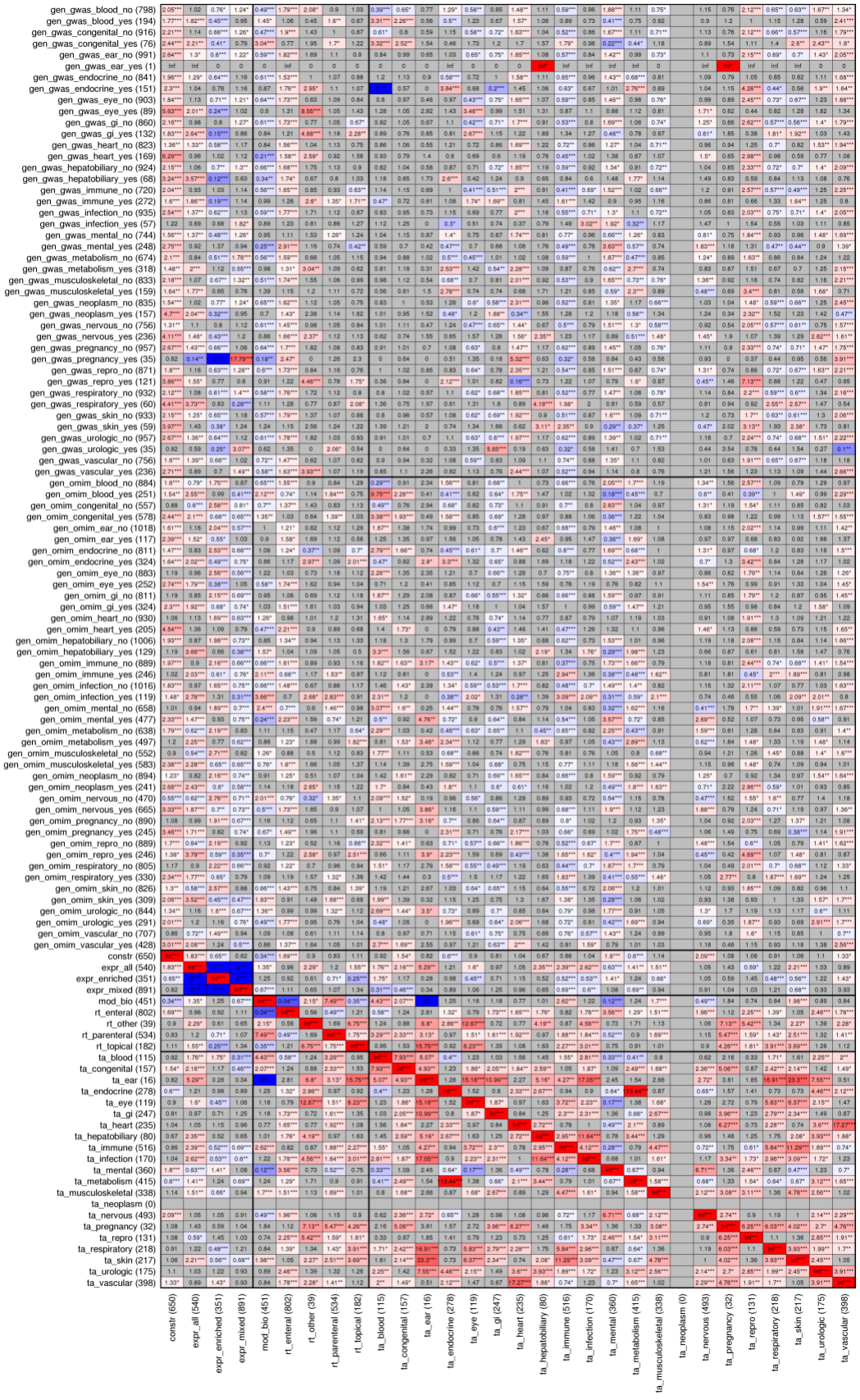
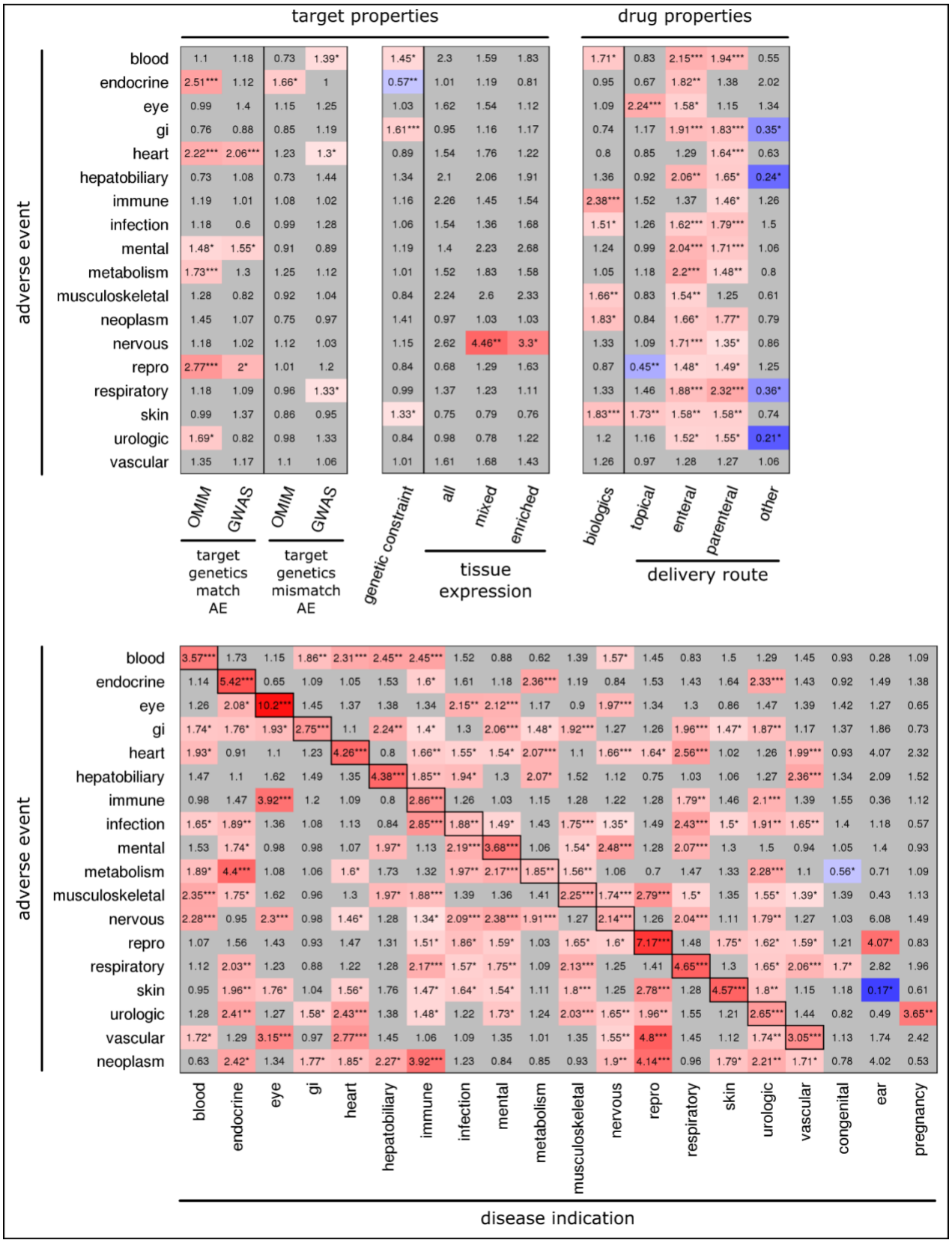
Supplementary Information for

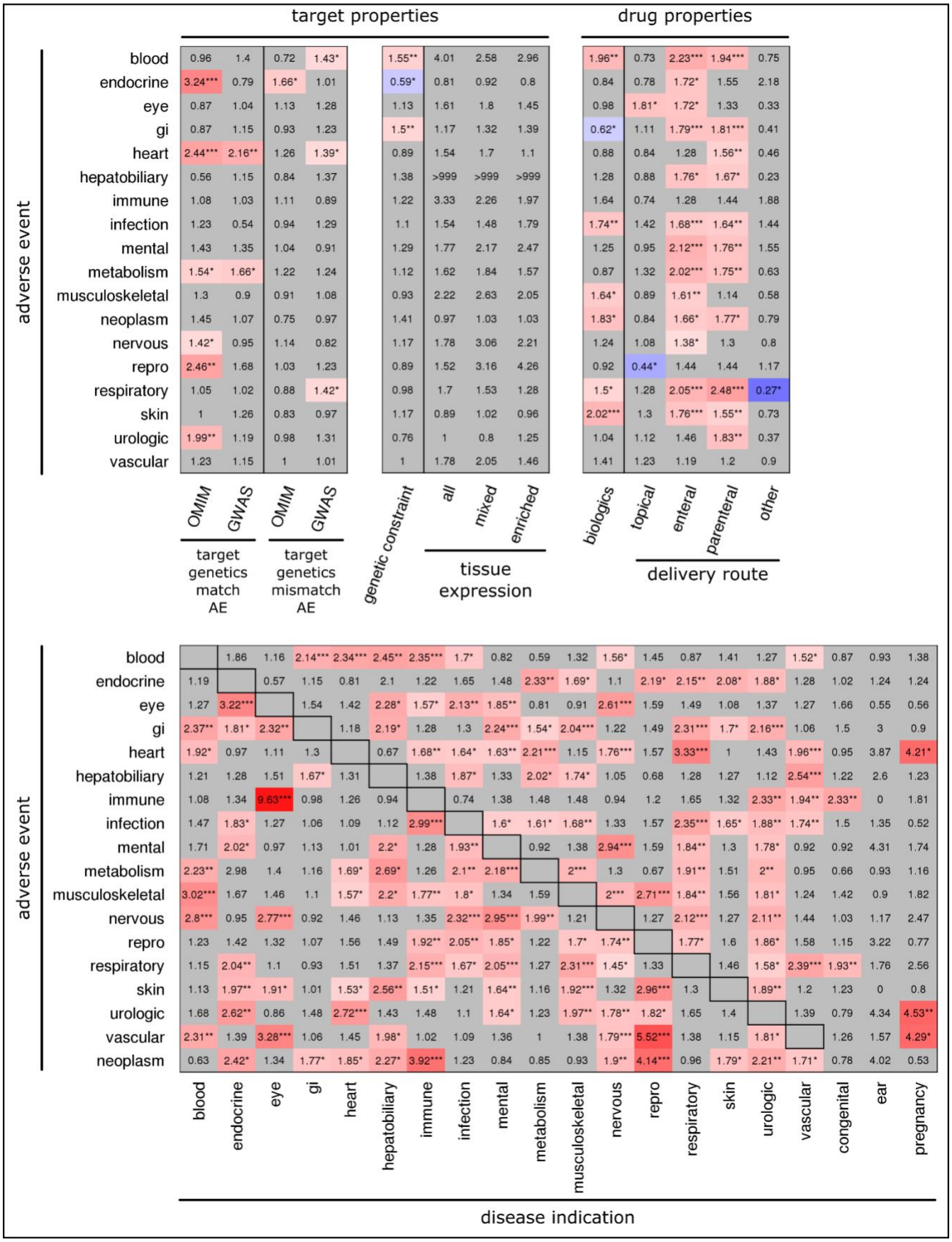
Nguyen et al., “Phenotypes associated with genes encoding drug targets are predictive of clinical trial side effects”



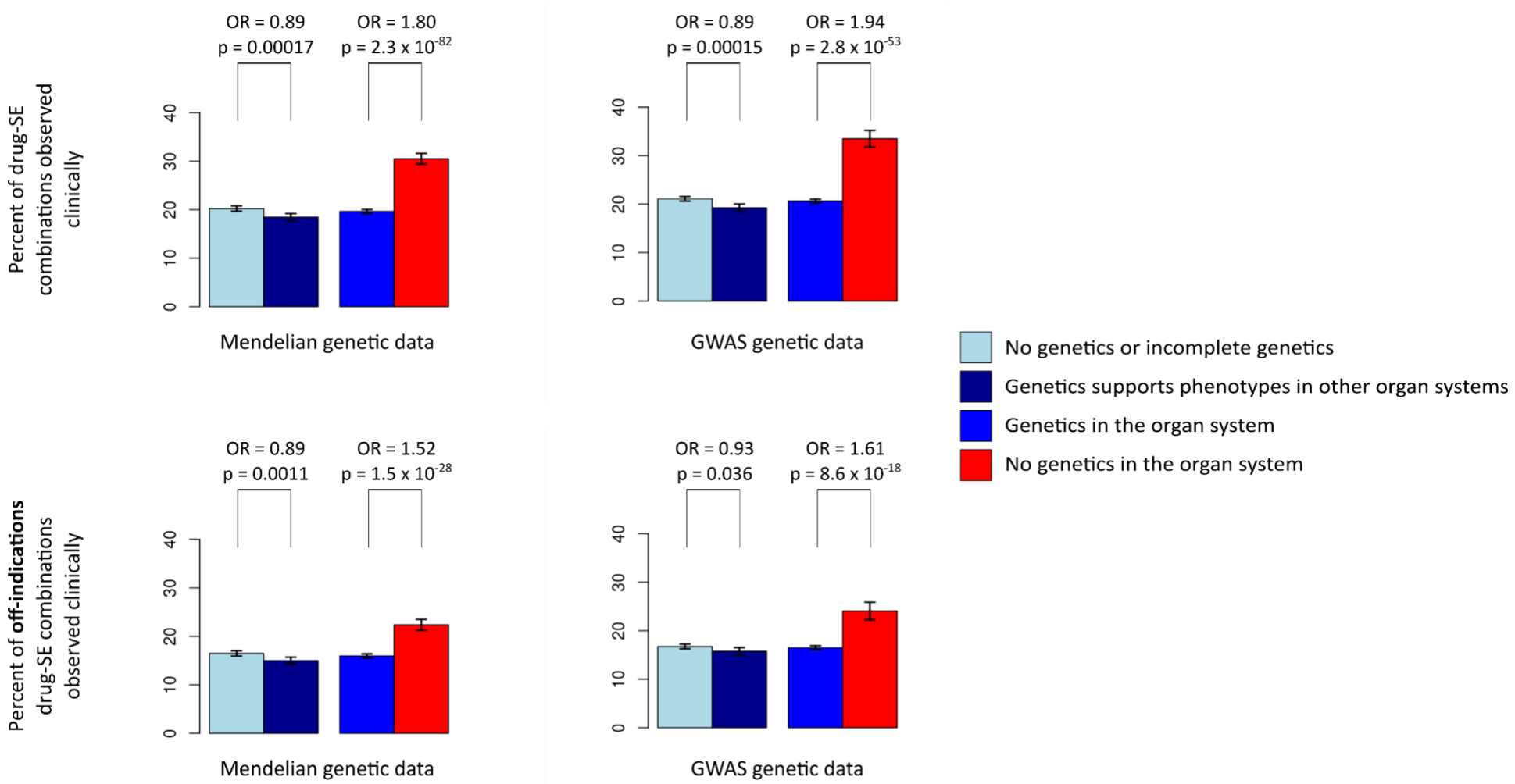
Supplementary Figure 1. Correlation of independent variables in side effect model. All variables are binary; correlations displayed are odds ratios (ORs); asterisks show P-value from Fisher's exact test (*, P < 0.05; **, P < 0.005; ***, P < 0.0005).



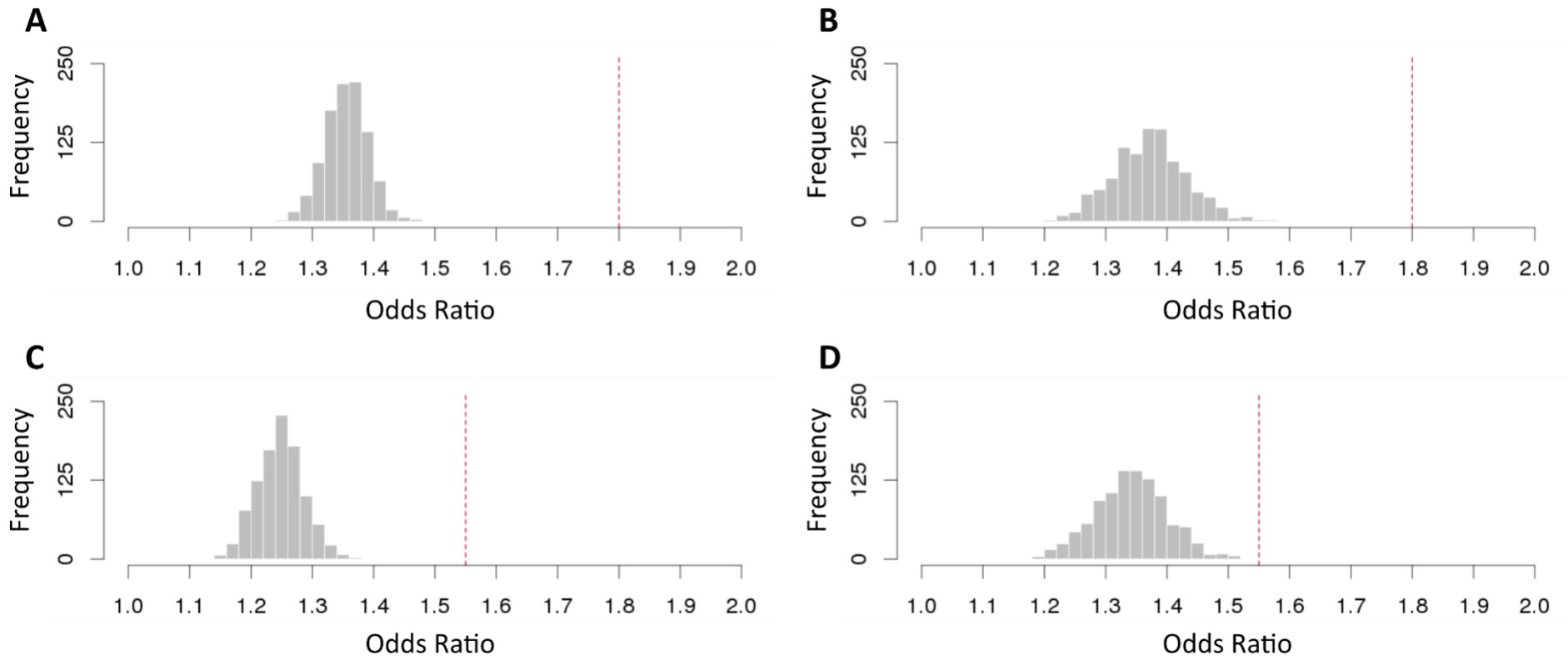
Supplementary Figure 2. All coefficients from each of the 18 side effect regression models, where "on-indication" side effects are retained in the data. Asterisks show P-value of the coefficient (*, P < 0.05; **, P < 0.005; ***, P < 0.0005).



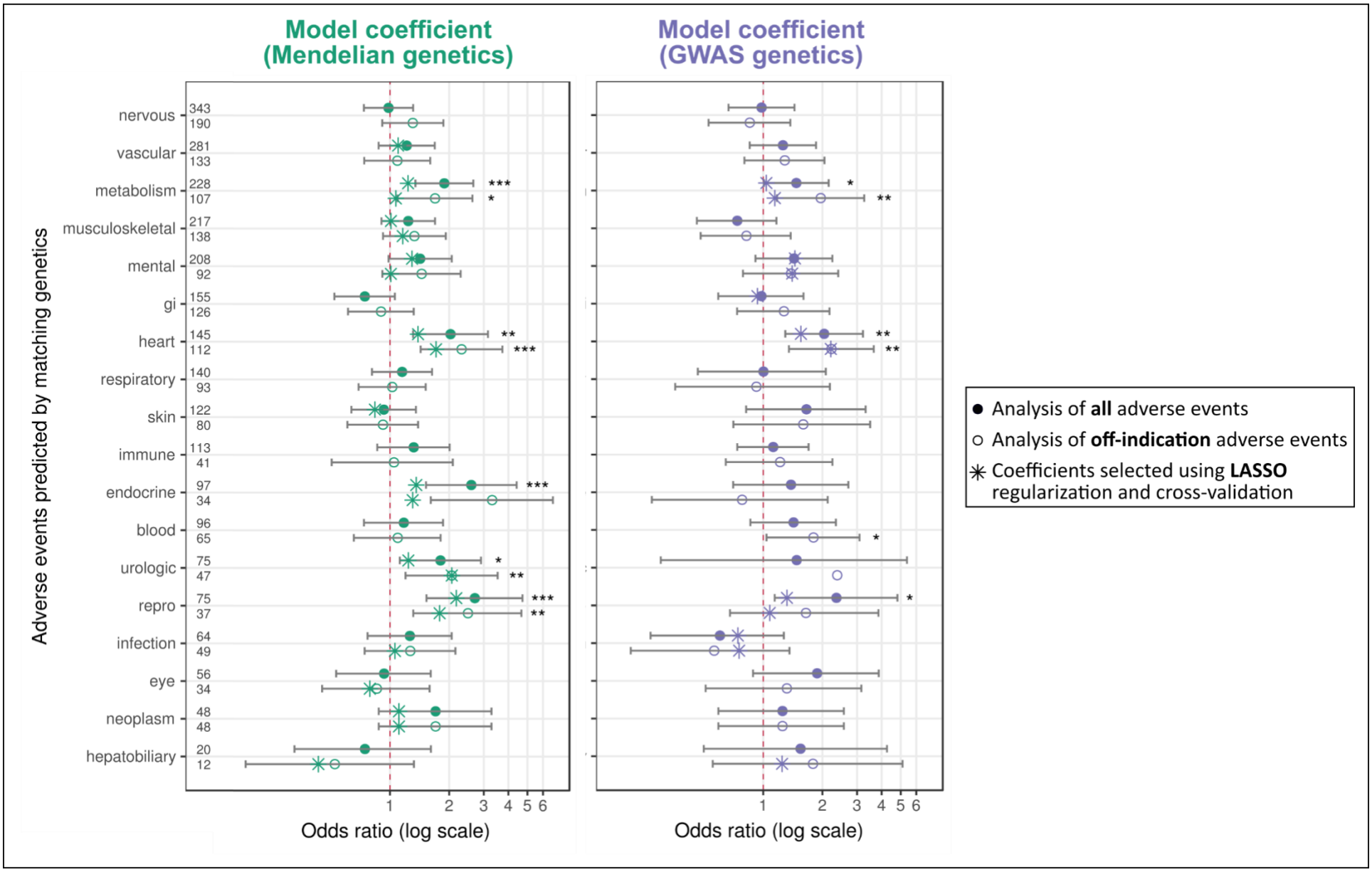
Supplementary Figure 3. All coefficients from each of the 18 side effect regression models, where only "off-indication" side effects are retained in the data. Asterisks show P-value of the coefficient (*, P < 0.05; **, P < 0.005; ***, P < 0.0005).



Supplementary Figure 4. Comparison of the rate at which all possible drug-SE (side effect) combinations are manifested as side effects in the clinical trial data set, between drug-SE pairs with or without genetic support. OR, odds ratio; P, P-value from Fisher's exact test (two-tailed). The top two panels show analyses based on all 38,199 drug-SE combinations; the bottom two panels show analyses based on 33,489 "off-indication" drug-SE combinations. The left two panels show analyses based on Mendelian genetic data; the right two panels show analyses based on GWAS genetic data. Error bars represent the 95% confidence interval of the reported proportions. Underlying data and confidence intervals for the OR values are shown in **Supplementary Table 1**.



Supplementary Figure 5. Result of permutation test for significance of genetics-SE enrichment relative to randomized SEs and randomized target genetics. In each analysis, gray histogram shows ORs resulting from 1,000 simulations and dashed vertical line shows the OR of the study data. Mean and standard deviation of the simulation ORs are provided in **Supplementary Table 2**. In each analysis, the simulation OR never exceeds the study data OR (Monte Carlo empirical $P < 0.001$). Analyses used: (A) all drug-SE pairs, randomized SEs; (B) all drug-SE pairs, randomized target genetics; (C) only off-indication drug-SE pairs, randomized SEs; (D) only off-indication drug-SE pairs, randomized target genetics.



Supplementary Figure 6. Summary of side effect modeling results with quantitative, tissue-specific target gene expression values included in the models. LEFT: coefficients of the Mendelian genetics predictors in each of the 18 side effect models (from **Supplementary Table 9**). RIGHT: coefficients of the GWAS genetics predictors in each of the 18 side effect models (from **Supplementary Table 9**). Coefficients from the regression models were exponentiated to obtain odds ratios. Along each row, circular points indicate odds ratios from the glm models; error bars are 95% confidence intervals from the glm models; large eight-pointed stars indicate odds ratios when the genetics predictors are selected as predictors in the glmnet models (which are built using feature selection, lasso regularization, and cross-validation). Small asterisks offset from the data indicate P-values of the the Fisher's exact test (LEFT) and P-values of the coefficients from the glm models (CENTER and RIGHT); (*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$).

Data inclusion	Comparison	GS	GN	GS+GN	NS	NN	NS+NN	GS/GN	NS/NN	Odds Ratio	p	OR 95% CI		GS/GS+GN	NS/NS+NN	stderr(GS/GS+GN)	sderr(NS/NS+NN)
All drug-SE combinations, all genetics	Overall: Genetic support vs no genetic support	2512	5862	8374	5729	24096	29825	0.43	0.24	1.80	1.73E-94	1.71	1.90	30.00%	19.21%	0.50%	0.23%
	Among no genetic support: incomplete genetic info vs complete genetic info	2759	12165	14924	2970	11931	14901	0.23	0.25	0.91	0.00158	0.86	0.97	18.49%	19.93%	0.32%	0.33%
All drug-SE combinations, Mendelian genetics	Overall: Genetic support vs no genetic support	2092	4765	6857	6149	25193	31342	0.44	0.24	1.80	2.28E-82	1.70	1.91	30.51%	19.62%	0.56%	0.22%
	Among no genetic support: incomplete genetic info vs complete genetic info	2014	8893	10907	4135	16300	20435	0.23	0.25	0.89	0.00017	0.84	0.95	18.47%	20.23%	0.37%	0.28%
All drug-SE combinations, GWAS genetics	Overall: Genetic support vs no genetic support	962	1911	2873	7279	28047	35326	0.50	0.26	1.94	2.75E-53	1.79	2.11	33.48%	20.61%	0.88%	0.22%
	Among no genetic support: incomplete genetic info vs complete genetic info	1745	7334	9079	5534	20713	26247	0.24	0.27	0.89	0.00015	0.84	0.95	19.22%	21.08%	0.41%	0.25%
Off-indication drug-SE combinations, all genetics	Overall: Genetic support vs no genetic support	1458	5062	6520	4219	22750	26969	0.29	0.19	1.55	1.70E-36	1.45	1.66	22.36%	15.64%	0.52%	0.22%
	Among no genetic support: incomplete genetic info vs complete genetic info	2067	11595	13662	2152	11155	13307	0.18	0.19	0.92	0.01892	0.86	0.99	15.13%	16.17%	0.31%	0.32%
Off-indication drug-SE combinations, Mendelian genetics	Overall: Genetic support vs no genetic support	1180	4095	5275	4497	23717	28214	0.29	0.19	1.52	1.47E-28	1.41	1.63	22.37%	15.94%	0.57%	0.22%
	Among no genetic support: incomplete genetic info vs complete genetic info	1503	8528	10031	2994	15189	18183	0.18	0.20	0.89	0.00111	0.84	0.96	14.98%	16.47%	0.36%	0.28%
Off-indication drug-SE combinations, GWAS genetics	Overall: Genetic support vs no genetic support	506	1597	2103	5171	26215	31386	0.32	0.20	1.61	8.61E-18	1.44	1.78	24.06%	16.48%	0.93%	0.21%
	Among no genetic support: incomplete genetic info vs complete genetic info	1292	6919	8211	3879	19296	23175	0.19	0.20	0.93	0.0362	0.87	1.00	15.73%	16.74%	0.40%	0.25%

Supplementary Table 1. Comparison of the rate at which all possible drug-SE (side effect) combinations are manifested as side effects in the clinical trial data set, between drug-SE pairs with or without genetic support. OR, odds ratio; p, p-value from Fisher's exact test (two-tailed). GS = genetics + side effect; GN = genetics + no side effect; NS = no genetics + side effect; NN = no genetics + no side effect. For the overall comparison, "genetics" indicates a match between the side effect and genetic phenotype. For the "among no genetic support" comparison, "genetics" indicates that there is a genetic phenotype for the targets that mismatches; "no genetics" indicates there is no or incomplete genetic information for the target gene(s).

	Main analysis															Off-indication analysis													
Phenotype category	(Drug x organ system) combinations	Drugs with genetics and side effect	Drugs with genetics and no side effect	Drugs with no genetics and side effect	Drugs with no genetics and no side effect	Rate of side effect when genetic association exists (precision) (PPV)	Rate of side effect when genetic association does not exist (FOR)	TPR (recall) (SEN)	TNR (SPE)	NPV	LR+	iLR-	OR	95% CI		p	(Drug x organ system) combinations	Drugs with genetics and side effect	Drugs with genetics and no side effect	Drugs with no genetics and side effect	Drugs with no genetics and no side effect	Rate of side effect when genetic association exists (precision) (PPV)	Rate of side effect when genetic association does not exist (FOR)	TPR (recall) (SEN)	TNR (SPE)	NPV	LR+	iLR-	OR	95% CI		p
blood		96	269	234	1220	26.3%	16.1%	29.1%	81.9%	83.9%	1.61	1.16	1.86	1.40	2.46	1.34E-05		65	234	212	1193	21.7%	15.1%	23.5%	83.6%	84.9%	1.43	1.09	1.56	1.13	2.15	0.005724
heart		145	176	451	1047	45.2%	30.1%	24.3%	85.6%	69.9%	1.69	1.13	1.91	1.48	2.46	3.92E-07		112	162	318	992	40.9%	24.3%	26.0%	86.0%	75.7%	1.86	1.16	2.16	1.63	2.85	5.90E-08
congenital		17	572	22	1208	2.9%	1.8%	43.6%	67.9%	98.2%	1.36	1.20	1.63	0.81	3.25	0.165102913		9	507	11	1135	1.7%	1.0%	45.0%	69.1%	99.0%	1.46	1.26	1.83	0.67	4.89	0.222399
ear		5	112	74	1628	4.3%	4.3%	6.3%	93.6%	95.7%	0.98	1.00	0.98	0.30	2.47	1		4	112	65	1622	3.4%	3.9%	5.8%	93.5%	96.1%	0.90	0.99	0.89	0.23	2.46	1
endocrine		97	252	177	1293	27.8%	12.0%	35.4%	83.7%	88.0%	2.17	1.30	2.81	2.09	3.76	3.71E-12		34	207	96	1204	14.1%	7.4%	26.2%	85.3%	92.6%	1.78	1.16	2.06	1.31	3.17	0.001412
eye		56	256	193	1314	17.9%	12.8%	22.5%	83.7%	87.2%	1.38	1.08	1.49	1.05	2.08	0.018630562		34	250	148	1268	12.0%	10.5%	18.7%	83.5%	89.5%	1.13	1.03	1.17	0.76	1.75	0.4617
gi		155	276	497	891	36.0%	35.8%	23.8%	76.3%	64.2%	1.01	1.00	1.01	0.80	1.27	0.95420768		126	244	379	823	34.1%	31.5%	25.0%	77.1%	68.5%	1.09	1.03	1.12	0.87	1.44	0.373119
hepatobiliary		20	153	160	1486	11.6%	9.7%	11.1%	90.7%	90.3%	1.19	1.02	1.21	0.70	2.01	0.42299002		12	150	134	1443	7.4%	8.5%	8.2%	90.6%	91.5%	0.87	0.99	0.86	0.42	1.60	0.766027
immune		113	335	251	1120	25.2%	18.3%	31.0%	77.0%	81.7%	1.35	1.12	1.51	1.16	1.95	0.001757385		41	232	116	914	15.0%	11.3%	26.1%	79.8%	88.7%	1.29	1.08	1.39	0.92	2.07	0.09472
infection		64	104	536	1115	38.1%	32.5%	10.7%	91.5%	67.5%	1.25	1.02	1.28	0.91	1.80	0.143708732		49	89	455	1056	35.5%	30.1%	9.7%	92.2%	69.9%	1.25	1.02	1.28	0.87	1.87	0.20933
metabolism		228	400	280	911	36.3%	23.5%	44.9%	69.5%	76.5%	1.47	1.26	1.85	1.49	2.30	1.34E-08		107	292	185	820	26.8%	18.4%	36.6%	73.7%	81.6%	1.40	1.16	1.62	1.22	2.15	0.0006
musculoskeletal		217	435	322	845	33.3%	27.6%	40.3%	66.0%	72.4%	1.18	1.11	1.31	1.06	1.62	0.01184709		138	373	221	749	27.0%	22.8%	38.4%	66.8%	77.2%	1.16	1.08	1.25	0.97	1.61	0.07435
neoplasm		48	305	122	1344	13.6%	8.3%	28.2%	81.5%	91.7%	1.53	1.14	1.73	1.19	2.50	0.003098258		48	305	122	1344	13.6%	8.3%	28.2%	81.5%	91.7%	1.53	1.14	1.73	1.19	2.50	0.003098
nervous		343	421	401	654	44.9%	38.0%	46.1%	60.8%	62.0%	1.18	1.13	1.33	1.09	1.61	0.003732245		190	312	266	558	37.8%	32.3%	41.7%	64.1%	67.7%	1.16	1.10	1.28	1.01	1.62	0.042694
pregnancy		7	268	35	1509	2.5%	2.3%	16.7%	84.9%	97.7%	1.11	1.02	1.13	0.42	2.61	0.826676608		7	262	32	1486	2.6%	2.1%	17.9%	85.0%	97.9%	1.20	1.04	1.24	0.46	2.90	0.648859
mental		208	350	255	1006	37.3%	20.2%	44.9%	74.2%	79.8%	1.74	1.35	2.34	1.87	2.94	5.16E-14		92	278	177	912	24.9%	16.3%	34.2%	76.6%	83.7%	1.46	1.16	1.71	1.27	2.29	0.000342
urologic		75	245	220	1279	23.4%	14.7%	25.4%	83.9%	85.3%	1.58	1.13	1.78	1.30	2.41	0.000219979		47	215	162	1220	17.9%	11.7%	22.5%	85.0%	88.3%	1.50	1.10	1.65	1.13	2.37	0.008259
repro		75	199	186	1359	27.4%	12.0%	28.7%	87.2%	88.0%	2.25	1.22	2.75	2.00	3.77	5.75E-10		37	185	148	1318	16.7%	10.1%	20.0%	87.7%	89.9%	1.62	1.10	1.78	1.17	2.66	0.005417
respiratory		140	211	464	1004	39.9%	31.6%	23.2%	82.6%	68.4%	1.33	1.08	1.44	1.12	1.84	0.003676008		93	197	361	950	32.1%	27.5%	20.5%	82.8%	72.5%	1.19	1.04	1.24	0.93	1.65	0.130584
skin		122	224	413	1060	35.3%	28.0%	22.8%	82.6%	72.0%	1.31	1.07	1.40	1.08	1.80	0.00874946		80	211	307	1004	27.5%	23.4%	20.7%	82.6%	76.6%	1.19	1.04	1.24	0.92	1.66	0.150424
vascular		281	299	436	803	48.4%	35.2%	39.2%	72.9%	64.8%	1.44	1.20	1.73	1.41	2.13	8.31E-08		133	245	304	739	35.2%	29.1%	30.4%	75.1%	70.9%	1.22	1.08	1.32	1.02	1.71	0.031836
TOTAL	**38199**	**2512**	**5862**	**5729**	**24096**	**30.0%**	**19.2%**	**30.5%**	**80.4%**	**80.8%**	**1.56**	**1.16**	**1.80**	**1.71**	**1.90**	**1.73E-94**	**33489**	**1458**	**5062**	**4219**	**22750**	**22.4%**	**15.6%**	**25.7%**	**81.8%**	**84.4%**	**1.41**	**1.10**	**1.55**	**1.45**	**1.66**	**1.70E-36**
	Main analysis with randomized data categories															Main analysis with randomized data categories															
Random genetics (mean of 1000 randomizations)	**38199**	**2623**	**7615**	**5618**	**22343**	**25.6%**	**20.1%**	**31.8%**	**74.6%**	**79.9%**	**1.25**	**1.09**	**1.37**	**1.30**	**1.45**	**1.99687E-11**	**33489**	**1762**	**6987**	**3915**	**20825**	**20.1%**	**15.8%**	**31.0%**	**74.9%**	**84.2%**	**1.24**	**1.09**	**1.34**	**1.26**	**1.43**	**2.78E-09**
Standard deviation of random genetics		121	334	121	334	0.58%	0.22%	1.46%	1.12%	0.22%	0.04	0.02	0.06	0.06	0.06	6.11543E-10		85	317	85	317	0.5%	0.2%	1.5%	1.1%	0.2%	0.04	0.01	0.06	0.06	0.06	6.41E-08
Random side effects (mean of 1000 randomizations)	**38199**	**2528**	**5846**	**7213**	**22612**	**30.2%**	**24.2%**	**26.0%**	**79.5%**	**75.8%**	**1.26**	**1.07**	**1.36**	**1.28**	**1.43**	**3.06273E-18**	**33489**	**1705**	**4815**	**5964**	**21005**	**26.2%**	**22.1%**	**22.2%**	**81.4%**	**77.9%**	**1.19**	**1.05**	**1.25**	**1.17**	**1.33**	**2.53E-06**
Standard deviation of random side effects		47	47	109	109	0.6%	0.4%	0.4%	0.1%	0.37%	0.02	0.01	0.03	0.03	0.04	8.94689E-17		37	37	100	100	0.6%	0.4%	0.4%	0.1%	0.4%	0.03	0.01	0.04	0.04	0.04	6.96E-05
	Main analysis using target annotations from single sources															Main analysis using target annotations from single sources															
DrugBank	**15981**	**1402**	**2123**	**3788**	**8668**	**39.8%**	**30.4%**	**27.0%**	**80.3%**	**69.6%**	**1.37**	**1.10**	**1.51**	**1.40**	**1.63**	**4.28442E-25**	**13438**	**755**	**1861**	**2694**	**8128**	**28.9%**	**24.9%**	**21.9%**	**81.4%**	**75.1%**	**1.17**	**1.04**	**1.22**	**1.11**	**1.35**	**3.84E-05**
Citeline Pharmaprojects	**34944**	**1923**	**4480**	**5588**	**22953**	**30.0%**	**19.6%**	**25.6%**	**83.7%**	**80.4%**	**1.57**	**1.12**	**1.76**	**1.66**	**1.87**	**3.25909E-71**	**30661**	**1073**	**3797**	**4108**	**21683**	**22.0%**	**15.9%**	**20.7%**	**85.1%**	**84.1%**	**1.39**	**1.07**	**1.49**	**1.38**	**1.61**	**3.83E-24**
Santos et al (2017)	**14133**	**1395**	**2012**	**3535**	**7191**	**40.9%**	**33.0%**	**28.3%**	**78.1%**	**67.0%**	**1.29**	**1.09**	**1.41**	**1.30**	**1.53**	**2.96E-17**	**11770**	**765**	**1791**	**2481**	**6733**	**29.9%**	**26.9%**	**23.6%**	**79.0%**	**73.1%**	**1.12**	**1.03**	**1.16**	**1.05**	**1.28**	**0.002911**
	Replication analysis using OFFSIDES data															Replication analysis using OFFSIDES data															
TOTAL	**5523**	**1230**	**326**	**2940**	**1027**	**79.0%**	**74.1%**	**29.5%**	**75.9%**	**25.9%**	**1.22**	**1.08**	**1.32**	**1.14**	**1.52**	**0.000112548**	**4998**	**1003**	**317**	**2669**	**1009**	**76.0%**	**72.6%**	**27.3%**	**76.1%**	**27.4%**	**1.14**	**1.05**	**1.20**	**1.03**	**1.39**	**0.016452**
Random genetics (mean of 1000 randomizations)	**5523**	**1632**	**523**	**2538**	**830**	**75.7%**	**75.4%**	**39.1%**	**61.3%**	**24.6%**	**1.01**	**1.01**	**1.02**	**0.90**	**1.16**	**0.472879439**	**4998**	**1425**	**515**	**2247**	**811**	**73.5%**	**73.5%**	**38.8%**	**61.2%**	**26.5%**	**1.00**	**1.00**	**1.00**	**0.88**	**1.14**	**0.483419**
Standard deviation of random genetics		85	35	85	35	0.8%	0.5%	2.0%	2.6%	0.5%	0.04	0.03	0.07	0.06	0.08	0.301098261		79	34	79	34	0.9%	0.5%	2.1%	2.6%	0.5%	0.04	0.03	0.07	0.06	0.08	0.29747
	Analysis of placebo contribution to side effects using AACT data															Analysis of placebo contribution to side effects using AACT data															
Placebo-controlled side effects	**4809**	**291**	**943**	**460**	**3115**	**23.6%**	**12.9%**	**38.7%**	**76.8%**	**87.1%**	**1.67**	**1.25**	**2.09**	**1.77**	**2.47**	**6.61954E-18**	**4275**	**198**	**798**	**379**	**2900**	**19.9%**	**11.6%**	**34.3%**	**78.4%**	**88.4%**	**1.59**	**1.19**	**1.90**	**1.56**	**2.30**	**1.11E-10**
All placebo group side effects	**4746**	**529**	**690**	**1151**	**2376**	**43.4%**	**32.6%**	**31.5%**	**77.5%**	**67.4%**	**1.40**	**1.13**	**1.58**	**1.38**	**1.81**	**2.32827E-11**	**4041**	**330**	**590**	**910**	**2211**	**35.9%**	**29.2%**	**26.6%**	**78.9%**	**70.8%**	**1.26**	**1.08**	**1.36**	**1.16**	**1.59**	**0.00013**
All drug group side effects	**4809**	**604**	**630**	**1232**	**2343**	**48.9%**	**34.5%**	**32.9%**	**78.8%**	**65.5%**	**1.55**	**1.17**	**1.82**	**1.60**	**2.08**	**4.12156E-19**	**4091**	**386**	**544**	**966**	**2195**	**41.5%**	**30.6%**	**28.6%**	**80.1%**	**69.4%**	**1.44**	**1.12**	**1.61**	**1.38**	**1.88**	**7.35E-10**

Supplementary Table 2. Analysis of enrichment between genetic phenotypes and side effects in individual organ systems. P value is from Fisher's exact test (two-sided.) PPV, positive predictive value; FOR, false omission rate; TPR, true positive rate; TNR, true negative rate; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio positive (SEN/1-SPE); iLR-, inverse likelihood ratio negative (SPE/1-SEN)

		Model: glm (all data used)							Model: glm (only off-indication side effects used)							Model: glmnet (all data used)		Model:glmnet (only off-indication data used)	
Model (Side effect predicted)	**Variable**	**beta**	**95% CI**		**OR**	**95% CI**		**p**	**beta**	**95% CI**		**OR**	**95% CI**		**p**	**beta**	**OR**	**beta**	**OR**
blood	gen_omim_blood_yes	0.099252	-0.34305	0.53315	1.104344	0.709606	1.704292	0.656639	-0.04189	-0.53206	0.433955	0.95898	0.587394	1.5433489	0.86482	NA	NA	NA	NA
heart	gen_omim_heart_yes	0.798367	0.40002	1.196922	2.221909	1.491855	3.309912	8.48E-05	0.893515	0.461857	1.324631	2.443704	1.587018	3.7607955	4.83E-05	0.379982	1.462257677	0.443476494	1.55811459
congenital	gen_omim_congenital_yes	0.621939	-0.41148	1.675398	1.862537	0.662668	5.340923	0.238712	1.426093	-0.03082	2.992485	4.162406	0.969653	19.935167	0.061713	NA	NA	NA	NA
ear	gen_omim_ear_yes	0.103855	-1.12003	1.144788	1.10944	0.32627	3.141776	0.855014	-0.05183	-1.37712	1.042855	0.949494	0.252304	2.8373059	0.931646	NA	NA	NA	NA
endocrine	gen_omim_endocrine_yes	0.920205	0.433658	1.405786	2.509804	1.542892	4.07873	0.000202	1.176142	0.520462	1.824507	3.241844	1.682805	6.1997361	0.000389	0.402171	1.495067668	0.517774649	1.678288709
eye	gen_omim_eye_yes	-0.01432	-0.54349	0.498809	0.985786	0.580716	1.646759	0.956975	-0.14153	-0.73845	0.430976	0.868025	0.477852	1.538758	0.634138	NA	NA	NA	NA
gi	gen_omim_gi_yes	-0.2791	-0.61287	0.050886	0.756466	0.541792	1.052203	0.099073	-0.13512	-0.49874	0.224737	0.873614	0.607296	1.2519929	0.463764	NA	NA	NA	NA
hepatobiliary	gen_omim_hepatobiliary_yes	-0.31603	-1.08987	0.398177	0.729037	0.336262	1.489108	0.403114	-0.58539	-1.54517	0.254625	0.556886	0.213276	1.2899775	0.19804	NA	NA	-1.4535634	0.233735908
immune	gen_omim_immune_yes	0.173179	-0.23424	0.57302	1.189079	0.791174	1.773615	0.399819	0.081383	-0.61842	0.739655	1.084786	0.538796	2.0952133	0.813348	NA	NA	NA	NA
infection	gen_omim_infection_yes	0.166921	-0.30967	0.637908	1.181661	0.733687	1.892518	0.489208	0.208626	-0.3043	0.715541	1.231985	0.73764	2.0452932	0.42181	NA	NA	0.097292406	1.102182611
metabolism	gen_omim_metabolism_yes	0.546033	0.226133	0.866761	1.726391	1.253742	2.379191	0.000827	0.433503	0.019678	0.845068	1.542653	1.019873	2.3281362	0.039288	0.274074	1.315311652	0.107500297	1.113491191
musculoskeletal	gen_omim_musculoskeletal_yes	0.249683	-0.04309	0.542835	1.283618	0.957828	1.720878	0.094643	0.262713	-0.08025	0.606263	1.300453	0.922887	1.8335675	0.133269	0.189056	1.208108824	0.206192739	1.228990055
neoplasm	gen_omim_neoplasm_yes	0.369504	-0.21864	0.94674	1.447017	0.803608	2.577293	0.213025	0.369504	-0.21864	0.94674	1.447017	0.803608	2.5772932	0.213025	0.107302	1.113270488	0.116158947	1.123174384
nervous	gen_omim_nervous_yes	0.164469	-0.09983	0.429047	1.178767	0.904993	1.535794	0.222629	0.35222	0.029312	0.676456	1.422222	1.029745	1.9668946	0.032763	NA	NA	0.001909478	1.001911303
pregnancy	gen_omim_pregnancy_yes	0.421696	-0.70824	1.493486	1.524545	0.492511	4.452591	0.447656	0.61356	-0.56868	1.75126	1.846995	0.566272	5.7618578	0.294489	0.431174	1.539063673	0.235694415	1.265787446
mental	gen_omim_mental_yes	0.394375	0.056778	0.731652	1.483456	1.058421	2.078512	0.021885	0.354422	-0.06954	0.775564	1.425356	0.932819	2.1718161	0.099758	0.242969	1.27502867	NA	NA
urologic	gen_omim_urologic_yes	0.523558	0.086856	0.957154	1.688023	1.09074	2.604275	0.01822	0.686187	0.190969	1.176972	1.986129	1.210422	3.2445342	0.006277	0.319198	1.376023453	0.676594242	1.967166618
repro	gen_omim_repro_yes	1.018365	0.486548	1.542835	2.768663	1.626692	4.677832	0.000153	0.900936	0.281338	1.503347	2.461906	1.324901	4.4967137	0.003764	0.735977	2.087520169	0.553897702	1.740021904
respiratory	gen_omim_respiratory_yes	0.162156	-0.17579	0.498038	1.176044	0.838793	1.645489	0.345175	0.049954	-0.32414	0.420287	1.051223	0.723149	1.522399	0.792341	NA	NA	NA	NA
skin	gen_omim_skin_yes	-0.0127	-0.37601	0.346651	0.987381	0.686597	1.414324	0.945036	0.002884	-0.39431	0.394377	1.002888	0.674148	1.4834594	0.988552	NA	NA	NA	NA
vascular	gen_omim_vascular_yes	0.296978	-0.00848	0.601999	1.345786	0.99156	1.825765	0.056386	0.205072	-0.15162	0.559345	1.227613	0.859311	1.7495254	0.257793	0.062813	1.064827403	NA	NA
blood	gen_omim_blood_no	-0.30922	-0.63336	0.014408	0.734019	0.530805	1.014512	0.061078	-0.33352	-0.67043	0.002645	0.716398	0.51149	1.0026486	0.051854	NA	NA	NA	NA
heart	gen_omim_heart_no	0.209043	-0.05175	0.471349	1.232498	0.949566	1.602154	0.117013	0.229932	-0.05484	0.51703	1.258514	0.946638	1.6770403	0.11474	NA	NA	NA	NA
congenital	gen_omim_congenital_no	0.174663	-0.85064	1.183732	1.190845	0.427142	3.266544	0.733438	-0.8046	-2.77941	0.773803	0.447269	0.062075	2.1679949	0.358564	NA	NA	NA	NA
ear	gen_omim_ear_no	0.303676	-0.26813	0.896471	1.35483	0.764805	2.450939	0.304859	0.341274	-0.24694	0.953078	1.406739	0.781185	2.5936797	0.262961	NA	NA	NA	NA
endocrine	gen_omim_endocrine_no	0.507616	0.121747	0.899541	1.661325	1.129468	2.458475	0.010412	0.50697	0.018401	1.010406	1.660253	1.018572	2.7467165	0.044543	NA	NA	NA	NA
eye	gen_omim_eye_no	0.14363	-0.21984	0.510929	1.154457	0.802647	1.666839	0.440448	0.119536	-0.28465	0.529013	1.126974	0.752274	1.697256	0.564026	NA	NA	NA	NA
gi	gen_omim_gi_no	-0.16726	-0.42457	0.089663	0.845983	0.654051	1.093805	0.202097	-0.07373	-0.35468	0.207464	0.928925	0.701401	1.2305536	0.606949	NA	NA	NA	NA
hepatobiliary	gen_omim_hepatobiliary_no	-0.31032	-0.70888	0.089617	0.733215	0.492193	1.093755	0.127056	-0.17617	-0.5964	0.248737	0.838472	0.550791	1.2824051	0.412964	NA	NA	NA	NA
immune	gen_omim_immune_no	0.076126	-0.24497	0.398987	1.079098	0.782727	1.490314	0.642807	0.103422	-0.34213	0.557787	1.108959	0.710258	1.7468024	0.65176	NA	NA	NA	NA
infection	gen_omim_infection_no	-0.01469	-0.27189	0.243534	0.985421	0.761937	1.275749	0.911021	-0.06175	-0.33389	0.211443	0.94012	0.716135	1.2354594	0.656951	NA	NA	NA	NA
metabolism	gen_omim_metabolism_no	0.222239	-0.08712	0.532415	1.24887	0.916571	1.703041	0.159371	0.201384	-0.15832	0.562911	1.223094	0.853574	1.7557755	0.273223	NA	NA	NA	NA
musculoskeletal	gen_omim_musculoskeletal_no	-0.08862	-0.38384	0.204997	0.915197	0.681241	1.227521	0.554984	-0.08956	-0.42875	0.24736	0.914335	0.651326	1.2806406	0.603254	NA	NA	NA	NA
neoplasm	gen_omim_neoplasm_no	-0.28779	-0.7287	0.151101	0.74992	0.482537	1.163114	0.19889	-0.28779	-0.7287	0.151101	0.74992	0.482537	1.1631137	0.19889	NA	NA	NA	NA
nervous	gen_omim_nervous_no	0.11666	-0.16462	0.397413	1.123737	0.848214	1.487971	0.41562	0.134306	-0.18593	0.454024	1.143742	0.830329	1.5746365	0.410373	NA	NA	NA	NA
pregnancy	gen_omim_pregnancy_no	0.030128	-0.72425	0.803572	1.030586	0.484686	2.233505	0.93792	0.070496	-0.7275	0.895624	1.07304	0.483116	2.4488642	0.863672	NA	NA	NA	NA
mental	gen_omim_mental_no	-0.09919	-0.41892	0.2194	0.905569	0.657758	1.24533	0.542113	0.03848	-0.32143	0.39865	1.03923	0.725115	1.4898116	0.833887	NA	NA	NA	NA
urologic	gen_omim_urologic_no	-0.02075	-0.37194	0.332309	0.979466	0.689398	1.394184	0.90795	-0.02529	-0.4146	0.367039	0.975028	0.660607	1.4434536	0.898916	NA	NA	NA	NA
repro	gen_omim_repro_no	0.005603	-0.37212	0.386664	1.005619	0.689268	1.472061	0.976875	0.028488	-0.38166	0.44305	1.028897	0.682728	1.5574506	0.89211	NA	NA	NA	NA
respiratory	gen_omim_respiratory_no	-0.04264	-0.31978	0.234755	0.958256	0.726308	1.264599	0.762962	-0.12972	-0.42998	0.170356	0.87834	0.650521	1.1857275	0.396656	NA	NA	NA	NA
skin	gen_omim_skin_no	-0.14825	-0.42036	0.123786	0.862217	0.656809	1.131773	0.285255	-0.18289	-0.48146	0.11543	0.832861	0.617882	1.1223559	0.22938	NA	NA	NA	NA
vascular	gen_omim_vascular_no	0.092819	-0.16625	0.352135	1.097263	0.846832	1.4221	0.482538	0.002697	-0.28467	0.289839	1.0027	0.752264	1.3362127	0.98531	NA	NA	NA	NA
blood	gen_gwas_blood_yes	0.162028	-0.31809	0.630367	1.175893	0.72754	1.8783	0.502461	0.336192	-0.185	0.842622	1.399608	0.8311	2.3224477	0.19882	NA	NA	NA	NA
heart	gen_gwas_heart_yes	0.724534	0.298394	1.149306	2.063768	1.347692	3.156001	0.000835	0.772248	0.307414	1.233709	2.164627	1.359904	3.4339432	0.001068	0.463002	1.588836587	0.487335477	1.627972665
congenital	gen_gwas_congenital_yes	0.569231	-1.00026	1.974004	1.766908	0.367784	7.199449	0.445803	-20.0239	NA	233.7091	2.01E-09	NA	3.15E+101	0.996595	NA	NA	NA	NA
ear	gen_gwas_ear_yes	-14.8072	NA	93.63155	3.71E-07	NA	4.61E+40	0.977937	-14.8801	NA	93.5294	3.45E-07	NA	4.16E+40	0.977828	NA	NA	-0.448159095	0.638803046
endocrine	gen_gwas_endocrine_yes	0.115439	-0.48692	0.713419	1.122366	0.614513	2.040958	0.705844	-0.23799	-1.16635	0.637846	0.788211	0.311503	1.8924005	0.603265	NA	NA	NA	NA
eye	gen_gwas_eye_yes	0.334411	-0.38748	1.022525	1.397117	0.678767	2.780205	0.351392	0.038179	-0.8748	0.868451	1.038917	0.416947	2.3832159	0.93119	NA	NA	NA	NA
gi	gen_gwas_gi_yes	-0.12771	-0.60508	0.335362	0.880105	0.546032	1.398447	0.593831	0.135538	-0.37781	0.633118	1.145153	0.685358	1.8834745	0.598429	NA	NA	NA	NA
hepatobiliary	gen_gwas_hepatobiliary_yes	0.075288	-1.02472	1.039194	1.078194	0.358898	2.826938	0.885083	0.140888	-0.97956	1.121122	1.151296	0.375475	3.0682958	0.790253	NA	NA	0.528095345	1.695699508
immune	gen_gwas_immune_yes	0.0117	-0.39377	0.407634	1.011769	0.674512	1.503257	0.954304	0.025344	-0.57959	0.600225	1.025668	0.56013	1.8225293	0.932645	NA	NA	NA	NA
infection	gen_gwas_infection_yes	-0.51125	-1.30461	0.211812	0.599748	0.271278	1.235916	0.183923	-0.60729	-1.55772	0.237838	0.544827	0.210615	1.2685041	0.181764	-0.29694	0.743089249	-0.451750667	0.636512854
metabolism	gen_gwas_metabolism_yes	0.262958	-0.09483	0.618067	1.300772	0.909524	1.855339	0.147905	0.50413	0.032969	0.968735	1.655544	1.033519	2.6346094	0.034466	0.09425	1.098834273	0.159039195	1.172383898
musculoskeletal	gen_gwas_musculoskeletal_yes	-0.20233	-0.65468	0.236152	0.816826	0.51961	1.266366	0.37262	-0.10698	-0.62214	0.389184	0.898545	0.536796	1.4757755	0.67781	-0.09985	0.904974139	NA	NA
neoplasm	gen_gwas_neoplasm_yes	0.069713	-0.63759	0.739822	1.072201	0.528563	2.095562	0.842241	0.069713	-0.63759	0.739822	1.072201	0.528563	2.0955617	0.842241	NA	NA	NA	NA
nervous	gen_gwas_nervous_yes	0.023392	-0.33625	0.379993	1.023668	0.714447	1.462274	0.898046	-0.05043	-0.4853	0.377362	0.950818	0.615516	1.4584324	0.818508	NA	NA	NA	NA
pregnancy	gen_gwas_pregnancy_yes	-13.2782	-211.482	15.82898	1.71E-06	1.43E-92	7489241	0.983308	-13.9709	-361.641	29.85508	8.56E-07	8.74E-158	9.245E+12	0.989312	-0.10241	0.902663585	NA	NA
mental	gen_gwas_mental_yes	0.437294	0.040021	0.832048	1.548512	1.040833	2.29802	0.030312	0.301085	-0.21169	0.803571	1.351324	0.809219	2.2335026	0.244285	0.354446	1.425390886	0.161250944	1.174979786
urologic	gen_gwas_urologic_yes	-0.19243	-1.68314	0.982415	0.824955	0.185789	2.670899	0.772721	0.175497	-1.20196	1.295228	1.191838	0.300604	3.6518277	0.779012	NA	NA	NA	NA
repro	gen_gwas_repro_yes	0.693758	0.041341	1.333841	2.001223	1.042207	3.795593	0.035124	0.51693	-0.30272	1.290003	1.676871	0.738806	3.6327963	0.201307	0.245466	1.278216898	0.040778328	1.041621182
respiratory	gen_gwas_respiratory_yes	0.088458	-0.64665	0.788274	1.092488	0.523798	2.199597	0.808494	0.015078	-0.90957	0.847273	1.015193	0.402696	2.3332745	0.972961	NA	NA	NA	NA
skin	gen_gwas_skin_yes	0.31313	-0.35707	0.969059	1.367699	0.699723	2.635463	0.353218	0.231386	-0.55479	0.978249	1.260346	0.574194	2.6597953	0.552149	NA	NA	NA	NA
vascular	gen_gwas_vascular_yes	0.156618	-0.2055	0.516452	1.169549	0.814242	1.67607	0.394734	0.143537	-0.29822	0.576597	1.15435	0.742137	1.7799706	0.519491	NA	NA	NA	NA
blood	gen_gwas_blood_no	0.330367	0.012208	0.650592	1.391478	1.012283	1.916676	0.042318	0.36034	0.025948	0.697693	1.433817	1.026288	2.0091128	0.035302	NA	NA	NA	NA
heart	gen_gwas_heart_no	0.265152	0.007513	0.523299	1.30363	1.007542	1.687586	0.043771	0.331716	0.050142	0.614512	1.393357	1.05142	1.8487546	0.021134	NA	NA	NA	NA
congenital	gen_gwas_congenital_no	0.412451	-0.45215	1.298133	1.510516	0.636258	3.662451	0.352042	-0.45341	-1.79347	0.859144	0.635459	0.166382	2.3611392	0.498311	NA	NA	NA	NA
ear	gen_gwas_ear_no	-0.20717	-0.77257	0.35721	0.812882	0.461826	1.429336	0.470948	-0.15516	-0.73549	0.425886	0.856281	0.479269	1.5309455	0.59932	NA	NA	NA	NA
endocrine	gen_gwas_endocrine_no	-0.00306	-0.35738	0.351539	0.996944	0.699506	1.421253	0.986481	0.010078	-0.43665	0.458916	1.010129	0.646199	1.582357	0.964744	NA	NA	NA	NA
eye	gen_gwas_eye_no	0.222911	-0.13113	0.580324	1.249709	0.877101	1.786616	0.218795	0.244383	-0.14241	0.635587	1.276833	0.867262	1.8881308	0.217465	NA	NA	NA	NA
gi	gen_gwas_gi_no	0.171583	-0.07477	0.418337	1.187183	0.927956	1.519433	0.172369	0.206053	-0.06418	0.476928	1.228818	0.937835	1.611117	0.135289	NA	NA	NA	NA
hepatobiliary	gen_gwas_hepatobiliary_no	0.363878	-0.02841	0.762437	1.438899	0.97199	2.143494	0.070843	0.318192	-0.10007	0.743142	1.37464	0.904772	2.1025311	0.138343	NA	NA	NA	NA
immune	gen_gwas_immune_no	0.015307	-0.30534	0.335707	1.015425	0.73687	1.398929	0.925365	-0.11551	-0.55926	0.328036	0.890915	0.571632	1.3882396	0.60927	NA	NA	NA	NA
infection	gen_gwas_infection_no	0.244918	-0.00694	0.498062	1.277517	0.993086	1.64553	0.057158	0.257716	-0.00893	0.525931	1.293971	0.991107	1.6920326	0.058772	NA	NA	NA	NA
metabolism	gen_gwas_metabolism_no	0.116282	-0.17323	0.405294	1.123313	0.840941	1.499744	0.430443	0.216994	-0.12709	0.561864	1.242337	0.880651	1.753939	0.216509	NA	NA	NA	NA
musculoskeletal	gen_gwas_musculoskeletal_no	0.043324	-0.21715	0.303843	1.044276	0.804809	1.355056	0.744309	0.076667	-0.22573	0.379333	1.079682	0.797935	1.4613092	0.619136	NA	NA	NA	NA
neoplasm	gen_gwas_neoplasm_no	-0.02746	-0.45743	0.402286	0.972909	0.632908	1.495238	0.900173	-0.02746	-0.45743	0.402286	0.972909	0.632908	1.4952382	0.900173	NA	NA	NA	NA
nervous	gen_gwas_nervous_no	0.031054	-0.2095	0.271275	1.031541	0.810988	1.311636	0.80004	-0.20306	-0.49095	0.083172	0.816231	0.612044	1.0867288	0.165358	NA	NA	NA	NA
pregnancy	gen_gwas_pregnancy_no	0.854052	0.095443	1.656801	2.349146	1.100146	5.242514	0.030914	1.099616	0.271011	1.993582	3.003014	1.311289	7.3417838	0.011664	NA	NA	NA	NA
mental	gen_gwas_mental_no	-0.11378	-0.4059	0.176855	0.892454	0.666376	1.193458	0.443734	-0.09244	-0.42892	0.242449	0.911707	0.651214	1.2743662	0.589008	NA	NA	NA	NA
urologic	gen_gwas_urologic_no	0.285575	-0.0431	0.616815	1.330527	0.957816	1.853016	0.089501	0.266717	-0.09996	0.636713	1.305671	0.904874	1.890258	0.155294	NA	NA	NA	NA
repro	gen_gwas_repro_no	0.182218	-0.17715	0.543505	1.199876	0.837656	1.722032	0.321005	0.204212	-0.18628	0.596753	1.226558	0.830044	1.8162115	0.305911	NA	NA	NA	NA
respiratory	gen_gwas_respiratory_no	0.28734	0.031085	0.544987	1.332877	1.031573	1.724587	0.02831	0.350579	0.072679	0.63048	1.419889	1.075386	1.8785126	0.01369	NA	NA	NA	NA
skin	gen_gwas_skin_no	-0.04879	-0.30734	0.209843	0.952379	0.735402	1.233484	0.711361	-0.03205	-0.31406	0.250091	0.968463	0.730478	1.2841427	0.823679	NA	NA	NA	NA
vascular	gen_gwas_vascular_no	0.06188	-0.1845	0.307699	1.063835	0.831522	1.360292	0.621975	0.009343	-0.26536	0.283141	1.009386	0.766932	1.3272921	0.946734	NA	NA	NA	NA

Supplementary Table 3. Coefficients (as beta, and transformed to odds ratios) for genetics variables in side effect models. Confidence intervals and p values are outputs from the *glm* function in R.

side effect modeled	AUC.real.genetics	AUC.no.genetics	median.AUC.random.genetics	CI95.AUC.random.genetics	p
heart	0.703	0.684	0.682	0.675-0.695	< 0.001
metabolism	0.706	0.701	0.691	0.687-0.7	< 0.001
repro	0.731	0.72	0.712	0.706-0.725	0.006
endocrine	0.704	0.678	0.671	0.658-0.695	0.007
urologic	0.739	0.732	0.723	0.716-0.736	0.007
mental	0.712	0.716	0.702	0.697-0.714	0.037

Supplementary Table 4. Results of cross validataion analysis of six off-indication side effect models where genetics was significant in any of the regression models. Distribution of permutation values are shown in **Figure 4** and are reflected in 95% CI values. The p values are derived from the frequency of permutation runs that exceed the AUC of the true model.

Adverse Event	# drugs	% drugs	UMLS ID
headache	1446	54.9	C0018681
nausea	1209	45.9	C0027497
diarrhea	959	36.4	C0011991
emesis	708	26.9	C0042963
dizziness	617	23.4	C0012833,C0042571
fatigue	607	23.1	C0015672
pain	606	23.0	C0030193
rhinopharyngitis	531	20.2	C0027441
upper respiratory tract infection	498	18.9	C0041912
constipation	462	17.5	C0009806
vertigo	440	16.7	C0042571
skin rash	422	16.0	C0015230
abdominal pain	410	15.6	C0000737
gastrointestinal disease	388	14.7	C0017178
fever	386	14.7	C0015967
back pain	381	14.5	C0004604
pruritus	381	14.5	C0033774
drowsiness	368	14.0	C2830004
death	353	13.4	C1306577
insomnia	339	12.9	C0917801
cough	332	12.6	C0010200
dyspepsia	327	12.4	C0013395
arthralgia	322	12.2	C0003862
infectious disease	316	12.0	C0009450
urinary tract infection	307	11.7	C0042029
hypertension	304	11.5	C0020538
edema	285	10.8	C0013604

Supplementary Table 5. Common side effects removed from analysis.

enteral	parenteral	topical	other
buccal	epidural	dental	instillation, bladder
nasograstric	infiltration	inhaled	instillation, intravesical
oral	intraarterial	intranasal	intrabone
oro-pharingeal	intraarterial (hepatic artery)	intranasal spray	intrabronchial
rectal	intraarticular	mouth rinse	intracameral
sublingual	intracoronary	ophthalmic	intracardiac
	intracutaneous	percutaneous	intracavernosal
	intradermal	topical	intracerebral
	intralymphatic	topical (buccal)	intracerebroventricular
	intramuscular	topical (ophthalmic)	intradiscal
	intramuscular (cremaster)	topical (otic)	intragastric
	intramuscular (deltoid)		intra-locus coeruleus
	intramuscular (gluteal)		intramammary
	intraspinal		intramyocardial
	intrathecal		intranodal
	intrathecal, lumbar		intraocular
	intravenous		intraotic
	intravenous (portal)		intrapericardial
	parenteral		intraperitoneal
	subcutaneous		intrapleural
	subcutaneous (abdomen)		intraprostatic
	subcutaneous (arm)		intrastriatal
	subcutaneous (thigh)		intratendinous
	transarterial		intratracheal
	transdermal		intratumor
			intratumoral
			intratympanic
			intrauterine
			intravaginal
			intraventricular
			intravitreous
			percutaneous hepatic perfusion
			peritumoral
			subconjunctiva
			subgingivally
			subretinal
			subtenon
			urethral

Supplementary Table 6. Coding of delivery route.

Organ System Abbreviation	MedDRA System Organ Class (SOC) Term	UMLS id	Comment
blood	Blood and lymphatic system disorders	C0851353	
heart	Diseases, Heart	C0018799	
congenital	Congenital, familial and genetic disorders	C0851352	
ear	Ear and labyrinth disorders	C0851354	
endocrine	System Diseases, Endocrine	C0014130	
eye	Diseases, Eye	C0015397	
gi	Diseases, Gastrointestinal	C0017178	
general	General disorders and administration site conditions	C0851362	mapped to other SOC terms
hepatobiliary	Hepatobiliary disease NOS	C0267792	
immune	Diseases, Immune System	C0021053	
infection	Diseases, Communicable	C0009450	
injury	Injury, poisoning and procedural complications	C0947733	mapped to other SOC terms
investigation	Investigation NOS	C1261322	mapped to other SOC terms
metabolism	Metabolism and nutrition disorders	C0851358	
musculoskeletal	Musculoskeletal and connective tissue disorders	C0263660	
neoplasm	Neoplasm NOS	C0027651	
nervous	Diseases, Nervous System	C0027765	
pregnancy	Pregnancy, puerperium and perinatal conditions	C0851363	
mental	Mental disorder	C0004936	
urologic	Diseases, Urologic	C0042075	
repro	Reproductive system and breast disorders	C0851366	
respiratory	Respiratory, thoracic and mediastinal disorders	C0851355	
skin	Skin and subcutaneous tissue disorders	C0178298	
social	Social circumstances	C0851364	exclude from study
procedures	Surgical and medical procedures	C1948041	exclude from study
vascular	Diseases, Vascular	C0042373	

Supplementary Table 7. MedDRA System Organ Class (SOC) terms inclusion and remapping criteria.

		This study (human x 21 organ systems)	IQ Consortium (3 species x 12 organ systems)
Translatability of positive findings			
Number of species-phenotype combinations with:	LR+ ≤ 1	1	7
	1 < LR+ < 10	20	22
	LR+ ≥ 10	0	4
Sensitivity		30%	48%
PPV		30%	43%
Translatability of negative findings			
Number of species-phenotype combinations with:	iLR- ≤ 1	1	10
	1 < iLR- < 10	20	25
	iLR- ≥ 10	0	0
Specificity		80%	84%
NPV		81%	86%

Supplementary Table 8. Comparison of summary statistics between results of this study and the results of the IQ Consortium (Monticello *et al.*, 2017). PPV, positive predictive value. NPV, negative predictive value. LR+, positive likelihood ratio. iLR-, inverse negative likelihood ratio.

		Model: glm (all data used)								Model: glm (only off-indication side effects used)								Model: glmnet (all data used)			Model:glmnet (only off-indication data used)	
Model (Side effect predicted)	**Variable**	**beta**	**95% CI**		**OR**	**95% CI**		**p**		**beta**	**95% CI**		**OR**	**95% CI**		**p**		**beta**	**OR**		**beta**	**OR**
blood	gen_omim_blood_yes	0.162092	-0.3047	0.621131	1.175968	0.737347	1.861032	0.491958		0.091146	-0.42316	0.59299	1.095429	0.654972	1.80939	0.724693		NA	NA		NA	NA
heart	gen_omim_heart_yes	0.709114	0.270634	1.14718	2.03219	1.310796	3.1493	0.001505		0.838638	0.359089	1.316276	2.313214	1.432024	3.729507	0.000586		0.287803	1.333495		0.325952305	1.385349293
congenital	gen_omim_congenital_yes	0.935395	-0.26439	2.229239	2.548219	0.767676	9.292789	0.13694		2.345718	0.124561	5.306846	10.44077	1.132651	201.7131	0.063		NA	NA		NA	NA
ear	gen_omim_ear_yes	0.184921	-1.08308	1.283147	1.203124	0.338553	3.607978	0.755659		-0.01987	-1.39101	1.135715	0.980325	0.248823	3.113398	0.974913		NA	NA		NA	NA
endocrine	gen_omim_endocrine_yes	0.952153	0.421856	1.482671	2.591283	1.524789	4.404696	0.000426		1.196117	0.478165	1.907841	3.307249	1.613112	6.738521	0.000998		0.217877	1.243434		0.154896338	1.167536926
eye	gen_omim_eye_yes	-0.06875	-0.63011	0.477691	0.933563	0.532535	1.612347	0.807445		-0.15367	-0.79461	0.464039	0.857556	0.451755	1.590485	0.631254		NA	NA		NA	NA
gi	gen_omim_gi_yes	-0.29415	-0.65022	0.057828	0.745167	0.521929	1.059533	0.10319		-0.10457	-0.4915	0.27835	0.900714	0.611708	1.320948	0.594114		NA	NA		NA	NA
hepatobiliary	gen_omim_hepatobiliary_yes	-0.293	-1.1182	0.479707	0.746022	0.326867	1.615602	0.470619		-0.64547	-1.68957	0.280241	0.524418	0.1846	1.323449	0.195131		NA	NA		NA	NA
immune	gen_omim_immune_yes	0.278185	-0.14869	0.698569	1.320731	0.861839	2.010873	0.197499		0.046765	-0.68232	0.73583	1.047875	0.505443	2.087213	0.896641		NA	NA		NA	NA
infection	gen_omim_infection_yes	0.233047	-0.26189	0.722432	1.262441	0.769594	2.059435	0.352636		0.238231	-0.29628	0.766419	1.269002	0.743579	2.152046	0.378714		NA	NA		NA	NA
metabolism	gen_omim_metabolism_yes	0.636062	0.298069	0.97566	1.889027	1.347254	2.652917	0.000231		0.527928	0.08995	0.965871	1.695416	1.09412	2.627075	0.018008		0.084695	1.088385		0.011376563	1.011441523
musculoskeletal	gen_omim_musculoskeletal_yes	0.214049	-0.09963	0.527754	1.238684	0.905175	1.69512	0.180807		0.2859	-0.08112	0.653439	1.33096	0.922084	1.92214	0.126746		NA	NA		0.039245178	1.040025443
neoplasm	gen_omim_neoplasm_yes	0.533812	-0.13093	1.188392	1.705421	0.87728	3.281801	0.111976		0.533812	-0.13093	1.188392	1.705421	0.87728	3.281801	0.111976		NA	NA		NA	NA
nervous	gen_omim_nervous_yes	-0.01654	-0.3053	0.271444	0.983596	0.736905	1.311857	0.910448		0.267309	-0.09063	0.625795	1.306444	0.913354	1.869732	0.14326		NA	NA		NA	NA
pregnancy	gen_omim_pregnancy_yes	0.311179	-1.01433	1.568157	1.365033	0.362644	4.797795	0.632798		0.559077	-0.86173	1.924256	1.749058	0.42243	6.850052	0.426027		NA	NA		NA	NA
mental	gen_omim_mental_yes	0.353576	-0.01715	0.723029	1.424151	0.982991	2.060665	0.060926		0.371056	-0.08904	0.82766	1.449264	0.914806	2.287959	0.112109		0.163284	1.177371		NA	NA
urologic	gen_omim_urologic_yes	0.591618	0.115107	1.06582	1.806909	1.121993	2.903218	0.014587		0.723119	0.181844	1.260413	2.060851	1.199427	3.526876	0.00846		0.11313	1.119777		0.296989895	1.3458017
repro	gen_omim_repro_yes	0.993491	0.428062	1.551227	2.700646	1.534282	4.717257	0.000513		0.913327	0.27293	1.538904	2.492601	1.313808	4.65948	0.004574		0.575129	1.777359		0.328021306	1.38821855
respiratory	gen_omim_respiratory_yes	0.142477	-0.21035	0.493275	1.153126	0.8103	1.637671	0.427019		0.027181	-0.36721	0.41789	1.027553	0.692664	1.518753	0.891956		NA	NA		NA	NA
skin	gen_omim_skin_yes	-0.07187	-0.45144	0.303625	0.930655	0.636711	1.354761	0.708848		-0.08137	-0.49811	0.329332	0.921856	0.607676	1.390039	0.699591		NA	NA		NA	NA
vascular	gen_omim_vascular_yes	0.196397	-0.13257	0.524479	1.21701	0.875839	1.689579	0.241024		0.086637	-0.3011	0.47102	1.090501	0.740006	1.601626	0.65975		0.016293	1.016426		NA	NA
blood	gen_omim_blood_no	-0.06826	-0.41805	0.281478	0.934015	0.658332	1.325087	0.701802		-0.07765	-0.44624	0.290561	0.925292	0.640033	1.337178	0.679215		NA	NA		NA	NA
heart	gen_omim_heart_no	0.18758	-0.08777	0.464246	1.206327	0.91597	1.590814	0.182585		0.217087	-0.08664	0.522831	1.242452	0.917011	1.686795	0.162311		NA	NA		NA	NA
congenital	gen_omim_congenital_no	0.556453	-0.75215	1.875506	1.744474	0.471353	6.524119	0.400224		-0.429	-3.69902	2.711292	0.651157	0.024748	15.04871	0.786016		NA	NA		NA	NA
ear	gen_omim_ear_no	0.283705	-0.36565	0.951975	1.328042	0.693746	2.59082	0.396474		0.290216	-0.3766	0.977593	1.336716	0.686187	2.658051	0.398499		NA	NA		NA	NA
endocrine	gen_omim_endocrine_no	0.435031	0.012475	0.863699	1.545012	1.012554	2.371919	0.044802		0.488916	-0.04701	1.03844	1.630547	0.954077	2.824806	0.076558		NA	NA		NA	NA
eye	gen_omim_eye_no	0.047614	-0.35236	0.449448	1.048766	0.703028	1.567447	0.815684		0.031798	-0.42396	0.489774	1.032309	0.65445	1.631947	0.891298		NA	NA		NA	NA
gi	gen_omim_gi_no	-0.19492	-0.47221	0.081635	0.822901	0.623622	1.08506	0.167483		-0.08399	-0.38774	0.219655	0.919442	0.678591	1.245646	0.587535		NA	NA		NA	NA
hepatobiliary	gen_omim_hepatobiliary_no	-0.15745	-0.59371	0.28023	0.854317	0.552273	1.323434	0.479237		-0.01814	-0.48015	0.448807	0.982025	0.618691	1.566442	0.938856		NA	NA		NA	NA
immune	gen_omim_immune_no	0.179531	-0.16292	0.523773	1.196655	0.849661	1.688386	0.305004		0.034616	-0.44613	0.522257	1.035222	0.6401	1.685828	0.888343		NA	NA		NA	NA
infection	gen_omim_infection_no	0.035065	-0.24121	0.312199	1.035687	0.785677	1.366426	0.803738		-0.02538	-0.31735	0.267362	0.974942	0.728073	1.306513	0.864824		NA	NA		NA	NA
metabolism	gen_omim_metabolism_no	0.197369	-0.14211	0.536591	1.218193	0.867528	1.710167	0.253936		0.22929	-0.1657	0.624887	1.257707	0.847297	1.868034	0.255031		NA	NA		NA	NA
musculoskeletal	gen_omim_musculoskeletal_no	-0.08626	-0.39685	0.222583	0.917359	0.672435	1.2493	0.584903		-0.08239	-0.44194	0.274764	0.92091	0.642789	1.31622	0.651931		NA	NA		NA	NA
neoplasm	gen_omim_neoplasm_no	-0.20252	-0.69404	0.287333	0.816667	0.499554	1.332867	0.417514		-0.20252	-0.69404	0.287333	0.816667	0.499554	1.332867	0.417514		NA	NA		NA	NA
nervous	gen_omim_nervous_no	0.123526	-0.17412	0.420969	1.131479	0.8402	1.523437	0.415581		0.209155	-0.13489	0.553539	1.232635	0.873812	1.739397	0.233317		NA	NA		NA	NA
pregnancy	gen_omim_pregnancy_no	-0.21143	-1.1365	0.706452	0.809426	0.32094	2.026786	0.650078		-0.24671	-1.24838	0.746712	0.781365	0.286968	2.11005	0.624435		NA	NA		NA	NA
mental	gen_omim_mental_no	0.076743	-0.27227	0.426049	1.079764	0.761648	1.531196	0.666353		0.2366	-0.15859	0.634078	1.266934	0.85335	1.885283	0.241378		NA	NA		NA	NA
urologic	gen_omim_urologic_no	-0.06371	-0.45245	0.325373	0.938276	0.636068	1.384547	0.747837		-0.03926	-0.47496	0.39765	0.961501	0.621908	1.488323	0.859769		NA	NA		NA	NA
repro	gen_omim_repro_no	-0.18886	-0.62197	0.243867	0.827903	0.536884	1.276174	0.391827		-0.15285	-0.62701	0.32164	0.858262	0.534189	1.379388	0.526901		NA	NA		NA	NA
respiratory	gen_omim_respiratory_no	0.017435	-0.28374	0.318731	1.017588	0.752966	1.375381	0.909625		-0.0855	-0.41672	0.245148	0.918052	0.659204	1.277811	0.612323		NA	NA		NA	NA
skin	gen_omim_skin_no	-0.24749	-0.54618	0.05007	0.78076	0.579156	1.051345	0.103498		-0.30631	-0.63671	0.022203	0.73616	0.529032	1.022451	0.068186		NA	NA		NA	NA
vascular	gen_omim_vascular_no	0.017479	-0.25792	0.292845	1.017632	0.772658	1.340235	0.900945		-0.05025	-0.3606	0.259874	0.950993	0.697255	1.296766	0.750731		NA	NA		NA	NA
blood	gen_gwas_blood_yes	0.354919	-0.14976	0.850343	1.426065	0.860912	2.34045	0.163569		0.588198	0.038603	1.127301	1.80074	1.039358	3.087313	0.033845		NA	NA		NA	NA
heart	gen_gwas_heart_yes	0.713666	0.258691	1.16798	2.041461	1.295233	3.215489	0.002073		0.798489	0.300843	1.293995	2.22218	1.350997	3.647328	0.001604		0.326082	1.38553		0.411220872	1.50865854
congenital	gen_gwas_congenital_yes	1.375561	-0.3206	2.978908	3.957297	0.725716	19.66634	0.096448		-18.9322	NA	132.4311	6.00E-09	NA	3.27E+57	0.994258		NA	NA		NA	NA
ear	gen_gwas_ear_yes	-14.9689	NA	93.37754	3.16E-07	NA	3.58E+40	0.977696		-14.911	NA	93.39451	3.34E-07	NA	3.64E+40	0.977782		NA	NA		NA	NA
endocrine	gen_gwas_endocrine_yes	0.325005	-0.35164	0.996775	1.384038	0.703535	2.709529	0.344111		-0.2471	-1.30438	0.754428	0.781066	0.271339	2.126396	0.6366		NA	NA		NA	NA
eye	gen_gwas_eye_yes	0.63102	-0.11954	1.352384	1.879528	0.887331	3.866634	0.092035		0.276686	-0.67362	1.148453	1.318752	0.509861	3.15331	0.549397		NA	NA		NA	NA
gi	gen_gwas_gi_yes	-0.02087	-0.52676	0.471569	0.979346	0.590514	1.602506	0.934585		0.242315	-0.306	0.776122	1.274196	0.736384	2.173028	0.379176		NA	NA		NA	NA
hepatobiliary	gen_gwas_hepatobiliary_yes	0.436959	-0.69645	1.448954	1.547993	0.498353	4.258659	0.42		0.582093	-0.59097	1.630988	1.78978	0.553788	5.108921	0.299306		NA	NA		NA	NA
immune	gen_gwas_immune_yes	0.117141	-0.30361	0.530757	1.124277	0.738146	1.700219	0.581612		0.197599	-0.43835	0.810552	1.218474	0.645099	2.24915	0.53365		NA	NA		NA	NA
infection	gen_gwas_infection_yes	-0.50691	-1.31933	0.24122	0.602354	0.267314	1.2728	0.200583		-0.57396	-1.55086	0.307662	0.563291	0.212065	1.360242	0.223055		-0.06381	0.938186		NA	NA
metabolism	gen_gwas_metabolism_yes	0.387763	0.008205	0.766002	1.47368	1.008239	2.15115	0.04471		0.673393	0.160949	1.182539	1.960879	1.174625	3.262648	0.009668		NA	NA		NA	NA
musculoskeletal	gen_gwas_musculoskeletal_yes	-0.30399	-0.77676	0.155086	0.737871	0.459894	1.167758	0.200355		-0.19664	-0.73299	0.321918	0.821485	0.480471	1.379772	0.464127		NA	NA		NA	NA
neoplasm	gen_gwas_neoplasm_yes	0.225651	-0.52521	0.944184	1.253139	0.591428	2.570714	0.545972		0.225651	-0.52521	0.944184	1.253139	0.591428	2.570714	0.545972		NA	NA		NA	NA
nervous	gen_gwas_nervous_yes	-0.01921	-0.40654	0.36527	0.980977	0.665953	1.440902	0.92223		-0.15743	-0.63971	0.317321	0.854335	0.527447	1.373444	0.518533		NA	NA		NA	NA
pregnancy	gen_gwas_pregnancy_yes	-13.1002	-354.394	30.43052	2.04E-06	1.23E-154	1.64E+13	0.98984		-12.5246	-346.384	30.97088	3.64E-06	3.69E-151	2.82E+13	0.990157		NA	NA		NA	NA
mental	gen_gwas_mental_yes	0.360976	-0.09129	0.80976	1.43473	0.912752	2.247368	0.116007		0.325475	-0.23716	0.878354	1.384688	0.788866	2.406935	0.251995		0.269078	1.308757		0.082018097	1.085475454
urologic	gen_gwas_urologic_yes	0.391469	-1.19961	1.682431	1.479152	0.301311	5.378615	0.587261		0.866324	-0.6407	2.125675	2.378152	0.526925	8.378547	0.211185		NA	NA		NA	NA
repro	gen_gwas_repro_yes	0.856832	0.134536	1.571122	2.355686	1.144006	4.812043	0.019206		0.499773	-0.38899	1.349439	1.648347	0.677744	3.855261	0.257918		0.150329	1.162216		NA	NA
respiratory	gen_gwas_respiratory_yes	0.00276	-0.76588	0.732457	1.002764	0.464923	2.080184	0.99422		-0.08004	-1.03061	0.780216	0.923077	0.356789	2.181943	0.861441		NA	NA		NA	NA
skin	gen_gwas_skin_yes	0.506035	-0.19968	1.198747	1.658701	0.818992	3.31596	0.154916		0.468862	-0.34964	1.251718	1.598175	0.70494	3.496343	0.248889		NA	NA		NA	NA
vascular	gen_gwas_vascular_yes	0.230687	-0.15872	0.61794	1.259465	0.853232	1.855103	0.243914		0.252312	-0.2203	0.716826	1.286998	0.802281	2.047922	0.290502		NA	NA		NA	NA
blood	gen_gwas_blood_no	0.518247	0.172945	0.867042	1.679082	1.188801	2.379862	0.003396		0.603241	0.23046	0.981304	1.828034	1.259179	2.667932	0.001619		NA	NA		NA	NA
heart	gen_gwas_heart_no	0.312906	0.036227	0.591103	1.367393	1.036892	1.805979	0.026973		0.422683	0.119162	0.728682	1.52605	1.126552	2.072348	0.006519		NA	NA		NA	NA
congenital	gen_gwas_congenital_no	0.641124	-0.40781	1.745746	1.898613	0.665106	5.730172	0.239304		-1.13879	-3.44451	1.009898	0.320207	0.03192	2.74532	0.305653		NA	NA		NA	NA
ear	gen_gwas_ear_no	0.022093	-0.61934	0.670513	1.022339	0.538301	1.955239	0.946291		0.086066	-0.57478	0.7556	1.089878	0.562827	2.128888	0.799086		NA	NA		NA	NA
endocrine	gen_gwas_endocrine_no	0.180966	-0.20947	0.57452	1.198375	0.81101	1.776279	0.364931		0.045755	-0.44905	0.542871	1.046818	0.638235	1.72094	0.856194		NA	NA		NA	NA
eye	gen_gwas_eye_no	0.265352	-0.13366	0.669477	1.30389	0.874886	1.953216	0.194648		0.308827	-0.12797	0.752914	1.361827	0.879882	2.123178	0.168599		NA	NA		NA	NA
gi	gen_gwas_gi_no	0.214063	-0.05619	0.48524	1.2387	0.945355	1.624564	0.120985		0.23841	-0.06425	0.542139	1.26923	0.937772	1.719681	0.123015		NA	NA		NA	NA
hepatobiliary	gen_gwas_hepatobiliary_no	0.692472	0.240887	1.157495	1.998649	1.272377	3.181953	0.003011		0.629181	0.149012	1.123258	1.876073	1.160687	3.074856	0.01119		NA	NA		NA	NA
immune	gen_gwas_immune_no	0.056089	-0.28731	0.399596	1.057691	0.750275	1.491222	0.748695		-0.00784	-0.48522	0.471166	0.992194	0.615564	1.601861	0.97433		NA	NA		NA	NA
infection	gen_gwas_infection_no	0.203814	-0.06352	0.47248	1.22607	0.938457	1.603967	0.135859		0.233104	-0.04916	0.51715	1.262513	0.95203	1.677241	0.106409		NA	NA		NA	NA
metabolism	gen_gwas_metabolism_no	0.217149	-0.09242	0.526995	1.24253	0.911726	1.693835	0.169072		0.266234	-0.10984	0.643297	1.305041	0.89598	1.902744	0.165363		NA	NA		NA	NA
musculoskeletal	gen_gwas_musculoskeletal_no	0.075156	-0.20292	0.353634	1.078053	0.816343	1.424233	0.596338		0.121616	-0.20625	0.450479	1.12932	0.813633	1.569064	0.467527		NA	NA		NA	NA
neoplasm	gen_gwas_neoplasm_no	0.164188	-0.32534	0.658913	1.178436	0.722284	1.93269	0.512396		0.164188	-0.32534	0.658913	1.178436	0.722284	1.93269	0.512396		NA	NA		NA	NA
nervous	gen_gwas_nervous_no	0.009146	-0.25066	0.268803	1.009188	0.778286	1.308398	0.944949		-0.2104	-0.52186	0.099933	0.810261	0.593414	1.105097	0.184383		NA	NA		NA	NA
pregnancy	gen_gwas_pregnancy_no	1.218645	0.319745	2.199971	3.382603	1.376777	9.024749	0.010458		1.448162	0.464396	2.540115	4.255284	1.591053	12.68113	0.005842		NA	NA		NA	NA
mental	gen_gwas_mental_no	-0.0304	-0.34907	0.287874	0.97006	0.705347	1.333589	0.851482		0.041489	-0.3317	0.415662	1.042361	0.7177	1.515373	0.827532		NA	NA		NA	NA
urologic	gen_gwas_urologic_no	0.369457	0.006558	0.737157	1.446949	1.00658	2.089984	0.047187		0.41922	0.008397	0.836829	1.520775	1.008432	2.309034	0.046962		NA	NA		NA	NA
repro	gen_gwas_repro_no	0.279904	-0.12372	0.687945	1.323003	0.883624	1.989622	0.175842		0.32728	-0.11682	0.778491	1.38719	0.889744	2.178183	0.151128		NA	NA		NA	NA
respiratory	gen_gwas_respiratory_no	0.309267	0.03593	0.584401	1.362426	1.036583	1.793917	0.026992		0.394382	0.092782	0.698712	1.483467	1.097222	2.011161	0.010675		NA	NA		NA	NA
skin	gen_gwas_skin_no	0.000245	-0.28265	0.283763	1.000245	0.753786	1.328118	0.998648		0.010519	-0.29773	0.319692	1.010575	0.742501	1.376703	0.946711		NA	NA		NA	NA
vascular	gen_gwas_vascular_no	0.087091	-0.17821	0.35244	1.090996	0.836766	1.422534	0.519773		0.006054	-0.29104	0.302836	1.006073	0.747484	1.353693	0.968101		NA	NA		NA	NA

Supplementary Table 9. Coefficients (as beta, and transformed to odds ratios) for genetics variables in side effect models with tissue-specific target gene expression included as quantitative variables. Confidence intervals and p values are outputs from the *glm* function in R.