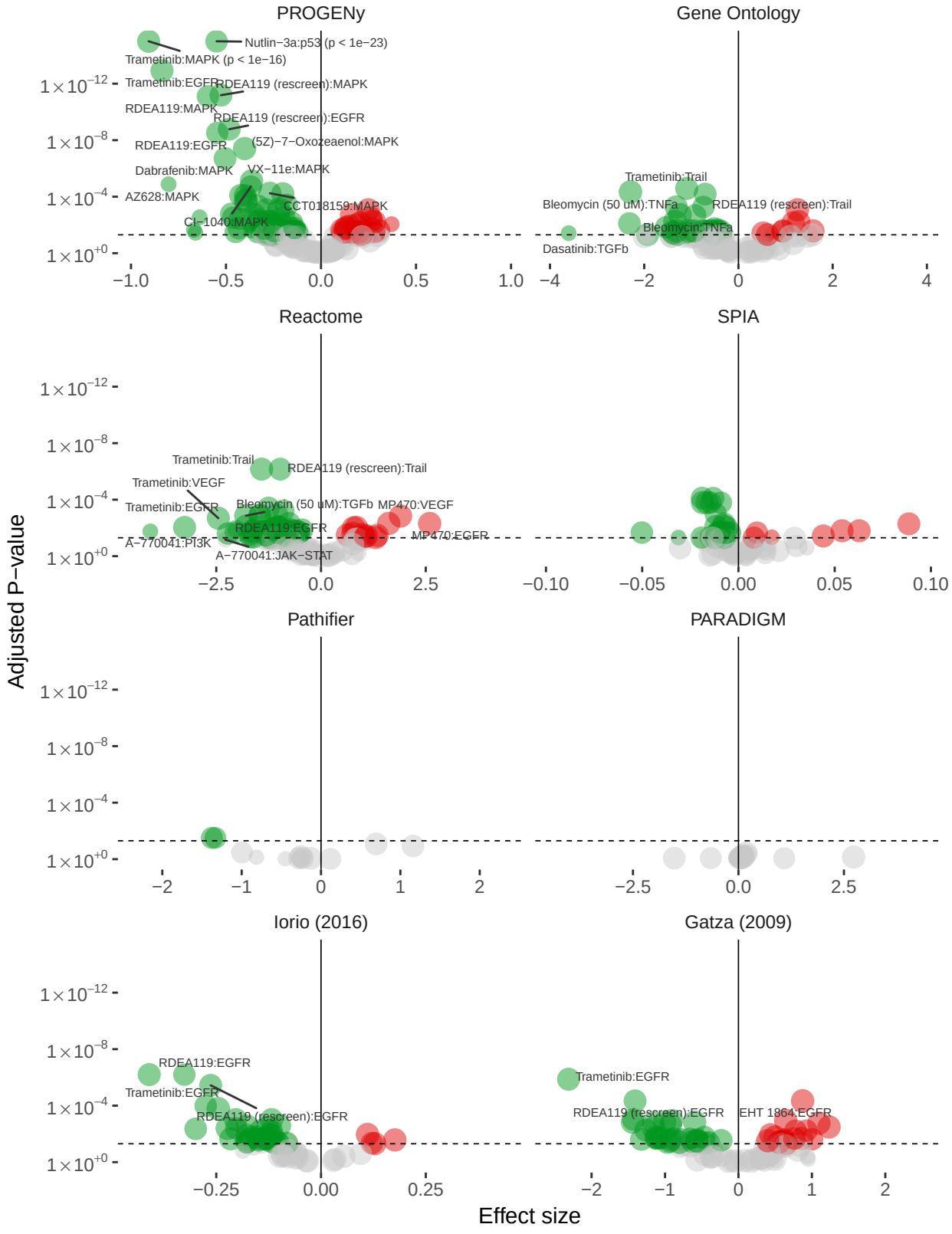


(f) PARADIGM

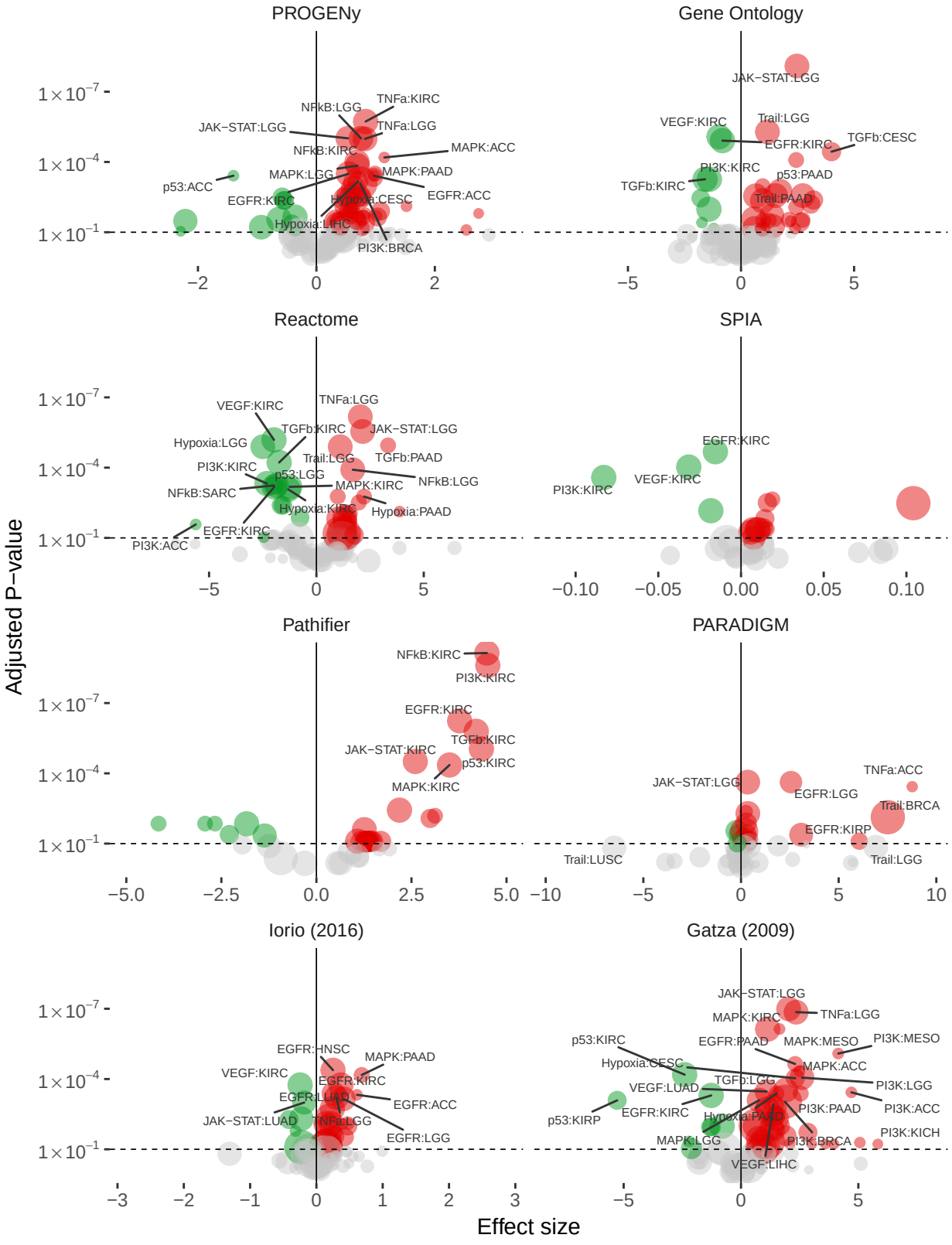
Supplementary Figure 8: Correlation of pathway scores in basal expression of primary tumors in the TCGA (left) and cell lines in the GDSC (right). Perturbation-response genes show similar correlation in basal correlation to cross-activation in the perturbation experiments. Gene Ontology, Reactome and Biocarta show a higher correlation overall, hinting at the fact that transcription of related pathways is less heterogeneous than the post-translational activity they mediate. For those methods, correlations within tumors vs. cell lines look similar. SPIA and Pathifier are less comparable between TCGA and GDSC because these methods require comparison to a reference condition (Tumor normals in the TCGA) that we could only provide by comparing each cell line in the GDSC to the rest of cell lines in that tissue. This makes those correlations less comparable between the two panels for each method. Apart from that, Pathifier shows very high correlation if computing scores against normals, suggesting that this method may not be suitable to differentiate between pathways using TCGA normals. PARADIGM shows almost no correlation between pathways.



Supplementary Figure 9: Volcano plot for associations between pathway scores and mutated driver genes. Effect size is standard deviations of pathway scores. P-values FDR-corrected. Associations corrected for cancer type. PROGENy provides stronger associations and are more in line with literature knowledge of signaling pathways.



Supplementary Figure 10: Volcano plots for associations between pathway scores and drug response (IC50). Effect size arbitrary units, p-values FDR-corrected. Pathway-response genes are the only method to recover highly significant oncogene addiction associations, the rest of methods show no obvious connection between the drug target and pathway.



Supplementary Figure 11: Volcano plots for tissue-specific survival associations. Effect size arbitrary units, p-values FDR-corrected. All methods show strongest associations with KIRC and LGG. Pathway-response genes only method to separate associations into classical oncogenic and tumor suppressor pathways, calling into question the meaning of associations obtained by mapping gene expression on pathway components.

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