Supplementary Table 1: Case study 1 ML performance

Cohort	Model	n folds	AUROC mean	AUROC sd	AUROC t stat vs chance	AUROC p value vs chance	Spearman mean	Spearman sd	Pearson mean	Pearson sd
Breast	ElasticNet	50	0.7749	0.1729	11.1319	5.08e-15	0.4324	0.2597	0.4576	0.2815
Breast	Random Forest	50	0.7002	0.1861	7.531	1.00e-09	0.3132	0.2833	0.3759	0.2667
Breast	Lassoed Forest	50	0.6933	0.1779	7.6043	7.73e-10	0.2812	0.2706	0.3272	0.2719
Lung	ElasticNet	30	0.7303	0.2447	5.067	2.11e-05	0.3425	0.4356	0.4257	0.3909
Lung	Random Forest	30	0.6885	0.2405	4.2216	2.19e-04	0.2878	0.411	0.3597	0.4135
Lung	Lassoed Forest	30	0.7887	0.2832	5.4916	6.48e-06	0.4552	0.3865	0.4918	0.4215

Supplementary Table 2: Case study 1 Hallmark GSEA

Pathway	NES breast	FDR breast	NES lung	FDR lung
Myc Targets V1	-2.9729	0	-2.4768	0
E2F Targets	-2.9126	0	-2.4427	0
G2-M Checkpoint	-2.2727	0	-2.6984	0
mTORC1 Signaling	-1.9926	0.0002962	-1.8832	0.0005378
Oxidative Phosphorylation	-1.667	0.0078	-1.8462	0.0007376

Supplementary Table 3: Case study 2 ML model performance

Model	n folds	Precision mean	Precision sd	Recall mean	Recall sd	F1 mean	F1 sd	Balanced Acc mean	Balanced Acc sd	BalancedAcc t stat vs chance	BalancedAcc p value vs chance
ResNet18	5	0.8401	0.0177	0.8508	0.0102	0.8434	0.014	0.8508	0.0102	127.3409	2.28e-08
Random Forest	5	0.8035	0.0316	0.7994	0.043	0.7979	0.035	0.7994	0.043	27.9037	9.81e-06

Supplementary Table 4: Case study 2 drug response per class performance

model	category	precision	recall	f1	support
ResNet18	cat1	0.8952	0.9246	0.9097	305
ResNet18	cat2	0.9048	0.8468	0.8748	359
ResNet18	cat3	0.8581	0.8294	0.8435	299
ResNet18	cat4	0.7577	0.8075	0.7818	213
ResNet18	cat5	0.77	0.8462	0.8063	91
RandomForest	cat1	0.8847	0.8557	0.87	305
RandomForest	cat2	0.8434	0.8552	0.8492	359
RandomForest	cat3	0.8163	0.8027	0.8094	299
RandomForest	cat4	0.7188	0.7559	0.7368	213
RandomForest	cat5	0.7333	0.7253	0.7293	91

Supplementary Table 5: Case study 3 NeST-VNN model performance

Cohort	n	n sensitive	n resistant	AUROC	AUROC ci lo	AUROC ci hi	AUROC bootstrap p vs chance
McGill cisplatin	29	16	13	0.4856	0.2596	0.697	9.16e-01
UHN carboplatin complete	68	12	56	0.5774	0.371	0.7711	4.80e-01
UHN carboplatin strict	36	5	31	0.8387	0.626	0.9844	1.20e-02

Supplementary Table 6: Case study 3 capped vs. uncapped response-window AUROC comparison

Cohort	AUROC capped	AUROC capped ci lo	AUROC capped ci hi	n sensitive capped	n capped	AUROC uncapped	AUROC uncapped ci lo	AUROC uncapped ci hi	n sensitive uncapped	n uncapped	delta capped minus uncapped
McGill cisplatin	0.4856	0.2596	0.697	16	29	0.4571	0.2308	0.6778	15	29	0.0284
UHN carboplatin complete	0.5774	0.371	0.7711	12	68	0.5865	0.4143	0.7547	16	68	-0.0092
UHN carboplatin strict	0.8387	0.626	0.9844	5	36	0.7615	0.55	0.9495	10	36	0.0772

Supplementary Table 7: Case study 3 AUROC sensitivity to response-threshold percentile

cohort	percentile	cutoff	n sensitive	auroc	ci lo	ci hi	bootstrap p vs chance
McGill cisplatin	10	-79.9331	3	0.4872	0	0.963	9.50e-01
McGill cisplatin	20	-74.6526	6	0.6087	0.3	0.9201	5.04e-01
McGill cisplatin	30	-63.4445	9	0.5611	0.3105	0.7949	6.28e-01
McGill cisplatin	40	-54.4338	12	0.4853	0.2667	0.7239	9.30e-01
McGill cisplatin	50	-44.7824	14	0.5048	0.2761	0.7164	9.38e-01
McGill cisplatin	60	56.5516	17	0.5245	0.3	0.7286	8.16e-01
McGill cisplatin	70	80.0154	20	0.5722	0.3384	0.7843	5.22e-01
McGill cisplatin	80	86.9632	23	0.413	0.1888	0.6451	4.62e-01
McGill cisplatin	90	87.5849	26	0.4487	0.2	0.6786	7.49e-01
UHN carboplatin complete	10	-55.4096	7	0.6909	0.4284	0.8889	1.28e-01
UHN carboplatin complete	20	20.4316	14	0.5899	0.399	0.7633	3.60e-01
UHN carboplatin complete	30	56.359	21	0.5147	0.346	0.6851	8.92e-01
UHN carboplatin complete	40	68.6501	27	0.5104	0.359	0.6577	9.04e-01
UHN carboplatin complete	50	74.6356	34	0.436	0.2925	0.5904	4.18e-01
UHN carboplatin complete	60	78.2098	41	0.4941	0.3436	0.6551	9.60e-01
UHN carboplatin complete	70	84.7067	47	0.464	0.3004	0.6415	6.74e-01
UHN carboplatin complete	80	86.4634	54	0.4696	0.2699	0.6708	7.66e-01
UHN carboplatin complete	90	88.1185	61	0.6136	0.3437	0.8476	3.44e-01
UHN carboplatin strict	10	-64.6715	4	0.8125	0.4854	0.9853	5.65e-02
UHN carboplatin strict	20	44.2254	7	0.8079	0.5936	0.9667	4.00e-03
UHN carboplatin strict	30	59.8864	11	0.5891	0.3604	0.8149	4.50e-01
UHN carboplatin strict	40	65.2752	14	0.6201	0.4186	0.8064	2.44e-01
UHN carboplatin strict	50	73.21	18	0.5278	0.3378	0.7219	8.30e-01
UHN carboplatin strict	60	76.7412	21	0.5016	0.3031	0.7001	1
UHN carboplatin strict	70	82.796	25	0.5055	0.2946	0.7084	9.88e-01
UHN carboplatin strict	80	84.7197	28	0.5268	0.2812	0.7679	8.30e-01
UHN carboplatin strict	90	85.7063	32	0.5781	0.3235	0.8286	5.91e-01

Supplementary Table 8: Case study 3 NeST-VNN gene coverage by cohort

cohort	data type	genes covered	total genes	pct covered
UHN Carboplatin	Mutation	670	718	93.3
UHN Carboplatin	CNV	711	718	99
McGill Cisplatin	Mutation	235	718	32.7
McGill Cisplatin	CNV	717	718	99.9

Supplementary Table 9: Case study 3 mutation/CNA/CND event burden comparison (Mann-Whitney U)

feature type	U stat	p value	n UHN	n McGill
Mutation	1823.5	4.02e-11	68	29
CNA	858.5	3.17e-01	68	29
CND	1175.5	1.36e-01	68	29

Supplementary Table 10: Case study 3 growth-curve slope distribution comparison (Kolmogorov-Smirnov)

measure	KS D	p value	n McGill	n UHN
slope.control	0.3222	2.24e-02	29	67
slope.treatment	0.4097	1.42e-03	29	68

Supplementary Table 11: Case study 4 curated paclitaxel-related gene list

Gene	Function
ABCB1	Drug efflux transporter; major mediator of taxane resistance via P-glycoprotein
ABCC1	ATP-binding cassette transporter involved in multidrug resistance
ABCC2	Drug efflux transporter associated with chemotherapy resistance
ABCC3	ABC transporter involved in xenobiotic/drug transport
ABCC10	Transporter implicated in taxane efflux and resistance
ABCG2	Breast cancer resistance protein; drug efflux transporter
AKT1	PI3K/AKT survival signaling; may protect cells from taxane-induced apoptosis
AKT2	AKT pathway kinase involved in survival and therapy resistance
AKT3	AKT pathway kinase with roles in growth and survival signaling
AURKA	Mitotic kinase regulating spindle assembly and chromosome segregation
AURKB	Chromosomal passenger kinase regulating mitosis and cytokinesis
BAK1	Pro-apoptotic BCL2-family protein involved in mitochondrial apoptosis
BAX	Pro-apoptotic BCL2-family protein promoting taxane-induced apoptosis
BCL2	Anti-apoptotic protein; may reduce paclitaxel-induced cell death
BCL2L1	Anti-apoptotic BCL-XL; promotes survival after mitotic stress
BUB1	Spindle assembly checkpoint kinase
BUB1B	Spindle checkpoint regulator also known as BUBR1
BUB3	Spindle assembly checkpoint component
CASP3	Executioner caspase mediating apoptosis
CASP7	Executioner caspase involved in apoptotic cell death
CASP8	Initiator caspase linking death receptor signaling to apoptosis
CASP9	Initiator caspase in mitochondrial apoptosis
CCNB1	Cyclin B1; controls G2/M transition with CDK1
CCNB2	Cyclin B2; regulates mitotic entry and progression
CDC20	APC/C activator controlling metaphase-anaphase transition
CDH1	Epithelial marker; loss associated with EMT and therapy resistance
CDK1	Core mitotic kinase controlling G2/M progression
CENPA	Centromere histone variant required for chromosome segregation
CENPE	Kinetochore motor protein involved in spindle checkpoint control
CENPF	Centromere-associated protein involved in mitosis
CYP2C8	Major paclitaxel-metabolizing enzyme
CYP3A4	Paclitaxel-metabolizing enzyme in xenobiotic metabolism
CYP3A5	CYP3A family enzyme involved in taxane metabolism

Gene	Function
ERBB2	HER2 receptor tyrosine kinase; breast cancer therapy-relevant signaling
ESR1	Estrogen receptor alpha; breast cancer subtype and therapy response marker
FOXM1	Mitotic transcription factor associated with proliferation and taxane resistance
KIF11	Mitotic kinesin required for bipolar spindle formation
KIF20A	Mitotic kinesin involved in cytokinesis and proliferation
KIF23	Kinesin involved in cytokinesis
KIF2C	Mitotic kinesin/MCAK involved in microtubule depolymerization
MAD1L1	Spindle assembly checkpoint regulator
MAD2L1	Spindle assembly checkpoint regulator
MDM2	Negative regulator of TP53-mediated apoptosis
MYC	Oncogenic transcription factor controlling proliferation and cell cycle programs
NDC80	Kinetochore complex component required for chromosome alignment
PIK3CA	PI3K pathway oncogene involved in survival signaling
PLK1	Mitotic kinase regulating spindle function and cell-cycle progression
PTEN	Negative regulator of PI3K/AKT signaling
RB1	Cell-cycle tumor suppressor controlling E2F activity
SLCO1B3	Drug uptake transporter implicated in taxane transport
SNAI1	EMT transcription factor associated with drug resistance
SNAI2	EMT transcription factor associated with invasive/resistant phenotypes
TP53	Tumor suppressor regulating DNA damage response, mitotic stress, and apoptosis
TUBA1A	Alpha-tubulin component of microtubules
TUBA1B	Alpha-tubulin component of microtubules
TUBA1C	Alpha-tubulin component of microtubules
TUBA3C	Alpha-tubulin family member
TUBA4A	Alpha-tubulin family member involved in microtubule structure
TUBB	Beta-tubulin; direct microtubule target class relevant to paclitaxel action
TUBB2A	Beta-tubulin isoform involved in microtubule structure
TUBB2B	Beta-tubulin isoform involved in microtubule dynamics
TUBB3	Beta-III tubulin; widely linked to taxane resistance
TUBB4A	Beta-tubulin isoform involved in microtubule structure
TUBB4B	Beta-tubulin isoform involved in microtubule structure
TUBB6	Beta-tubulin isoform involved in microtubule structure
TWIST1	EMT transcription factor associated with invasion and chemotherapy resistance
VIM	Mesenchymal marker associated with EMT and drug resistance
ZEB1	EMT transcription factor associated with therapy resistance

Gene	Function
ZEB2	EMT transcription factor associated with therapy resistance

Supplementary Table 12: Case study 4 classification model benchmark

analysis	omics	model	auroc mean	auroc sd	auroc ci lo	auroc ci hi	auroc p vs chance	auprc mean	auprc sd	balanced accuracy mean	balanced accuracy sd	f1 mean	sensitivity mean	specificity mean	n features mean	n folds	auroc p adj fdr
single omics	rna paired	random forest	0.7112	0.0966	0.6714	0.7511	8.28e-11	0.7708	0.1024	0.578	0.0838	0.7139	0.84	0.316	2045.6	25	8.28e-10
early fusion	rna cnv mutation	random forest	0.7045	0.1058	0.6608	0.7482	9.54e-10	0.7617	0.1073	0.6057	0.0975	0.7493	0.9007	0.3107	2969.8	25	4.77e-09
single omics	rna paired	logistic l2	0.6516	0.1066	0.6076	0.6956	2.36e-07	0.743	0.0964	0.6327	0.0889	0.6726	0.6521	0.6133	2045.6	25	7.85e-07
late fusion stacking	rna cnv mutation	stack random forest	0.6414	0.1544	0.5777	0.7052	1.21e-04	0.7342	0.1205	0.5983	0.1055	0.6293	0.6393	0.5573	3	25	3.03e-04
late fusion stacking	rna cnv mutation	stack logistic l2	0.6139	0.1272	0.5614	0.6663	1.57e-04	0.7246	0.1091	0.5844	0.1308	0.6146	0.5821	0.5867	3	25	3.14e-04
early fusion	rna cnv mutation	logistic l2	0.6092	0.162	0.5423	0.6761	2.53e-03	0.7035	0.1212	0.6441	0.1242	0.6953	0.7043	0.584	2969.8	25	3.62e-03
single omics	cnv	logistic l2	0.4824	0.1549	0.4185	0.5464	5.76e-01	0.6442	0.1	0.477	0.1284	0.5538	0.5714	0.3827	539.24	25	5.76e-01
single omics	cnv	random forest	0.4492	0.1587	0.3837	0.5147	1.23e-01	0.6174	0.1052	0.5131	0.1077	0.6499	0.7343	0.292	539.24	25	1.37e-01
single omics	mutation	random forest	0.4102	0.1835	0.3345	0.486	2.22e-02	0.5823	0.1009	0.4574	0.0916	0.6495	0.7907	0.124	385	25	2.77e-02
single omics	mutation	logistic l2	0.3591	0.1738	0.2874	0.4308	4.59e-04	0.5449	0.0825	0.4362	0.1359	0.5103	0.5164	0.356	385	25	7.65e-04

Supplementary Table 13: Case study 4 I-SPY2 paclitaxel-arm external validation

PDX pathway	PDX NES	PDX NES range	PDX direction	PDX FDR	ISPY2 biomarker	biomarker	n	OR	OR ci lo	OR ci hi	p value	gene overlap frac	ISPY2 direction	p bh	ISPY2 significant	concordant	call
Proliferation (E2F/G2M)	1.8135	1.72 to 1.90	Sensitive	0.0018	Module11 Prolif score	Module11 Prolif score	179	1.5166	0.9778	2.3523	6.29e-02	0.475	Sensitive	1.26e-01	False	True	concordant (not significant)
Interferon Alpha Response	-3.8493		Resistant	0	Module3 IFN score	Module3 IFN score	179	1.0215	0.6903	1.5118	9.15e-01	0.458	Sensitive	9.15e-01	False	False	null / inconclusive

Supplementary Table 14: Case study 4 UHN breast PDX intrinsic molecular subtype (AIMS)

model id	subtype	confidence	prob Basal	prob Her2	prob LumA	prob LumB	prob Normal
S67990	Basal	1	1	0	0	0	0
REF025	Basal	1	1	0	0	0	0
NOTCH01	Basal	1	1	0	0	0	0
REF057	Her2	1	0	1	0	0	0
S100534	Basal	1	1	0	0	0	0
REF043	Her2	0.5549	0	0.5549	0	0.4451	0
S108045	Basal	1	1	0	0	0	0
NOTCH18	Basal	1	1	0	0	0	0
NOTCH10	Basal	1	1	0	0	0	0
S71208	Basal	1	1	0	0	0	0
S48602	Basal	0.9896	0.9896	0.0104	0	0	0
S72877	Basal	1	1	0	0	0	0
S48342	Basal	1	1	0	0	0	0
REF006	Basal	1	1	0	0	0	0
S44441	LumB	1	0	0	0	1	0
S66684	Basal	1	1	0	0	0	0
S73230	Basal	1	1	0	0	0	0
S16720	Basal	1	1	0	0	0	0
REF005	Basal	1	1	0	0	0	0
S73471	Basal	1	1	0	0	0	0
S38807	Basal	1	1	0	0	0	0
REF014	Basal	1	1	0	0	0	0
S85277	Her2	1	0	1	0	0	0
REF063	Basal	0.8921	0.8921	0.1079	0	0	0
NOTCH06	Basal	1	1	0	0	0	0
REF036	Her2	1	0	1	0	0	0
REF034	Her2	0.9962	0.0038	0.9962	0	0	0
S66817	LumB	0.7546	0	0.2454	0	0.7546	0
S69196	Basal	1	1	0	0	0	0
REF044	Basal	1	1	0	0	0	0
INSB014	Basal	1	1	0	0	0	0
REF004	Her2	0.7631	0.2369	0.7631	0	0	0
S100804	Basal	1	1	0	0	0	0

model id	subtype	confidence	prob Basal	prob Her2	prob LumA	prob LumB	prob Normal
S48041	Her2	0.9993	0	0.9993	0	0.0007	0
REF037	LumB	0.9994	0	0.0006	0	0.9994	0
REF022	Basal	1	1	0	0	0	0
S67455	Basal	1	1	0	0	0	0
S44205	LumB	1	0	0	0	1	0
NOTCHB02	Basal	1	1	0	0	0	0
S70620	Basal	1	1	0	0	0	0
REF047	Basal	1	1	0	0	0	0
REF003	Her2	0.6937	0.3063	0.6937	0	0	0
INSB019	Her2	1	0	1	0	0	0
S18674	Basal	1	1	0	0	0	0
REF052	LumB	1	0	0	0	1	0
REF016	Basal	1	1	0	0	0	0
S28077	LumB	0.968	0	0.032	0	0.968	0
S73263	Basal	1	1	0	0	0	0
S71335	LumB	1	0	0	0	1	0
REF009	Her2	1	0	1	0	0	0
REF024	Basal	0.7733	0.7733	0.2267	0	0	0
S241417	Basal	1	1	0	0	0	0
REF007	Basal	1	1	0	0	0	0
S72955	Basal	1	1	0	0	0	0
S20710	Her2	1	0	1	0	0	0
S47904	Basal	1	1	0	0	0	0
REF002	Basal	1	1	0	0	0	0
REF035	Basal	1	1	0	0	0	0
S100672	Basal	1	1	0	0	0	0
REF001	Basal	1	1	0	0	0	0
S53782	Basal	1	1	0	0	0	0
REF023	Basal	1	1	0	0	0	0
REF019	Basal	1	1	0	0	0	0
REF041	Her2	1	0	1	0	0	0
S108099	Basal	1	1	0	0	0	0
REF048	Basal	1	1	0	0	0	0
REF013	Basal	0.8683	0.8683	0.1317	0	0	0