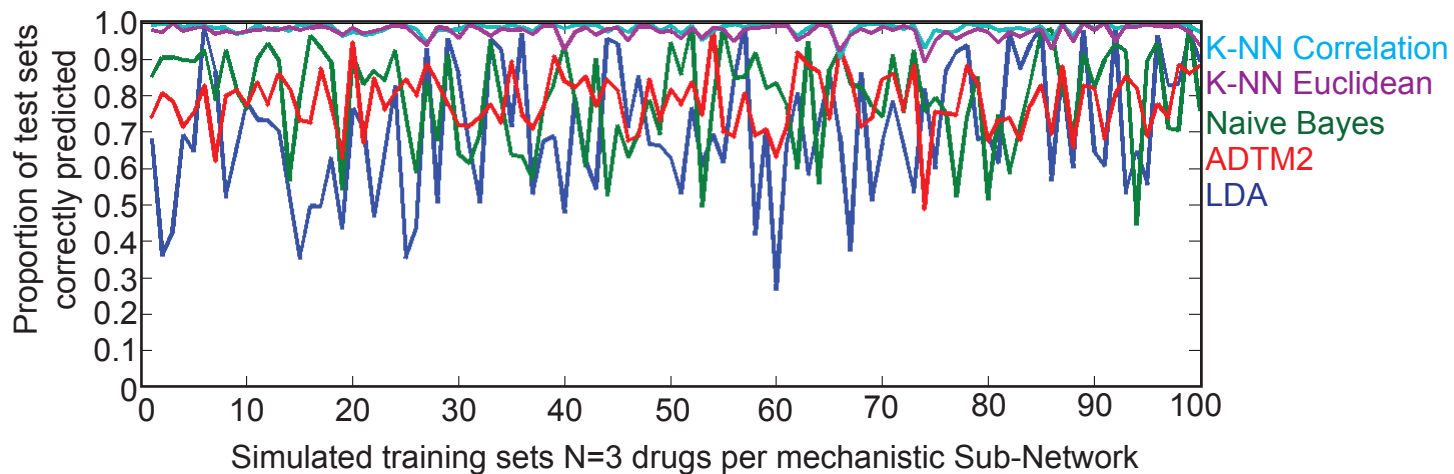
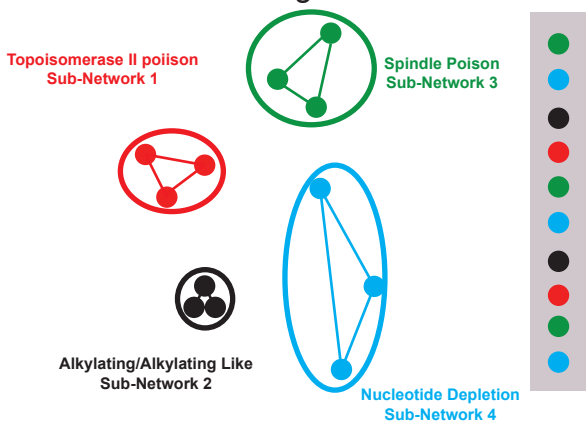
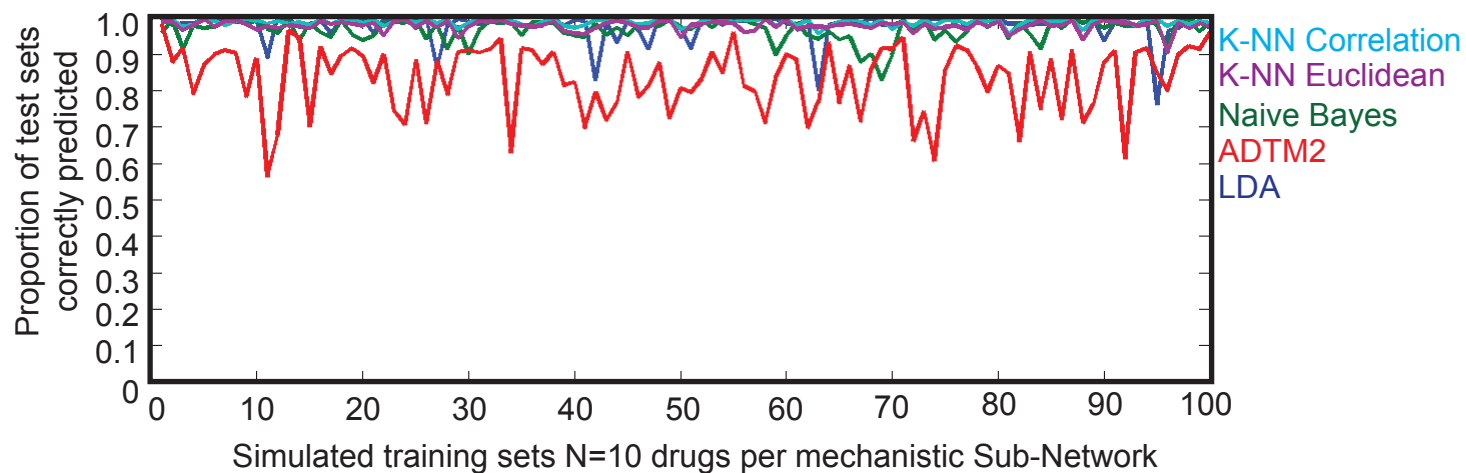
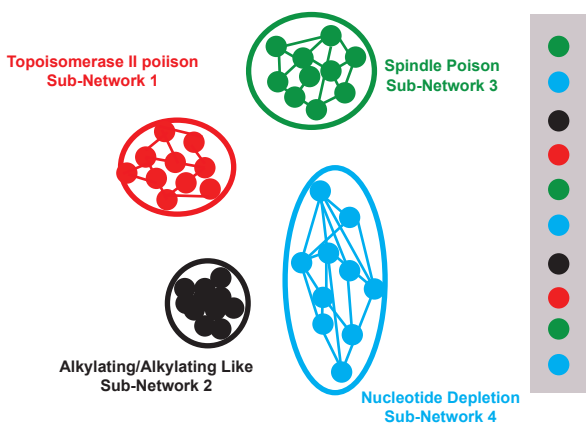


A. 100 training sets 4000 tests



B.



Supplementary Figure 2

A.

Experimental data

Sample 1000 signatures

Examine K-NN performance

shRNAs

p53 CHK2 ATR CHK1 ATX DNAPk Bok Bim

1	3.60839	3.84758	1.48554	-0.6066	-2.0117	-0.9856	-0.8393	1.51548
2	3.16651	3.31814	1.27385	-0.409	-1.6078	-1.0787	-0.9808	1.02093
3	4.10977	3.84127	1.27511	-0.928	-1.7282	-1.5891	-1.0612	1.509
4	4.34083	3.98457	1.61813	-0.7621	-1.5999	-1.1491	-1.8546	1.60586
5	3.44659	3.86095	1.29649	-0.6486	-1.2512	-1.0859	-0.9983	1.29578
6	3.25818	3.42181	1.22761	-0.6854	-1.2082	-0.8873	-1.2761	1.02785
7	3.05087	3.54727	1.1238	-0.5837	-1.3737	-0.8866	-0.9765	1.12415
8	4.23447	3.60448	1.76725	-0.7417	-1.5526	-1.4538	-1.2239	1.40468
9	3.40957	3.5932	1.05013	-0.5673	-1.49	-1.1199	-1.1654	1.29038
10	4.96318	3.76441	1.73976	-0.4676	-1.5295	-1.5665	-1.518	0.87447
11	3.14906	3.18752	1.19048	-0.4896	-1.7144	-1.3578	-0.9822	0.99722
12	3.05888	3.35518	1.05237	-0.416	-2.0251	-1.5694	-1.4531	1.34595
13	4.00981	3.76468	1.45631	-0.2331	-1.2228	-0.6704	-1.5713	2.00625
14	4.15649	3.88842	1.31068	-0.2977	-1.3531	-1.1138	-1.1391	1.57574
15	4.62982	4.04231	1.4296	-0.6189	-0.9416	-1.1331	-1.3126	1.69248
16	3.48605	2.85007	1.58386	-0.603	-1.8156	-1.2075	-1.2031	1.33653
17	3.055	3.70746	1.4831	-0.5055	-1.9038	-1.2441	0.41803	1.52931
18	3.59345	3.56292	1.60352	-0.6096	-1.713	-1.1866	-1.4745	1.92371
19	3.12522	3.09008	1.2302	-0.4843	-0.9395	-1.0115	-1.2222	1.55484
20	3.35574	3.55899	1.17521	-0.5138	-1.8819	-0.8393	-1.4014	1.50516
21	3.87774	4.09366	1.60447	-0.4046	-2.3237	-1.289	-0.9111	1.34783
22	4.09909	3.77594	1.49958	-0.4024	-1.7498	-0.9984	-1.734	1.85383
23	3.76613	4.05482	1.13876	-0.6787	-1.3022	-1.3603	-1.4354	1.79332
24	3.79353	4.00436	1.33831	-0.5904	-1.8075	-1.3349	-1.4591	1.75071
25	4.27434	4.01744	1.48166	-0.4775	-1.7757	-0.9983	-1.5571	1.61698
26	3.31729	2.74764	0.99921	-0.4942	-1.2577	-1.1867	-0.8011	1.46066
27	3.37962	3.57642	0.77466	-0.3995	-1.2632	-1.052	-1.2448	0.71068
28	2.81788	3.6055	0.39597	-0.4701	-0.8636	-1.1932	-1.3933	0.78148
29	2.84306	3.0773	1.08105	-0.5138	-1.1485	-1.0825	-1.2808	0.82327
30	3.63367	3.61039	1.18406	0.06322	-0.9823	-1.0874	-1.0878	0.94469

Replicates of Doxorubicin

plot eCDF for each shRNA
 perform inverse transform sampling
 to generate 1000 simulated signatures

Do this for Dox, Vin, CBL, 5-FU
 and assess performance



log₂(RI)

B.

Inverse Transform Sampled Signature Classification

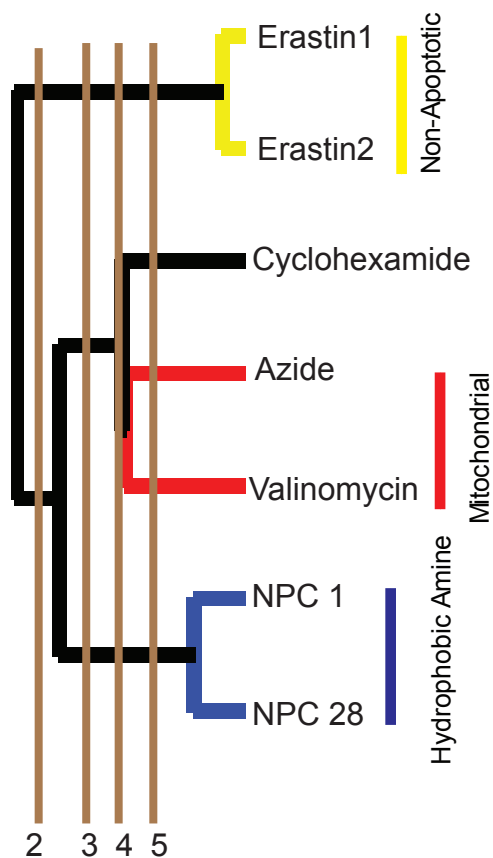
Drugs:	CBL	Vin	Dox	5-FU
Accuracy %	100	98.3	100	99

A.

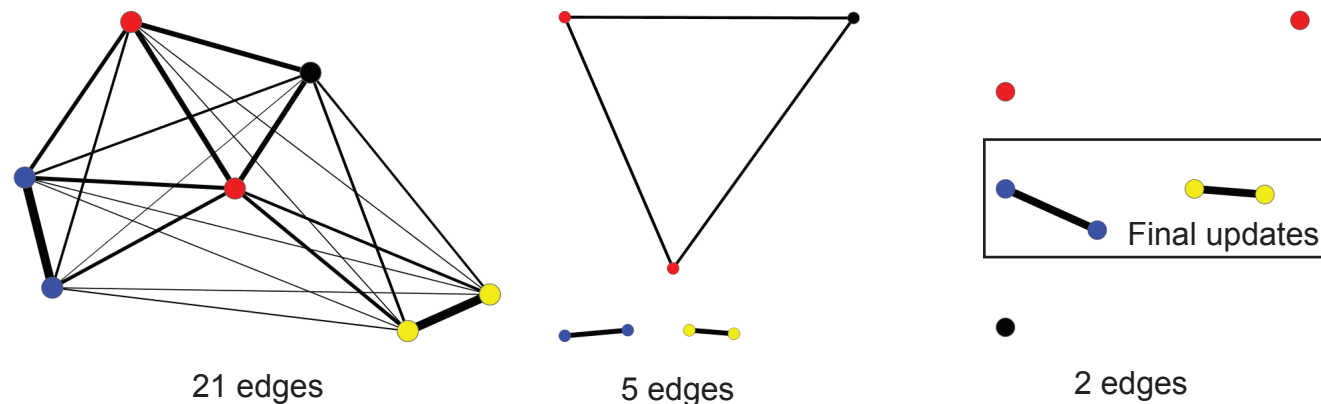
Drugs	Predicted Mechanism	p-val	LR	cutoff 0.1
Azide	"New"	0.71	1.62	
Valinomycin	"New"	0.81	3.13	
NPC1	"New"	0.41	2.28	
NPC28	"New"	0.35	2.35	
Cycloheximide	"New"	0.30	2.22	
Erastin_1	"New"	0.99	3.25	
Erastin_2	"New"	0.99	3.27	

Incorrect
 Correct

B.

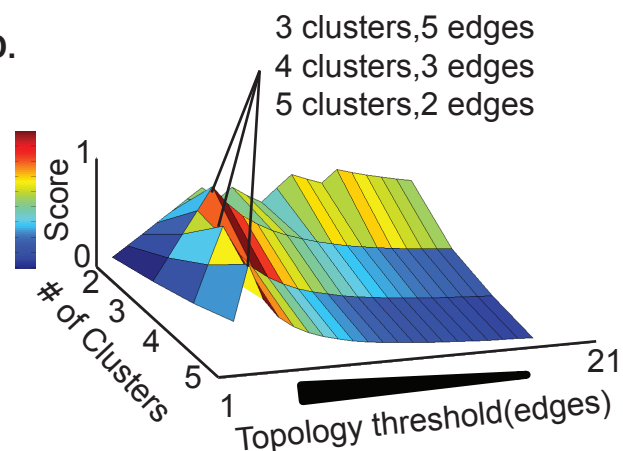


C.



Refine with supervised predictions
 (no support for Azide, Valinomycin, Cyclohexamide)
 Test biological and statistical generalization

D.



E.

Drugs	Predicted Mechanism	p-val	LR	cutoff 0.1	0.05	0.01
NPC25	Spindle Poison	0.000	1.27			
NPC7	Spindle Poison	0.015	1.65			
NPC4	Spindle Poison	0.036	1.77			
Rotenone	Spindle Poison	0.000	1.07			
Podophyllotoxin	Spindle Poison	0.000	1.03			
Scriptaid	HDACi	0.009	0.81			
Mitoxantrone	Topoisomerase II	0.003	0.94			
Lomustine	Alkylating	0.054	1.00			
Bortezomib	Proteasomei	0.034	1.58			
NPC10	Hydphbc. Amine	0.024	0.88			
NPC11	Hydphbc. Amine	0.032	0.95			
NPC20	Hydphbc. Amine	0.099	1.28			
NPC22	Hydphbc. Amine	0.127	1.38			
NPC23	Hydphbc Amine	0.041	1.01			
NPC2	Hydphbc. Amine	0.107	1.31			
RSL3	Non-Apoptotic	0.000	1.26			
Cycloheximide	"New"	0.288	2.22			
Staurosporine	"New"	0.403	2.32			
NPC26	"New"	0.312	2.30			

Incorrect
 Correct

Daurorubicin, MCF7 7507, 7525, 4983 0.08, -0.51							
rank	cmap name	mean	n	enrichment	p	specificity	percent non-null
1	camptothecin	0.619	3	0.999	0E+00	0.0357	100
2	alsterpaulone	0.561	3	0.997	0E+00	0.0058	100
3	GW-8510	0.581	4	0.997	0E+00	0.0166	100
4	daunorubicin	0.842	4	0.988	0E+00	0.0101	100
5	0175029-0000	0.47	6	0.967	0E+00	0.0118	100
6	ellipticine	0.455	4	0.947	0E+00	0.0276	100
7	cephaeline	-0.595	5	-0.909	0E+00	0.0181	100
8	vorinostat	0.334	12	0.851	0E+00	0.0905	100
9	trichostatin A	0.275	182	0.702	0E+00	0.0616	85
10	LY-294002	0.122	61	0.36	0E+00	0.2215	55
11	irinotecan	0.496	3	0.994	2E-05	0.0682	100
12	doxorubicin	0.59	3	0.993	2E-05	0.0168	100
13	azacitidine	0.466	3	0.992	2E-05	0.0096	100
14	mitoxantrone	0.51	3	0.985	4E-05	0	100
15	lycorine	-0.549	5	-0.873	8E-05	0.0067	100
16	digoxigenin	0.292	5	0.867	8E-05	0.0044	100
17	digitoxigenin	0.319	4	0.89	1E-04	0.0286	100
18	etoposide	0.307	4	0.873	4E-04	0.0461	100
19	resveratrol	0.233	9	0.644	4E-04	0.1324	77
20	ouabain	0.277	4	0.851	7E-04	0.0606	100
21	syrosingopine	0.243	4	0.848	8E-04	0.0233	100
22	acetololol	0.155	5	0.792	9E-04	0	80
23	SR-95531	-0.346	4	-0.852	9E-04	0	75
24	emetine	-0.416	4	-0.85	9E-04	0.0588	75
25	withaferin A	0.21	4	0.831	1E-03	0.1	100

B.

Trichostatin A 4112, 2268, 4153 .67, -.67							
rank	cmap name	mean	n	enrichment	p	specificity	percent non-null
1	vorinostat	0.682	12	0.975	0	0.0201	100
2	phenoxybenzamine	0.287	4	0.941	0	0.1337	100
3	trichostatin A	0.629	182	0.914	0	0.0047	98
4	thioridazine	0.19	20	0.585	0	0.137	95
5	valproic acid	0.234	57	0.534	0	0	80
6	LY-294002	0.17	61	0.481	0	0.0738	90
7	tanespimycin	0.163	62	0.387	0	0.1814	80
8	rifabutin	0.696	3	0.978	4E-05	0	100
9	scriptaid	0.625	3	0.976	4E-05	0	100
10	sirolimus	0.149	44	0.345	4E-05	0.2048	77
11	resveratrol	0.246	9	0.702	6E-05	0.0931	100
12	lycorine	-0.497	5	-0.863	8E-05	0.0133	80
13	trifluoperazine	0.191	16	0.525	1E-04	0.1731	87
14	geldanamycin	0.185	15	0.536	2E-04	0.1413	93
15	pioglitazone	-0.346	11	-0.604	3E-04	0.0242	63
16	prochlorperazine	0.166	16	0.492	3E-04	0.1553	81
17	vinblastine	-0.566	3	-0.92	9E-04	0.0305	100
18	CP-690334-01	0.245	8	0.644	1E-03	0.0485	87
19	15-delta prostaglandin J2	0.181	15	0.481	0.001	0.2793	86
20	wortmannin	0.077	18	0.436	0.001	0.2323	50
21	lobelanidine	-0.318	4	-0.843	0.001	0	75
22	MS-275	0.372	2	0.971	0.001	0.052	100
23	pyrvinium	0.19	6	0.694	0.002	0.1256	100
24	cloperastine	0.176	6	0.689	0.002	0.0363	100
25	Chicago Sky Blue 6B	-0.414	4	-0.81	0.003	0.0068	75