University of Luxembourg

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Model Ensembling as a Tool to Form Interpretable Multi-Omic Predictors of Cancer Pharmacosensitivity

January 11th
DLSM seminar

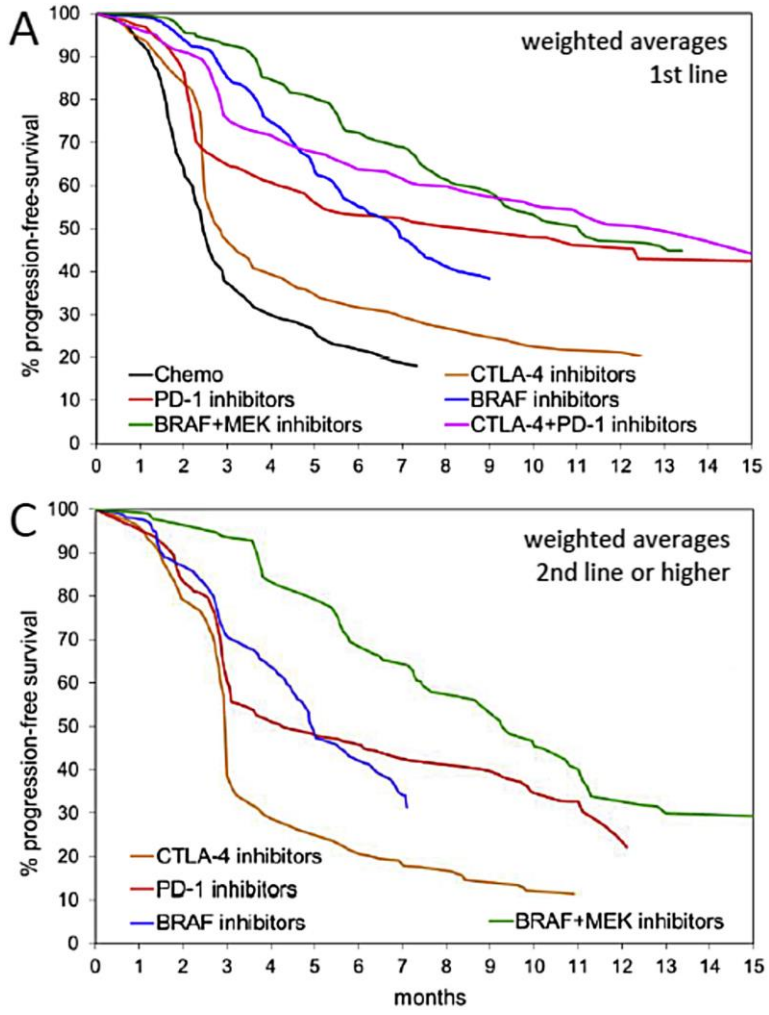
Systems Biology Group
DEPARTMENT OF LIFE SCIENCES AND MEDICINE

DLSM

UNIVERSITÉ DU LUXEMBOURG

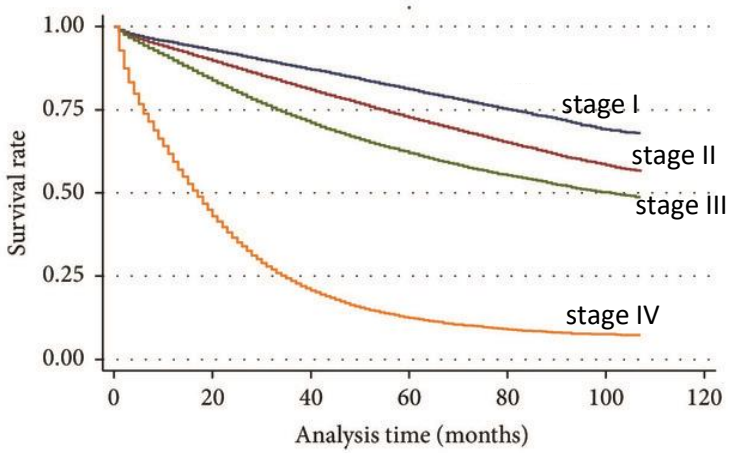
Patient responses to chemotherapies are highly variable

Melanoma



Ugurel *et al.*, Eur. J. Cancer (2016), 53; 125-34

Colon carcinoma



Ulanja *et al.*, J. Oncol. (2019):4315032

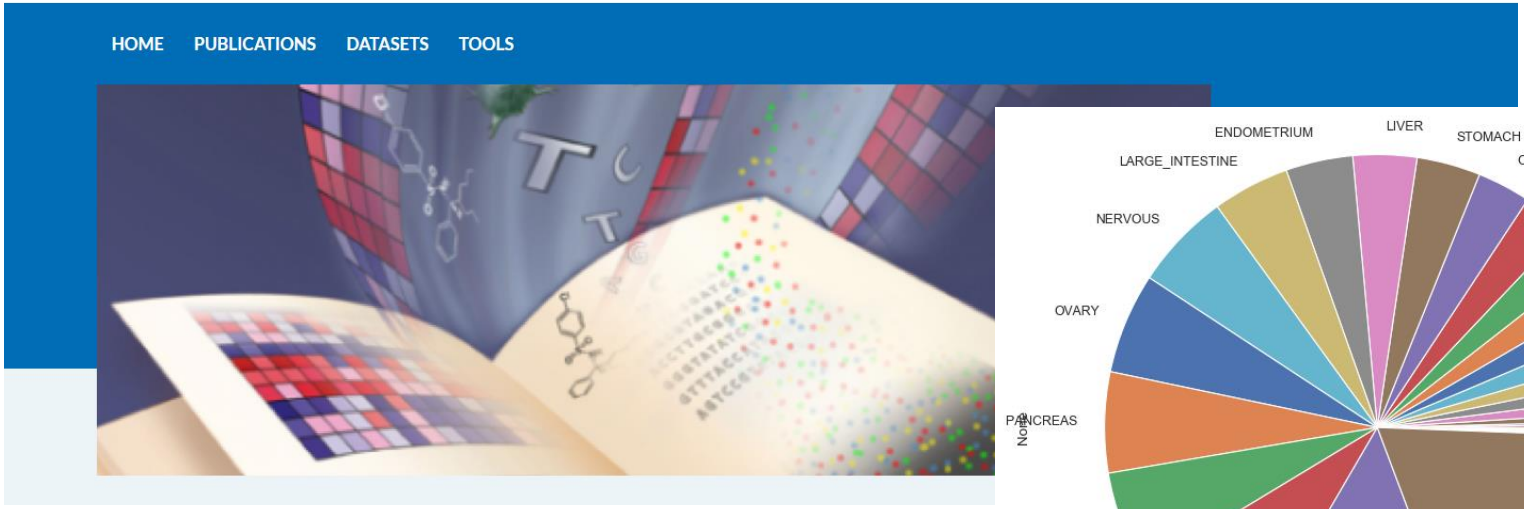
⇒ Unmet need for improvement of care of cancer patients

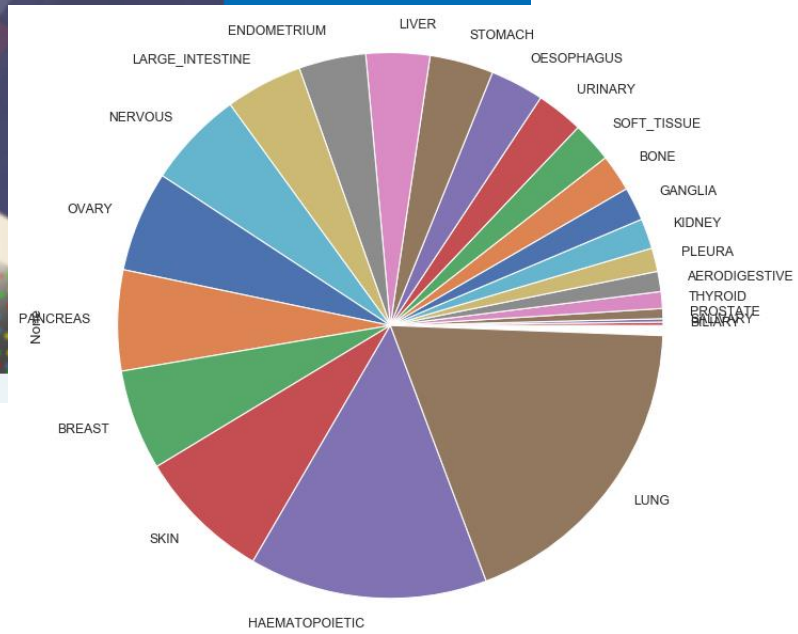
⇒ Nearly all biomarkers are genomic (BCR-ABL, EGFR, etc.)

⇒ Goal: develop predictors of drug response across omic types

CCLE dataset: a large-scale screening effort provides multi-omic data

CCLE Cancer Cell Line Encyclopedia



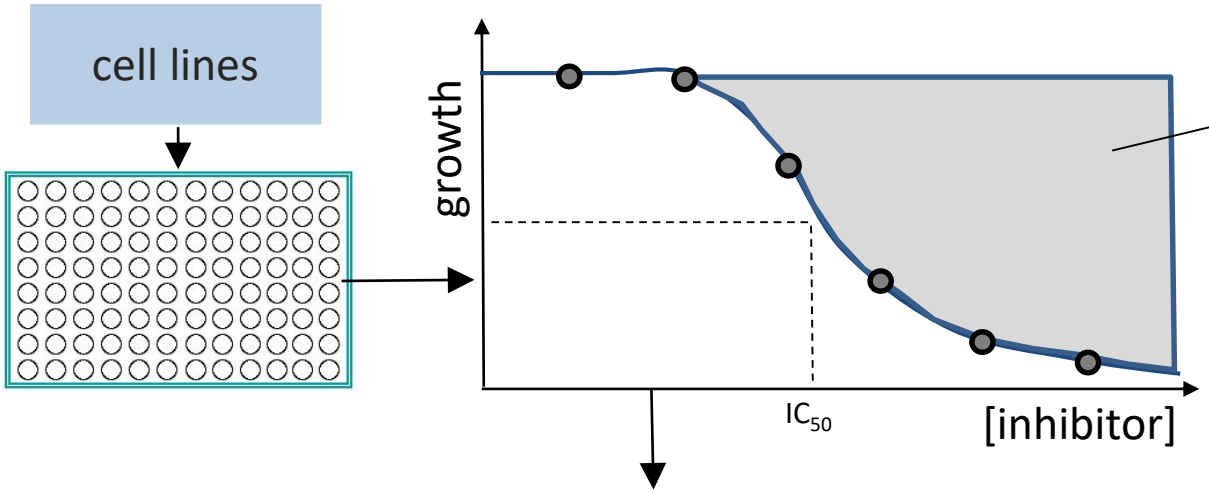


1000+ cell lines with near-complete multi-omics:
Genomics / Transcriptomics / Metabolomics / miRNA / RPPA and others
Dose-responses for 23 drugs

Barretina *et al.*, Nature (2012), 483,7391; 603-7

Ghandi *et al.*, Nature (2019), 569,7757; 503-8

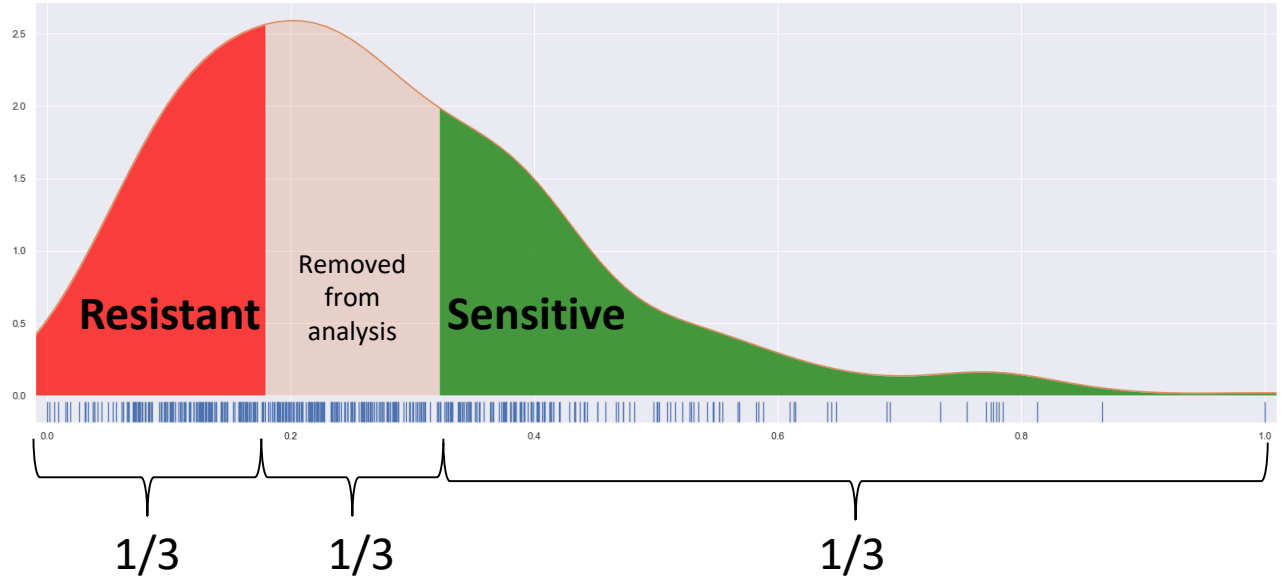
CCLE dataset: Activity Area as a proxy for cell line sensitivity



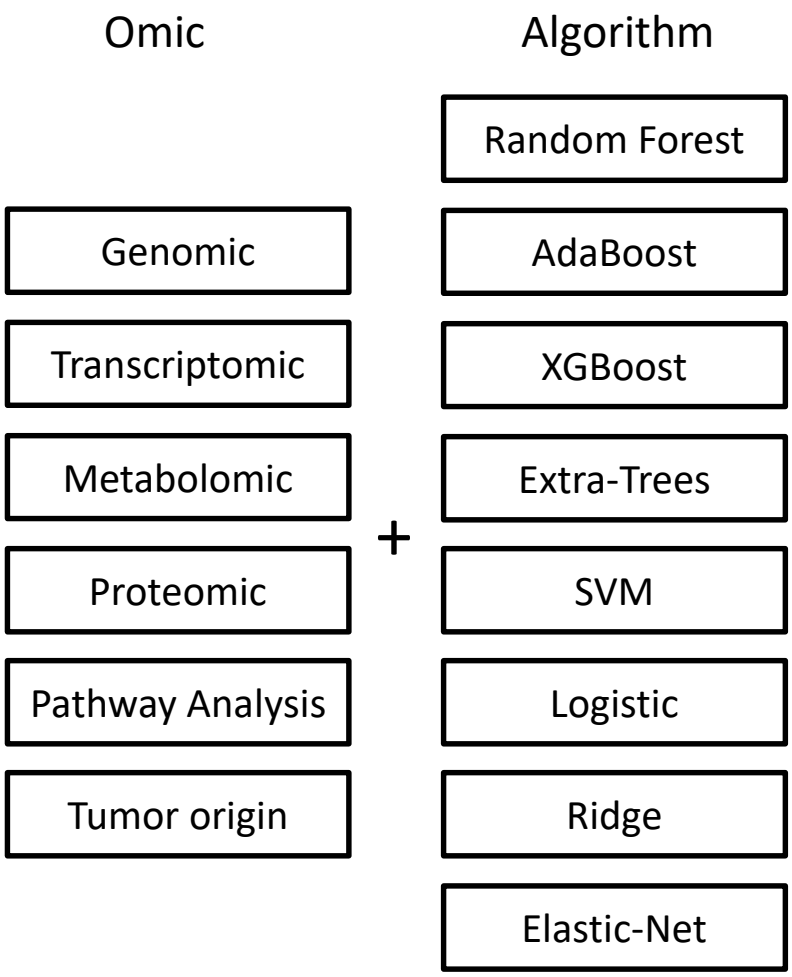
'Activity Area' : Area above the inhibition curve

Advantage vs IC_{50}: takes fractional killing into account

Distribution of **normalized ActArea**



Pipeline : Ensemble of omic-specific models and their predictions



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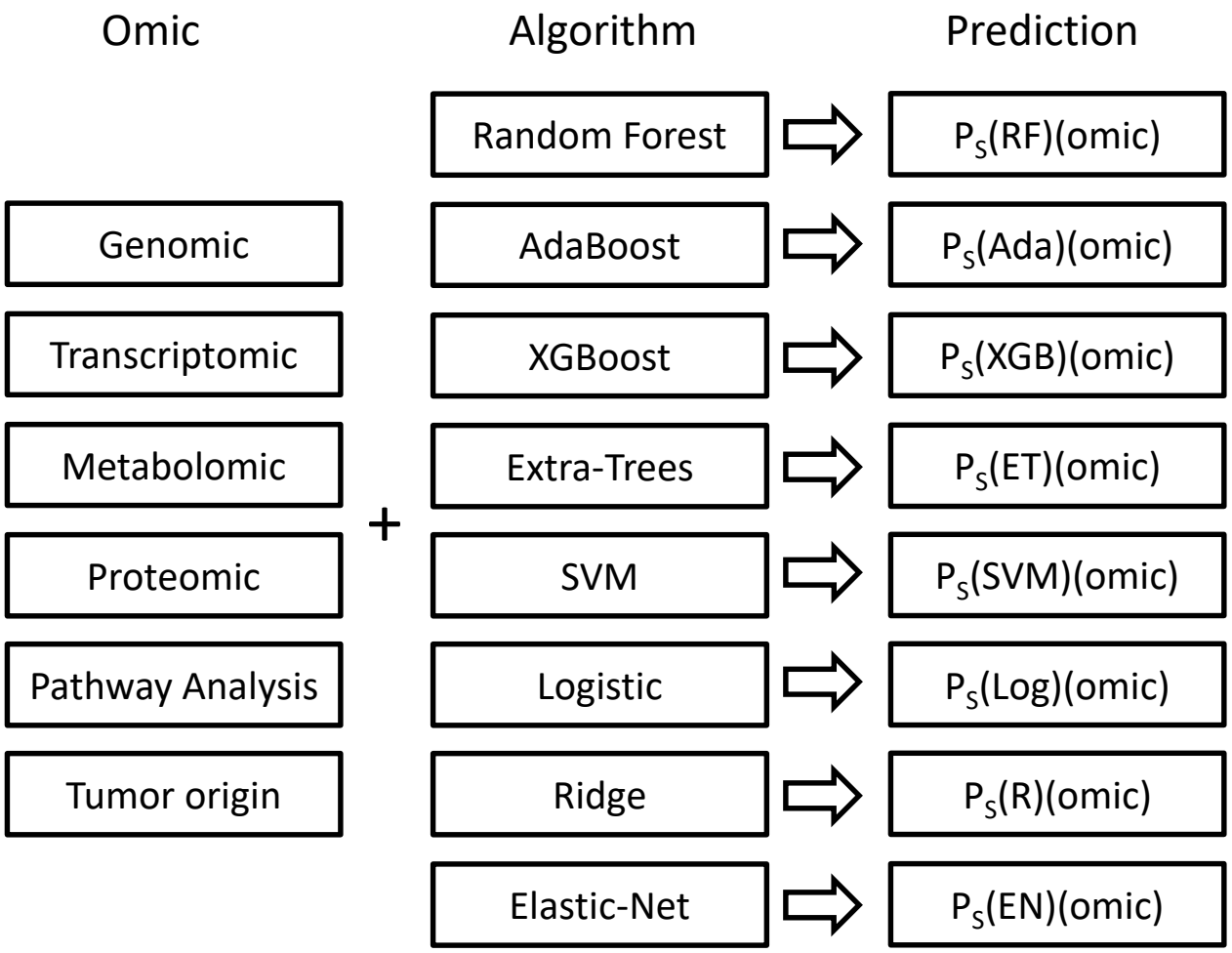

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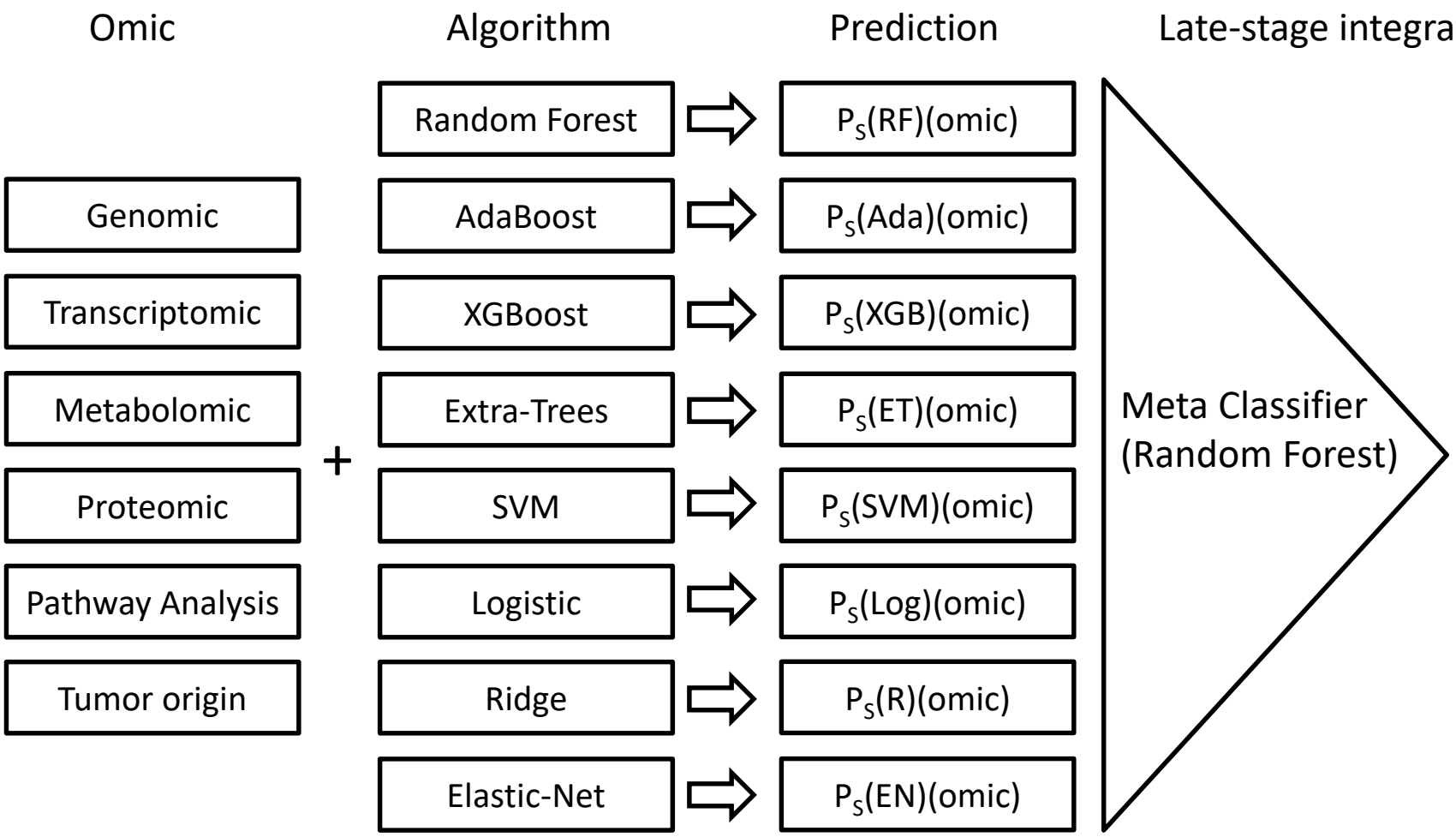
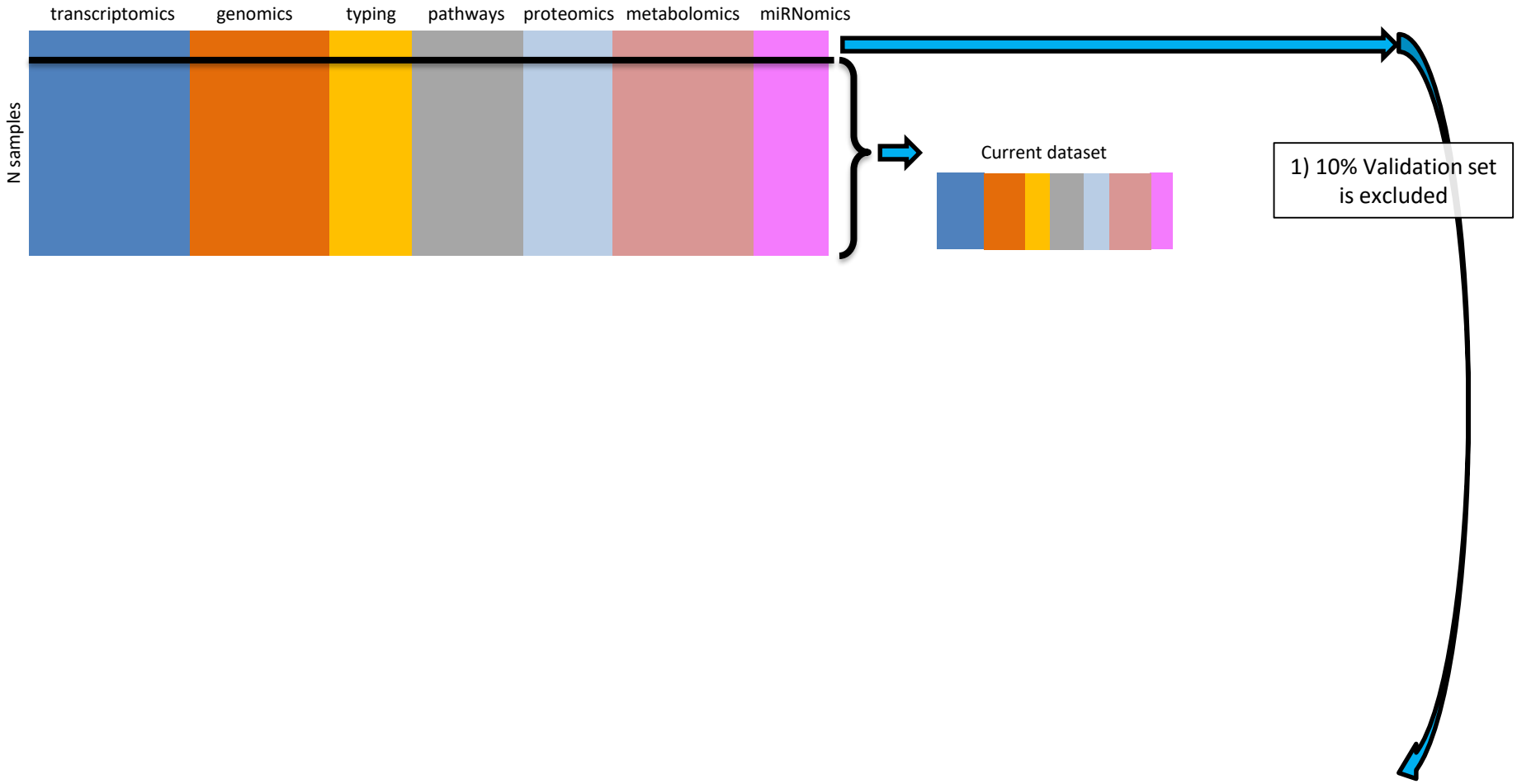


Validation procedure: nested cross-validation generates predictions for every sample while avoiding data leakage



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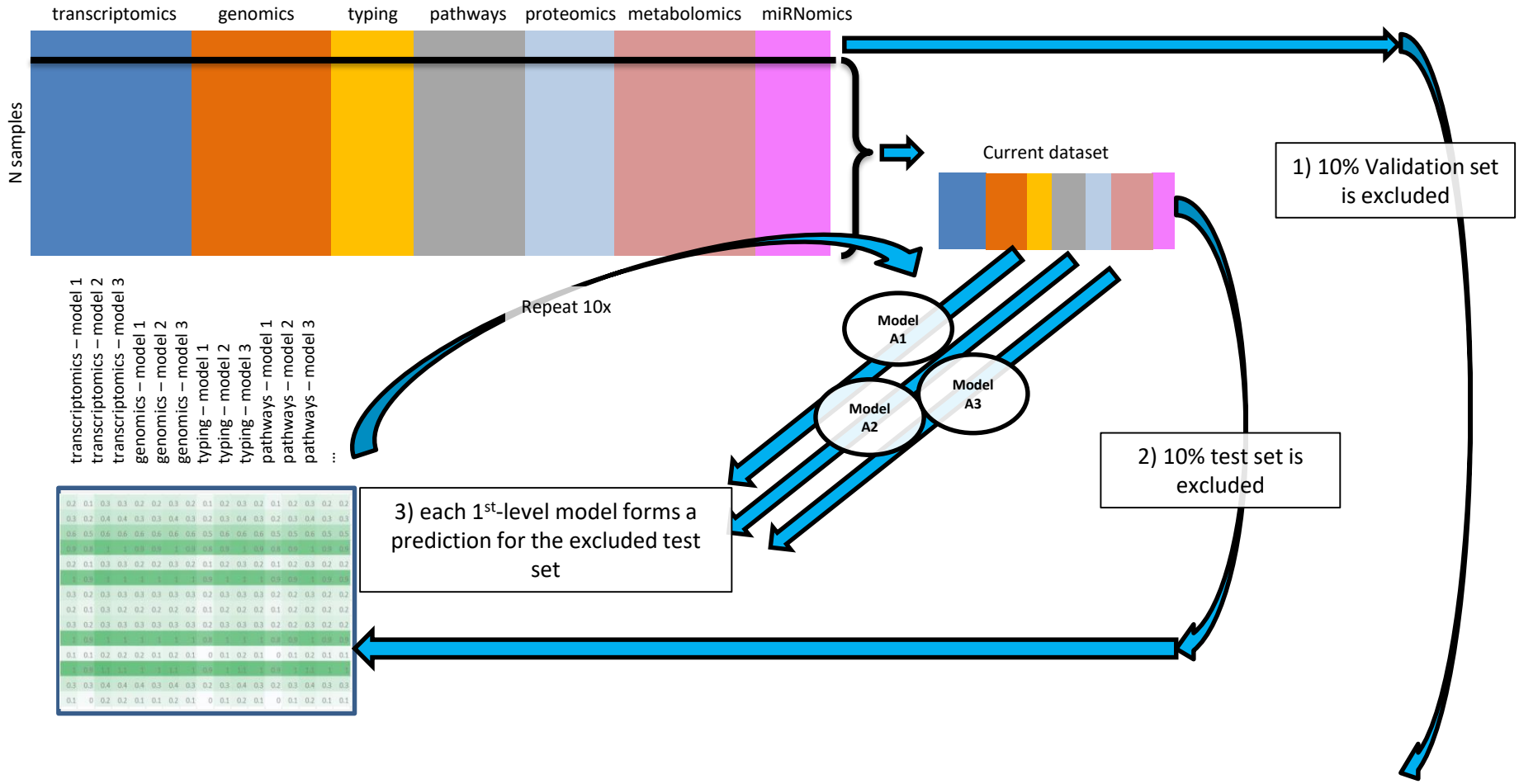

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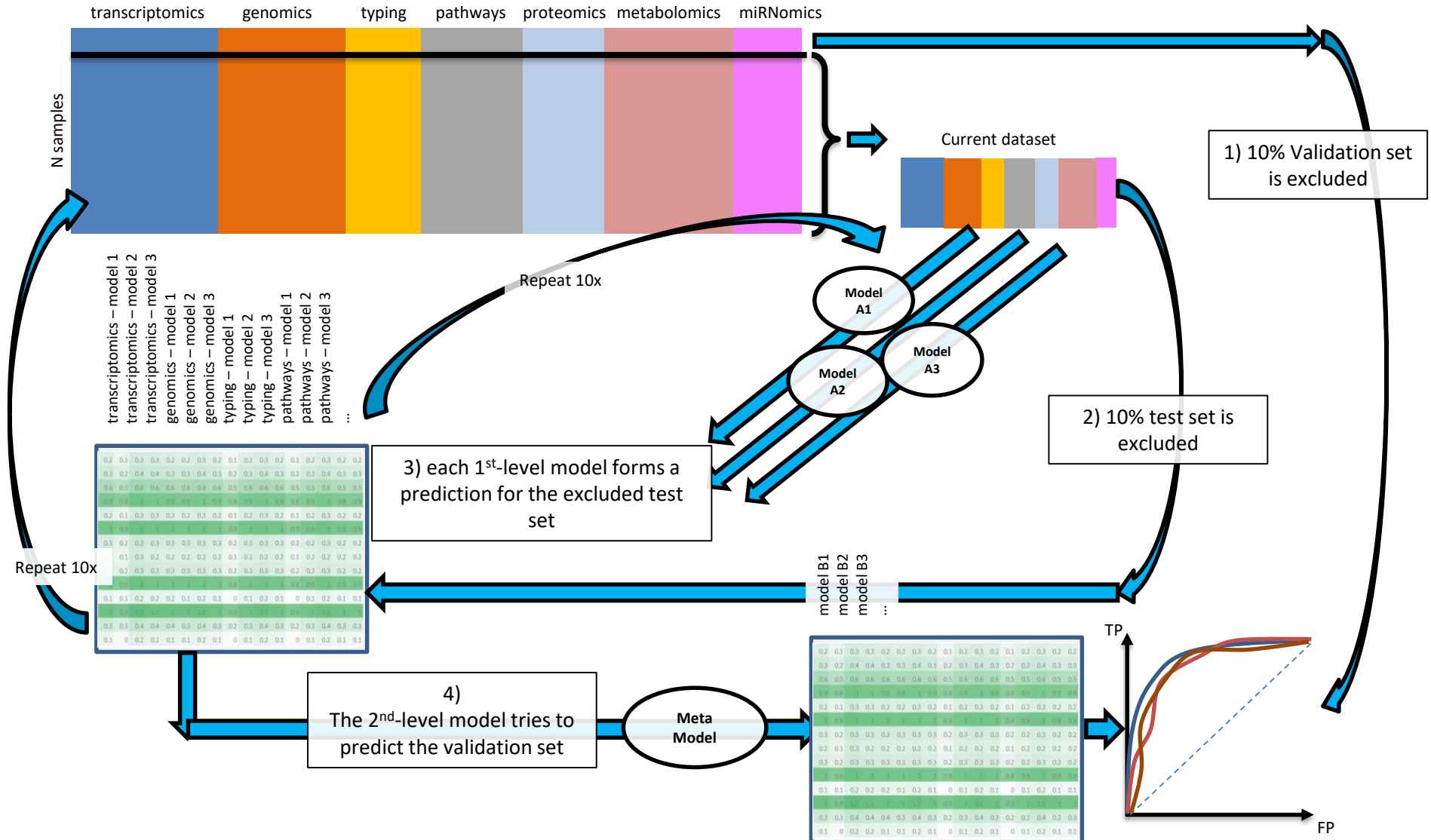
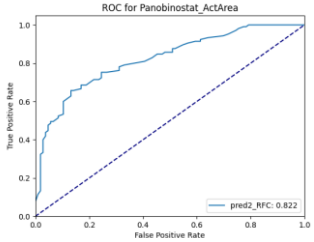
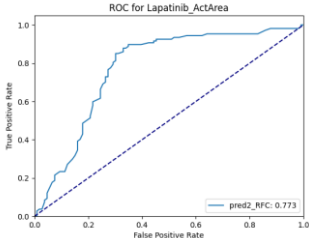
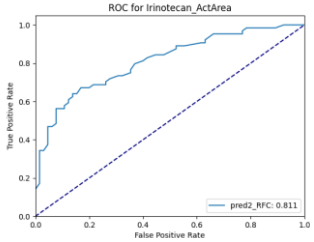
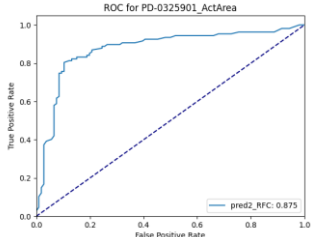


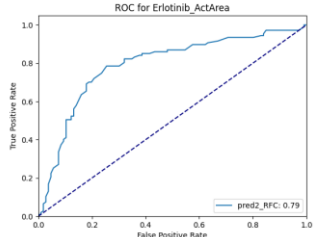
Mixed performance across 23 metaclassifiers

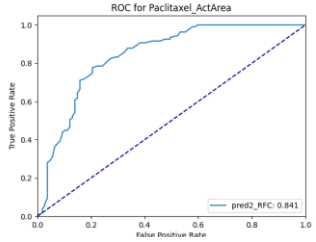


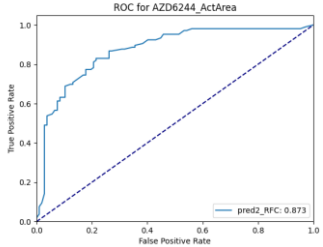


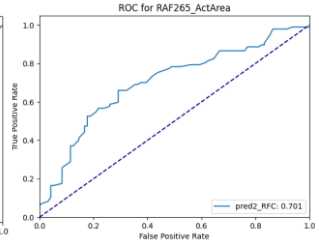


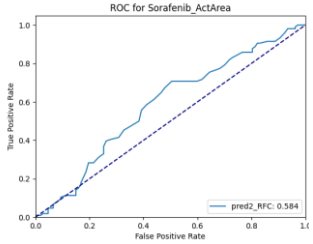


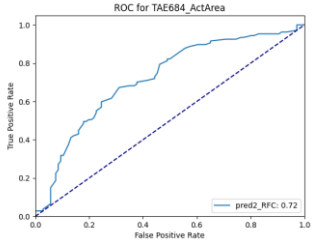


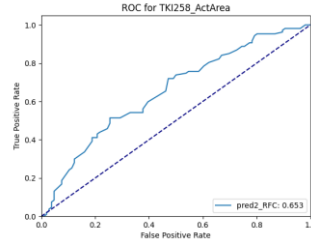


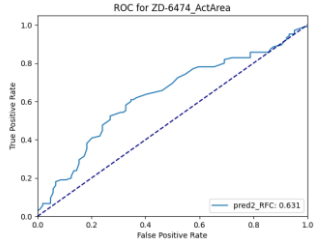


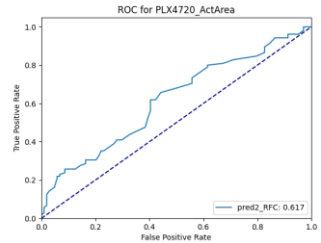


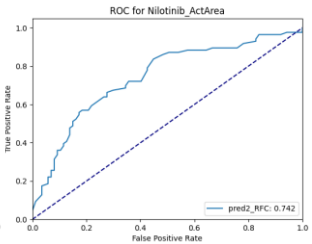


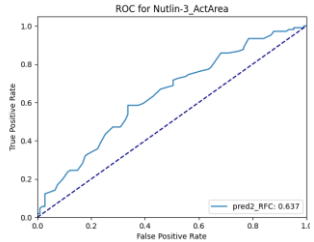


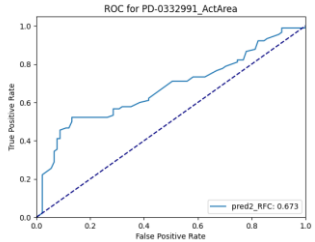


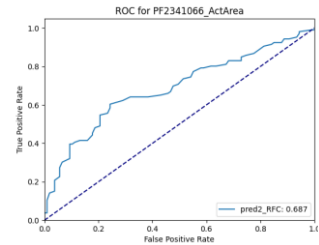


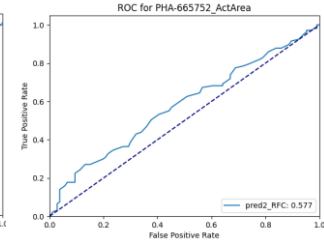


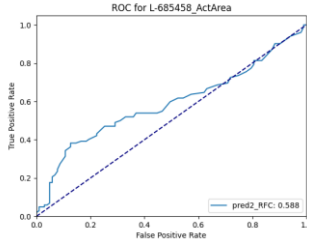


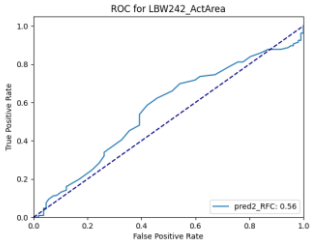


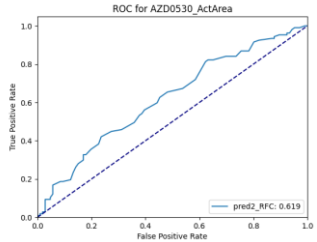


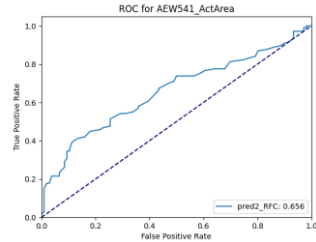


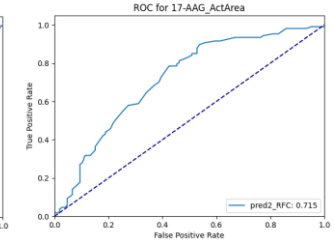












Accuracy varies across cell type and drugs

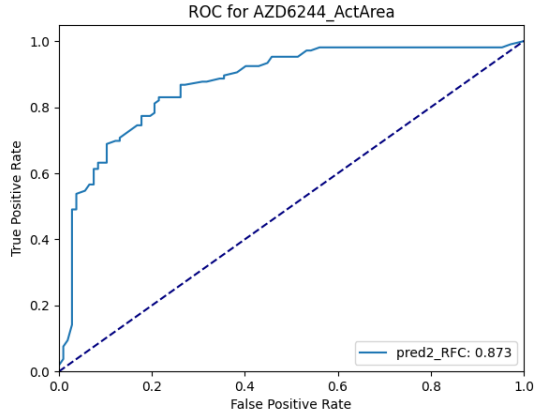
	Lapatinib_ActArea	Panobinostat_ActArea	Paclitaxel_ActArea	Irinotecan_ActArea	PD-0325901_ActArea	AZD6244_ActArea	Nilotinib_ActArea	AEW541_ActArea	17-AAG_ActArea	PHA-665752_ActArea	Nutlin-3_ActArea	AZD0530_ActArea	PF2341066_ActArea	L-685458_ActArea	ZD-6474_ActArea	Sorafenib_ActArea	LBW242_ActArea	PD-0332991_ActArea	PLX4720_ActArea	RAF265_ActArea	TAE684_ActArea	TKI258_ActArea	Erlotinib_ActArea
STOMACH	*0.78*	*0.80*	*0.67*	*0.00*	*0.86*	*0.78*	*0.86*	*0.20*	0.90	*0.75*	*0.50*	*0.44*	*0.50*	0.50	0.73	*0.75*	*0.20*	*0.71*	*0.22*	*0.71*	*0.43*	*0.60*	*0.75*
NERVOUS	1.00	1.00	0.50	0.91	0.88	0.85	0.73	0.75	0.57	0.71	0.69	0.55	0.54	0.67	0.83	0.53	0.64	*0.67*	0.58	*0.57*	0.33	0.57	1.00
OVARY	*0.75*	0.54	0.92	*1.00*	0.64	0.73	0.64	0.71	0.86	*0.89*	0.67	0.54	0.69	0.45	*0.40*	0.50	0.29	0.77	*0.78*	0.64	0.50	0.80	0.75
HAEMATOPOIETIC	0.63	0.94	0.81	0.96	0.93	0.70	0.88	0.62	0.61	0.85	0.63	0.53	0.83	0.86	0.61	0.78	0.52	0.91	0.66	0.67	0.74	0.67	0.67
SKIN	0.93	0.55	0.80	0.50	0.88	0.94	*0.38*	0.58	0.71	*0.67*	0.54	1.00	0.64	*0.78*	0.64	0.60	0.69	0.67	0.94	0.69	*1.00*	0.64	0.91
LUNG	0.71	0.78	0.82	0.73	0.81	0.81	0.53	0.60	0.74	0.45	0.45	0.45	0.61	0.42	0.59	0.66	0.68	0.58	0.63	0.69	0.52	0.60	0.76
BREAST	0.71	0.69	0.71	0.60	0.93	0.92	0.33	0.58	0.50	0.45	0.71	0.73	0.73	0.54	0.86	0.64	0.67	0.54	0.73	0.58	0.87	0.65	0.87
PANCREAS	0.58	0.80	1.00	1.00	0.88	0.80	0.62	0.43	0.67	0.40	0.64	0.64	0.56	0.67	0.79	0.67	0.63	0.78	0.50	0.83	0.67	0.89	0.54
LARGE_INTESTINE	0.85	0.55	0.71	0.75	1.00	1.00	*0.78*	0.80	0.64	*0.44*	0.60	*0.78*	*0.33*	0.40	0.83	0.42	*0.11*	0.40	*0.44*	0.58	*1.00*	*0.89*	0.83
OESOPHAGUS	0.82	*0.89*	0.60	*0.33*	*0.57*	*1.00*	*0.00*	0.50	*0.56*	0.30	*0.67*	0.82	0.75	*0.67*	0.50	*0.67*	*0.40*	*0.67*	*0.20*	*0.75*	*0.89*	*0.33*	*0.92*
LIVER	0.45	*1.00*	*0.63*	*0.50*	*0.71*	*1.00*	*0.80*	*0.78*	0.60	0.82	*0.33*	*0.67*	*0.63*	*0.67*	*0.56*	0.50	*0.67*	*0.80*	*0.25*	*0.88*	*0.67*	*0.78*	*0.75*

Italics: N < 10

Model analysis points to specific markers of sensitivity 1: Selumetinib (MEK inhibitor)

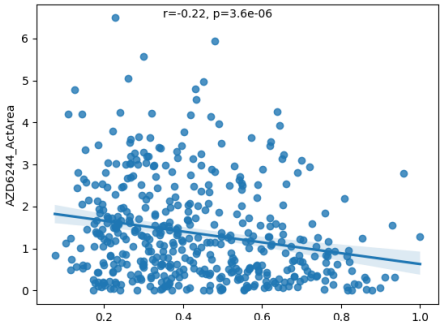
FACULTY OF SCIENCE, TECHNOLOGY AND MEDICINE

UNIVERSITÉ DU LUXEMBOURG



rank	Genomic							
	RFC	SVM	Log	Ridge	EN	ET	XGB	Ada
1	BRAF_MUT	GSTM1_DEL	GSTM1_DEL	GSTM1_DEL	BRAF_MUT	BRAF_MUT	NRAS_MUT	BRAF_MUT
2	BRAF.V600E_MUT	BRAF_MUT	BRAF_MUT	BRAF_MUT	GSTM1_DEL	BRAF.V600E_MUT	BRAF_MUT	KRAS.G12_13_MUT
3	BRAF.MC_MUT	BRAF.V600E_MUT	BRAF.V600E_MUT	BRAF.V600E_MUT	BRAF.V600E_MUT	BRAF.MC_MUT	KRAS.G12_13_MUT	NRAS_MUT
4	KRAS.G12_13_MUT	LOC727924_DEL	LOC727924_DEL	OR4M2_DEL	ERBB4_DEL	KRAS.G12_13_MUT	OR2T10_DEL	KRAS_MUT
5	ERBB4_DEL	OR4M2_DEL	ERBB4_DEL	OR4N4_DEL	KRAS.G12_13_MUT	ERBB4_DEL	NOTUM_AMP	PRODH_DEL
6	KRAS_MUT	OR4N4_DEL	EYA1_DEL	LOC727924_DEL	KRAS_MUT	NRAS_MUT	BRAF.V600E_MUT	ERBB4_DEL
7	LOC284344_DEL	EYA1_DEL	OR4M2_DEL	EYA1_DEL	TTN_MUT	GSTM1_DEL	GSTO2_DEL	EYA1_DEL
8	GSTM1_DEL	CDC73_DEL	OR4N4_DEL	CDC73_DEL	BRAF.MC_MUT	KRAS_MUT	LIPI_DEL	BRAF.V600E_MUT
9	NRAS_MUT	ERBB4_DEL	TTN_MUT	TTN_MUT	EYA1_DEL	STRA13_AMP	NSF_AMP	DMBT1_DEL
10	TTN_MUT	TTN_MUT	KRAS.G12_13_MUT	ERBB4_DEL	FRMPD2P1_AMP	TTN_MUT	ERBB4_DEL	TPTE2P3_DEL
11	OR4M2_DEL	BRAF.MC_MUT	CDC73_DEL	KRAS_MUT	LOC727924_DEL	FAM153C_AMP	DOCK10_AMP	NSFP1_AMP
12	PSG4_DEL	KRAS_MUT	KRAS_MUT	KRAS.G12_13_MUT	ARHGEF5_AMP	UNC13C_MUT	DSG1_DEL	SEMA3C_AMP
13	LOC727924_DEL	KRAS.G12_13_MUT	BRAF.MC_MUT	BRAF.MC_MUT	PRODH_DEL	LOC727924_DEL	PRODH_DEL	SLC44A5_DEL
14	RAD50_MUT	GOLGA8A_DEL	GOLGA8A_DEL	GOLGA8A_DEL	NRAS_MUT	OR4N4_DEL	LRBA_DEL	EIF2AK4_MUT
15	DOCK10_AMP	MCEE_AMP	LOC284344_DEL	MCEE_AMP	CDC73_DEL	OR4M2_DEL	SEMA3C_AMP	ARHGEF5_AMP
16	EYA1_DEL	LOC284344_DEL	PSG4_DEL	LOC284344_DEL	GOLGA8A_DEL	LINC00442_DEL	TNK2_MUT	GOLGA8A_DEL
17	OR4N4_DEL	PSG4_DEL	FRMPD2P1_AMP	PSG4_DEL	OR2A7_AMP	RNU6-52_DEL	PTPRT_AMP	FFAR3_DEL
18	OR2A7_AMP	SIRPB1_AMP	MCEE_AMP	SIRPB1_AMP	LOC728377_AMP	RAD50_MUT	GRM5_DEL	INHBA_MUT
19	NPB_AMP	KANK1_AMP	SIRPB1_AMP	KANK1_AMP	LOC284344_DEL	LOC284344_DEL	GUSBP1_AMP	SORCS3_DEL
20	LRRC37A2_AMP	FAM138A_DEL	FAM138A_DEL	FAM138A_DEL	OR4M2_DEL	ARL16_AMP	MIR4730_AMP	MLL_MUT

Transcriptomic							
RFC	SVM	Log	Ridge	EN	ET	XGB	Ada
ETV4	S100A4	CMTM7	CMTM7	ETV4	SH3TC2	TMC6	ETV4
TENM2	CMTM7	S100A4	S100A4	CMTM7	RP11-93EH1.5	ETV4	CMTM7
TM7SF3	CD24P4	ETV4	CD24P4	S100A4	UCHL1	LAMC3	TMC6
UBALD2	NGF	CD24P4	NGF	CD24P4	ASAP3	ASAP3	DECR2
DNAJB5	ETV4	NGF	TRPV2	SPRY2	HSD17B6	MAGEE1	S100A4
CMTM7	HOXB7	HOXB7	ETV4	NGF	SIGIRR	SPRY2	NGF
CTSE	NTN1	TRPV2	NTN1	UCHL1	TMEFF1	NGF	C2orf43
ASAP3	TRPV2	NTN1	HOXB7	ABO	CTD-2231H16	CMTM7	GEMIN2
VPS37B	RAB3IL1	RAB3IL1	RAB3IL1	TOR4A	ETV4	SAMD11	TSPAN31
TNFRSF14	KIAA1644	KIAA1644	CREB3L1	HOXB7	VPS37B	TENM2	ERCC1
ALX4	B4GALNT4	ABO	EVPL	SPRY4	NUPR1	GEMIN2	TRPV2
LY2	EVPL	SPRY2	KHDRBS3	SH3TC2	SLC16A2	ABO	ASAP3
PNMA1	ABO	EVPL	KIAA1644	KIAA1644	NGF	RAB30	ENAH
SH3TC2	MGLL	TOR4A	MGLL	TRPV2	B4GALNT1	RP6-99M1.2	LYZ
SMAGP	TUSC1	B4GALNT4	B4GALNT4	NTN1	RIPK3	TK2	MLTK
NGF	CREB3L1	SPRY4	ABO	RAB3IL1	NPR3	ENAH	BST1
RNF125	SNX18P16	SNX18P16	HMGA2	EVPL	RP3-395M20.6	RGS9	CTSE
CEACAM1	DIP2C	HMGA2	SLC17A9	SNX18P16	MAGEE1	CTSE	LYL1
SLC16A2	UCHL1	UCHL1	UCHL1	HMGA2	APLP1	UBALD2	EVPL
UCHL1	DCP1B	ETV5	TUSC1	ETV5	CIR	DUSP6	TMEFF1



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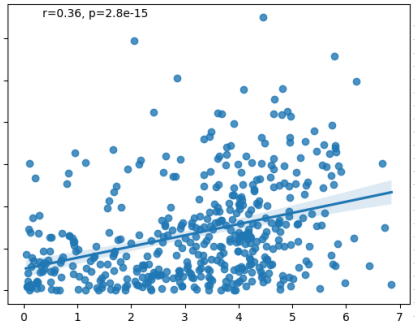
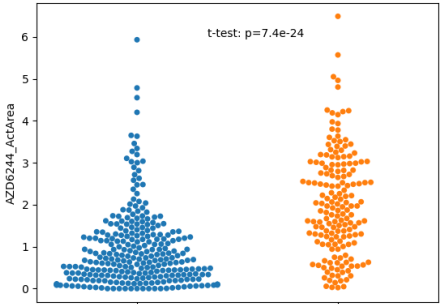


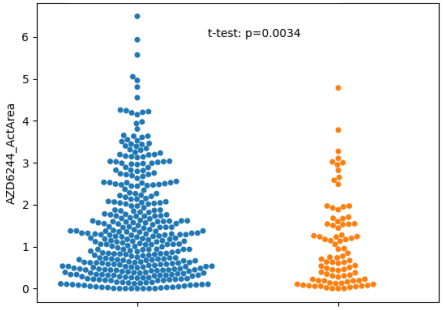
ETV4 expression

Proteomic							
RFC	SVM	Log	Ridge	EN	ET	XGB	Ada
Akt_pS473	c-Jun_pS73	Akt_pS473	c-Jun_pS73	Akt_pS473	Akt_pS473	Lck	Akt_pS473
CDK1	Src_pY527	c-Jun_pS73	Src_pY527	FRA1_Caution	AR	Akt_pS473	Smad3
PRAS40_pT246	c-Myc_Caution	FRA1_Caution	MEK1_pS217_S221	c-Jun_pS73	CDK1	HER3	CDK1
AR	Akt_pS473	Acetyl-a-Tubulin (Lys40)	Akt_pS473	Acetyl-a-Tubulin (Lys40)	c-Jun_pS73	XC-pan_Betall_pS66	c-Jun_pS73
Heregulin	Acetyl-a-Tubulin (Lys40)	MEK1_pS217_S221	c-Myc_Caution	MEK1_pS217_S221	MEK1_pS217_S221	Annexin 1	Annexin 1
c-Jun_pS73	MEK1_pS217_S221	AR	Acetyl-a-Tubulin (Lys40)	CDK1	TIGAR	CDK1	AR
MEK1_pS217_S221	TFRC	Src_pY527	TFRC	AR	HER3	MEK1_pS217_S221	Acetyl-a-Tubulin (Lys40)
HER3	Annexin_VII	CDK1	AR	Annexin 1	Acetyl-a-Tubulin (Lys40)	beta-Catenin_pT41	YB-1_pS102
Acetyl-a-Tubulin (Lys40)	PEA15	CD49b	p62 Lck ligand_Caution	HER3	Syk	B-Raf_Caution	TFRC
TIGAR	Smad3	TFRC	MAPK_pT202_Y204	CD49b	PRAS40_pT246	CD49b	HER3
Src_pY416_Caution	p62 Lck ligand_Caution	Annexin 1	PEA15	Src_pY527	FRA1_Caution	YB-1_pS102	PRAS40_pT246
Syk	FRA1_Caution	PRDX1	CDK1	PRDX1	Rab25	AR	XC-pan_Betall_pS660
TFRC	AR	HER3	FRA1_Caution	Src_pY416_Caution	E-Cadherin	Heregulin	Annexin_VII
FRA1_Caution	Gab2	PRAS40_pT246	PRDX1	PRAS40_pT246	Src_pY416_Caution	FOXO3a_Caution	JNK2_Caution
PKC-pan_Betall_pS660	CDK1	Elec	P-Cadherin_Caution	Elec	Heregulin	AMPK_alpha_Caution	PRDX1
JNK2_Caution	PRDX1	Annexin_VII	Chk2_pT68_Caution	TFRC	p70S6K_pT389	p38_MAPK	Heregulin
YB-1_pS102	CD49b	Src_pY416_Caution	Gab2	Gab2	Src	N-Cadherin	FRA1_Caution
Smad3	p53_Caution	Src	RBM15	Annexin_VII	JNK2_Caution	TFRC	Raptor
CD49b	Annexin 1	N-Cadherin	N-Cadherin	N-Cadherin	PKC-pan_Betall_pS660	MIG-6	MEK1_pS217_S221
Lck	PRAS40_pT246	YB-1_pS102	YB-1_pS102	YB-1_pS102	CD49b	PRAS40_pT246	Src_pY416_Caution

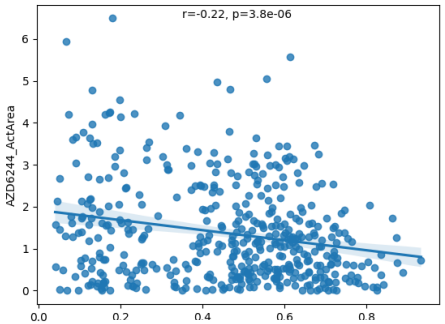
miRNA							
RFC	SVM	Log	Ridge	EN	ET	XGB	Ada
hsa-miR-130a_nmR	hsa-miR-1257_nmR	hsa-miR-1257_nmR	hsa-miR-1257_nmR	hsa-miR-1302_nmR	hsa-miR-130a_nmR	hsa-miR-130a_nmR	hsa-miR-1302_nmR
hsa-miR-1302_nmR	hsa-miR-22_nmR	hsa-miR-1302_nmR	hsa-miR-222_nmR	hsa-miR-22_nmR	hsa-miR-1302_nmR	hsa-miR-222_nmR	hsa-miR-130a_nmR
hsa-miR-342-3p_nmR	hsa-miR-548e_nmR	hsa-miR-22_nmR	hsa-miR-1268_nmR	hsa-miR-130a_nmR	hsa-miR-22_nmR	hsa-let-7c_nmR00	hsa-miR-1261_nmR
hsa-miR-222_nmR	hsa-miR-1302_nmR	hsa-miR-222_nmR	hsa-miR-22_nmR	hsa-miR-1257_nmR	hsa-miR-135b_nmR	hsa-miR-135b_nmR	hsa-miR-548p_nmR
hsa-miR-135b_nmR	hsa-miR-222_nmR	hsa-miR-135b_nmR	hsa-miR-135b_nmR	hsa-miR-222_nmR	hsa-miR-9-3_nmR00	hsa-miR-9-3_nmR00	hsa-miR-1257_nmR
hsa-let-7c_nmR00	hsa-miR-135b_nmR	hsa-miR-130a_nmR	ebv-miR-BART12	hsa-miR-135b_nmR	hsa-miR-193a-5p_nmR	hsa-miR-1302_nmR	hsa-miR-135b_nmR
hsa-miR-9_nmR00	ebv-miR-BART12	hsa-miR-1268_nmR	hsa-miR-1302_nmR	hsa-miR-34a_nmR	hsa-miR-22_nmR	hsa-let-7c_nmR00	hsa-miR-96_nmR00
hsa-miR-582-5p_nmR	hsa-miR-1268_nmR	hsa-miR-574-5p_nmR	hsa-miR-383_nmR	hsa-let-7c_nmR00	hsa-miR-22_nmR	hsa-miR-342-3p_nmR	hsa-let-7c_nmR00
hsa-miR-548p_nmR	hsa-miR-193a-5p_nmR	hsa-miR-221_nmR	hsa-miR-500-hsa-miR-1252_nmR	hsa-miR-342-3p_nmR	hsa-miR-221_nmR	hsa-miR-221_nmR	hsa-miR-34a_nmR
hsa-miR-34a_nmR	hsa-miR-383_nmR	hsa-miR-1252_nmR	hsa-miR-611_nmR	hsa-miR-1263_nmR	hsa-miR-1307_nmR	hsa-miR-22_nmR	hsa-miR-1307_nmR
hsa-miR-221_nmR	hsa-miR-1203_nmR	hsa-miR-662_nmR	hsa-miR-130a_nmR	hsa-miR-584_nmR	hsa-miR-34a_nmR	hsa-miR-22_nmR	hsa-miR-221_nmR
hsa-miR-96_nmR00	hsa-miR-1252_nmR	hsa-miR-584_nmR	hsa-miR-574-5p_nmR	hsa-miR-216a_nmR	hsa-miR-197_nmR	hsa-miR-1246_nmR	hsa-miR-1246_nmR
hsa-miR-22_nmR	hsa-miR-574-5p_nmR	hsa-let-7c_nmR00	hsa-miR-711_nmR	hsa-miR-221_nmR	hsa-miR-548p_nmR	hsa-miR-1268_nmR	hsa-miR-1252_nmR
hsa-miR-1307_nmR	hsa-miR-711_nmR	hsa-miR-611_nmR	hsa-miR-1203_nmR	hsa-miR-662_nmR	hsa-miR-423-3p_nmR	hsa-miR-326_nmR	hsa-miR-9_nmR00
hsa-miR-1180_nmR	hsa-miR-584_nmR	hsa-miR-34a_nmR	hsa-miR-662_nmR	hsa-miR-592-5p_nmR	hsa-miR-631_nmR	hsa-miR-886_nmR	hsa-miR-342-3p_nmR
hsa-miR-545_nmR	hsa-miR-662_nmR	hsa-miR-711_nmR	hsa-miR-548p_nmR	hsa-miR-96_nmR00	hsa-miR-1252_nmR	hsa-miR-1252_nmR	hsa-miR-125b_nmR
hsa-miR-631_nmR	hsa-miR-576-3p_nmR	hsa-miR-193a-5p_nmR	hsa-miR-584_nmR	hsa-miR-1268_nmR	hsa-let-7e_nmR00	hsa-miR-93_nmR00	hsa-miR-624_nmR
hsa-miR-193a-5p_nmR	kshv-miR-K12-12_nmR	ebv-miR-BART12_nmR	hsa-miR-26a_nmR	hsa-miR-574-5p_nmR	hsa-miR-592-5p_nmR	hsa-miR-1276_nmR	hsa-miR-568_nmR
hsa-miR-1252_nmR	hsa-miR-147_nmR	hsa-miR-500-hsa-miR-1252_nmR	hsa-miR-587_nmR	hsa-miR-193a-5p_nmR	hsa-miR-548a-3p_nmR	hsa-miR-34a_nmR	hsa-miR-1307_nmR
hsa-miR-345_nmR	hsa-miR-587_nmR	hsa-miR-383_nmR	hsa-miR-611_nmR	hsa-miR-548p_nmR	hsa-miR-29b_nmR	hsa-miR-30d_nmR	hsa-miR-589_nmR



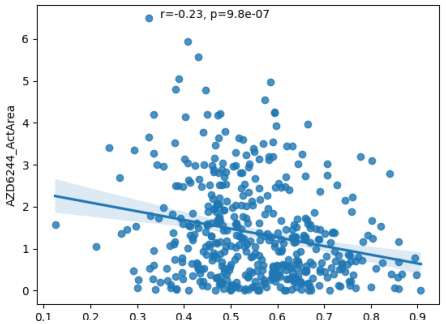
WT Ras/RAF mutated



WT ERBB4 deleted



miR-130a expression



miR-1302 expression

Model analysis points to specific markers of sensitivity 2: Irinotecan (Topoisomerase I inhibitor)

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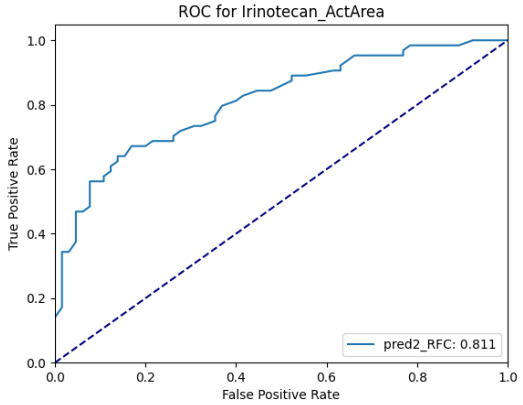
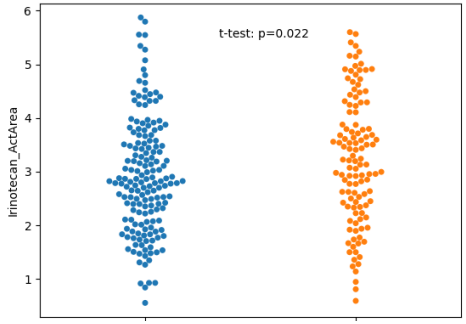


Genomic

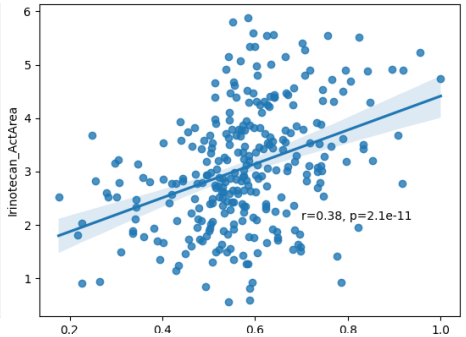
rank	RFC	SVM	Log	Ridge	EN	ET	XGB	Ada
1	HLA-DRB6_AMP	HLA-DRB6_AMP	HLA-DRB6_AMP	HLA-DRB6_AMP	HLA-DRB6_AMP	HLA-DRB6_AMP	FBXL7_DEL	HLA-DRB6_AMP
2	SCAPER_DEL	HLA-DRB1_AMP	HLA-DRB1_AMP	HLA-DRB1_AMP	HLA-DRB1_AMP	KRAS.G12_13_MU	MYH8_DEL	HEATR4_DEL
3	AKAP12_MUT	HEATR4_DEL	FBXL7_DEL	FBXL7_DEL	ZBTB20_AMP	MIR4473_DEL	TP63_DEL	OR4C11_DEL
4	ZBTB20_AMP	FBXL7_DEL	HEATR4_DEL	HEATR4_DEL	SIRPB1_AMP	HLA-DRB1_AMP	FGFR1_DEL	FBXL7_DEL
5	HLA-DRB1_AMP	KRAS.G12_13_MU	KRAS.G12_13_MU	KRAS.G12_13_MU	FBXL7_DEL	KIF26B_DEL	FAM153A_DEL	FAM153A_DEL
6	ADAMTSL1_DEL	KRAS_MUT	KRAS_MUT	KRAS_MUT	HLA-DRB5_AMP	GLI3_MUT	OR4C11_DEL	FGFR1_DEL
7	MIR4473_DEL	HLA-DRB5_AMP	HLA-DRB5_AMP	ACOT1_DEL	SCAPER_DEL	AKAP12_MUT	UCKL1-AS1_AMP	ZBTB20_AMP
8	GLI3_MUT	ACOT1_DEL	ACOT1_DEL	HLA-DRB5_AMP	HEATR4_DEL	FGFR1_DEL	FAM90A2P_DEL	KRAS.G12_13_MUT
9	LOC283914_AMP	SCAPER_DEL	SCAPER_DEL	SCAPER_DEL	SORD_AMP	FBXL7_DEL	SLC2A9_DEL	LINGO2_AMP
10	PIRT_DEL	FAM153A_DEL	GSTM1_DEL	FAM153A_DEL	KRAS.G12_13_MU	LOC283914_AMP	LINGO2_AMP	SLC2A9_DEL
11	KRAS.G12_13_MU	GTF2H2C_DEL	ZBTB20_AMP	GSTM1_DEL	GSTM1_DEL	SLC2A9_DEL	KIF26B_DEL	FAM90A2P_DEL
12	LINGO2_AMP	LOC100272216_D	FAM153A_DEL	GUSBP3_DEL	ACOT1_DEL	ZBTB20_AMP	KRAS.G12_13_MU	MYH8_DEL
13	ACOT1_DEL	GTF2H2D_DEL	LINGO2_AMP	GTF2H2C_DEL	DAP3_AMP	MIR4474_DEL	TSH2Z_AMP	CNTN5_DEL
14	UPK3B_AMP	LINGO2_AMP	AKAP12_MUT	LOC100272216_D	MSTO2P_AMP	OR2T5_DEL	GLI3_MUT	UNC13C_MUT
15	SCYL2_MUT	GSTM1_DEL	LGALS9C_DEL	GTF2H2D_DEL	KRAS_MUT	LOC146481_AMP	MIR4473_DEL	GSTM1_DEL
16	FBXL7_DEL	GUSBP3_DEL	GUSBP3_DEL	LGALS9C_DEL	RBFOX1_DEL	MCM3AP_MUT	DIAPH3_DEL	ODF4_DEL
17	MYH13_DEL	LGALS9C_DEL	GTF2H2C_DEL	LINGO2_AMP	KIF26B_DEL	PLA2G4F_DEL	MIR3152_DEL	SCAPER_DEL
18	MIR3152_DEL	ZBTB20_AMP	LOC100272216_D	AKAP12_MUT	TAG_DEL	DENND4C_DEL	FAM91A2_AMP	SIRPB1_AMP
19	KRAS_MUT	AKAP12_MUT	GTF2H2D_DEL	ZBTB20_AMP	DUSP22_DEL	CSPG4_MUT	ADPRM_DEL	SORD_AMP
20	DAP3_AMP	KGFLP2_DEL	SIRPB1_AMP	KGFLP2_DEL	HLA-DQB1_AMP	FAM153A_DEL	OR4N2_AMP	ACOT1_DEL

Transcriptomic

RFC	SVM	Log	Ridge	EN	ET	XGB	Ada
HNRNPA1	SLFN11	SLFN11	SLFN11	SLFN11	EFCAB4B	HNRNPA1	SLFN11
SLFN11	XIST	XIST	XIST	KHDC1	PRIM1	ARHGAP19	PPAP2A
ORC1	CTC-1337H24.	CTC-1337H24.	CTC-1337H24.	RP11-152P17.1	BCL11A	SLFN11	HNRNPA1
VRK1	LEPREL1	KHDC1	LEPREL1	IFITM10	RBPMS	DDX39A	BCL11A
ATP6AP2	KHDC1	LEPREL1	TSPYL5	LEPREL1	SLFN11	PTTG1IP	DDX39A
DUSP1	MX2	RP11-152P17.1	AFAP1L2	CTC-1337H24.	ARHGEF28	IL13RA1	IL13RA1
GPC1	IFITM10	TSPYL5	AC104135.3	AP000783.1	COL12A1	SGMS2	CTA-445C9.15
SGMS2	AFAP1L2	IFITM10	NDN	DPP4	LAPTM4B	LYAR	CD4
THRB	AC104135.3	MX2	RP11-152P17.1	TSPYL5	CENPH	RGS19	ECSIT
ANKLE1	RP11-152P17.1	AFAP1L2	MX2	XIST	NUPR1	SH3BGRL	CDH6
SLC25A19	TSPYL5	AP000783.1	GPX1P1	MX2	ITPRIPL1	CELSR1	PRICKLE2
CELSR1	FAM127C	DPP4	MAGEC2	PVRL3	SPATS2L	RBPMS	CTA-445C9.14
ARHGAP4	GSTT1	MGST2	IFITM10	TBC1D8B	PLK2	ADCY6	LYAR
PTTG1IP	MAGEC2	HIC1	GSTT1	RPSAP47	HNRNPA1	PHLDB2	C1GALT1C1
B4GALT4	MGST2	MAGEC2	SPTBN2	MGST2	FANCE	BCL11A	NCAPH
VASN	NDN	FAM127C	FAM127C	PRICKLE2	THRB	CD63	KHDC1
CTSD	ZNF215	TBC1D8B	RRAD	AFAP1L2	ARHGAP29	CTD-2203K17.	PDK4
RPS28	SUSD1	RP11-85M11.2	HIC1	RP11-85M11.2	LEPREL1	ORC1	PROSC
CDT1	TBC1D8B	RPSAP47	KHDC1	NUPR1	DUT	NCAPH	TMED3
RAC2	HIC1	SLFN12	RP11-834C11.4	LEPREL2	TPM1	LOXL4	ORC1



WT HLA amplified



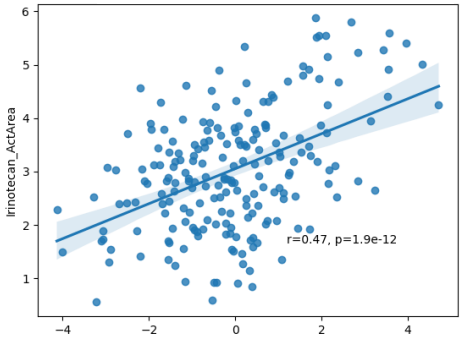
Chk1 protein expression

Proteomic

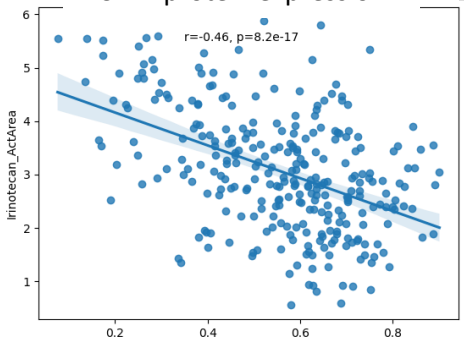
RFC	SVM	Log	Ridge	EN	ET	XGB	Ada
alpha-Catenin	INPP4B	Chk1_Caution	Chk1_Caution	Chk1_Caution	VAV1_Caution	YAP_pS127_C	Lck
Chk1_Caution	Caspase-7_cl	Caspase-7_cl	A-Raf_pS299	Lck	YAP_pS127_C	alpha-Catenin	Caspase-7_cleav
beta-Catenin	Chk1_Caution	Lck	Caspase-7_cl	A-Raf_pS299	alpha-Catenin	VAV1_Caution	ADAR1
VAV1_Caution	A-Raf_pS299	Stathmin	INPP4B	Stathmin	beta-Catenin	P-Cadherin_C	IRS1
MSH6_Caution	MSH6_Caution	PEA15	Notch1	4E-BP1	Stathmin	4E-BP1	PDK1_pS241
C-Raf(BD6101	GAPDH_Caut	A-Raf_pS299	PEA15	Caspase-7_cl	Fibronectin	NDRG1_pT346	NDRG1_pT346
C-Raf(MP05-7	Stathmin	4E-BP1	Beclin_Caution	PEA15	Chk1_Caution	beta-Catenin	Chk1_Caution
Fibronectin	CDK1	MSH6_Caution	GAPDH_Caut	beta-Catenin	C-Raf(BD6101	Fibronectin	4E-BP1
YAP_pS127_C	PDCD4_Caution	NDRG1_pT346	AR	MSH6_Caution	CD49b	C-Raf(MP05-7	Porin
RAD51	RAD51	PTEN	RAD51	Src_pY416_Ca	A-Raf_pS299_	C-Raf(BD6101	MSH6_Caution
CD49b	PEA15	INPP4B	PDCD4_Caution	Src	MSH6_Caution	AMPK_pT172	Beclin_Caution
Claudin-7	Notch1	Src_pY416_Ca	Src	Fibronectin	Rb_Caution	Chk1_Caution	Rb_Caution
NDRG1_pT346	NDRG1_pT346	Src	Shc_pY317	NDRG1_pT346	p62 Lck ligan	MSH6_Caution	Paxillin_Caution
Stathmin	Lck	PDCD4_Caution	CDK1	MDMX_MDM4	4E-BP1	ADAR1	A-Raf_pS299_Cau
4E-BP1	AR	Fibronectin	MSH6_Caution	INPP4B	Src_pY416_Ca	B-Raf_pS445	4E-BP1_pT37_T46
Lck	PTEN	IGFBP2	NDRG1_pT346	Akt_pS473	VEGFR2	Claudin-7	Bim(EP1036)
AMPK_pT172	MAPK_pT202	beta-Catenin	NF2_Caution	PTEN	Lck	Rb_Caution	Acetyl-a-Tubulin
PAI-1	4E-BP1	MDMX_MDM4	IGFBP2	Bim(EP1036)	Akt_pS473	VEGFR2	Stathmin
A-Raf_pS299	JNK_pT183_Y1	ADAR1	Bim(EP1036)	VEGFR2	C-Raf(MP05-7	SCD1	Fibronectin
Rb_pS807_S8	IGFBP2	RAD51	Stathmin	IGFBP2	Claudin-7	AMPK_alpha_	C-Raf(MP05-739)

miRNA

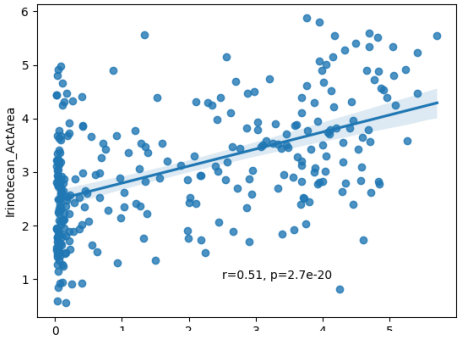
RFC	SVM	Log	Ridge	EN	ET	XGB	Ada
hsa-miR-574-	hsa-miR-608_	hsa-miR-608_	hsa-miR-608_	hsa-miR-22_r	hsa-miR-22_r	hsa-miR-574-	hsa-miR-548m_
hsa-miR-22_r	hsa-miR-613_	hsa-miR-19b_	hsa-miR-613_	hsa-miR-19b_	hsa-miR-574-	hsa-miR-548r	hsa-miR-19b_nr
hsa-miR-21_r	hsa-miR-583_	hsa-miR-22_r	hsa-miR-424_	hsa-miR-211	hsa-miR-211	hsa-miR-21_r	hsa-miR-22_nm
hsa-miR-24_r	hsa-miR-578_	hsa-miR-422a	hsa-miR-422a	hsa-miR-147b	hsa-miR-30a_	hsa-miR-558_	hsa-miR-545_nr
hsa-let-7e_n	hsa-miR-422a	hsa-miR-452_	hsa-miR-578_	hsa-miR-452_	hsa-miR-548r	hsa-miR-1308	hsa-miR-488_nr
hsa-miR-548r	hsa-miR-424_	hsa-miR-424_	hsa-miR-583_	hsa-miR-422a	hsa-let-7e_n	hsa-let-7e_n	hsa-miR-574-5p
hsa-miR-211	hsa-miR-644_	hsa-miR-147b	hsa-miR-129-	hsa-miR-608_	hsa-miR-147b	hsa-miR-22_r	hsa-miR-1308_n
hsa-miR-19b_	hsa-miR-19b_	hsa-miR-211	hcmv-miR-US	hsa-miR-424_	hsa-miR-19b_	hsa-miR-211	hsa-miR-34a_nr
hsa-miR-429_	hsa-miR-937_	hsa-let-7e_n	hsa-miR-182	hsa-miR-574-	hsa-miR-744_	hsa-miR-19b_	hsa-miR-590-5p
hsa-miR-545_	hcmv-miR-US	hsa-miR-583_	hsa-miR-19b_	hsa-miR-744_	hsa-miR-24_r	hsa-miR-422a_r	
hsa-miR-193a	hsa-miR-211	hsa-miR-548r	hsa-miR-937_	hsa-miR-548r	hsa-miR-378_	hsa-miR-15b_	hsa-miR-711_nr
hsa-miR-31_r	hsa-let-7e_n	hsa-miR-578_	hsa-miR-211	hsa-let-7e_n	hsa-miR-21_r	hsa-miR-30a_	hsa-miR-1269_n
hsa-miR-30a_	hsa-miR-129-	hsa-miR-129-	hsa-miR-384_	hsa-miR-626_	hsa-miR-125b	hsa-let-7b_n	ebv-miR-BART2-
hsa-miR-135b	hsa-miR-153	hsa-miR-744_	hsa-miR-147b	hsa-miR-129-	hsa-miR-711_	hsa-miR-490-	hsa-miR-153_nr
hsa-miR-711_	hsa-miR-147b	hsa-miR-626_	hsa-miR-644_	hsa-miR-668_	hsa-miR-193a	hsa-miR-153_	hsa-miR-943_nr
hsa-miR-211	hcmv-miR-US	hsa-miR-875-	hsa-let-7e_n	hsa-miR-30d_	hsa-miR-486-	hsa-miR-206_	hsa-miR-132_nr
hsa-miR-551b	hsa-miR-384_	hsa-miR-675_	hsa-miR-219-	hsa-miR-583_	hsa-miR-626_	hsa-miR-875-	kshv-miR-K12-6-
hsa-miR-191a	hsa-miR-452_	hsa-miR-875-	hsa-miR-491-	hsa-miR-545_	hsa-miR-146b	hsa-miR-606_nr	
hsa-let-7b_n	hsa-miR-675_	hsa-miR-219-	hsa-miR-227	hsa-miR-125b	ebv-miR-BART	hsa-miR-412_	hsa-miR-1246_n
hsa-miR-452_	hsa-miR-328_	hsa-miR-668_	hsa-miR-874_	hsa-miR-578_	hsa-miR-602_	hsa-miR-10a_	hsa-miR-30e_nr



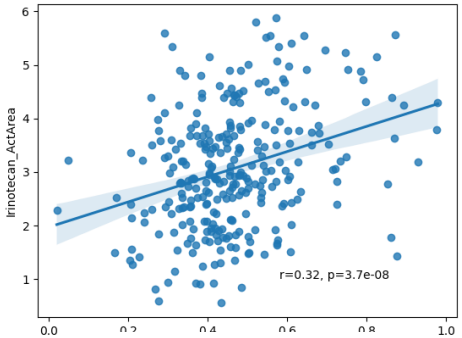
JAK-STAT pathway activity



miR-22 expression



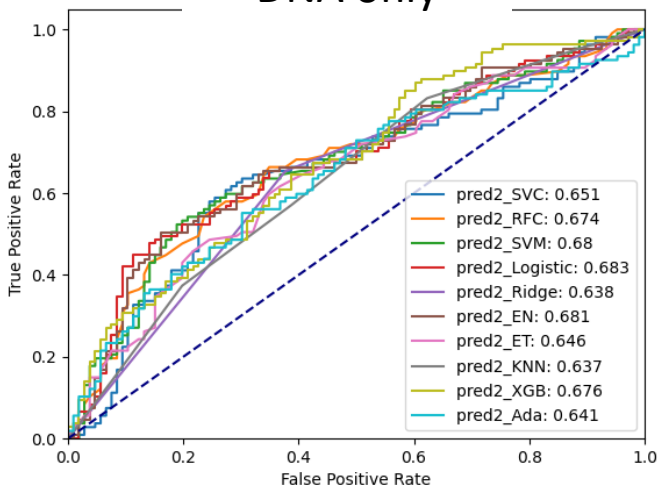
SLFN11 expression



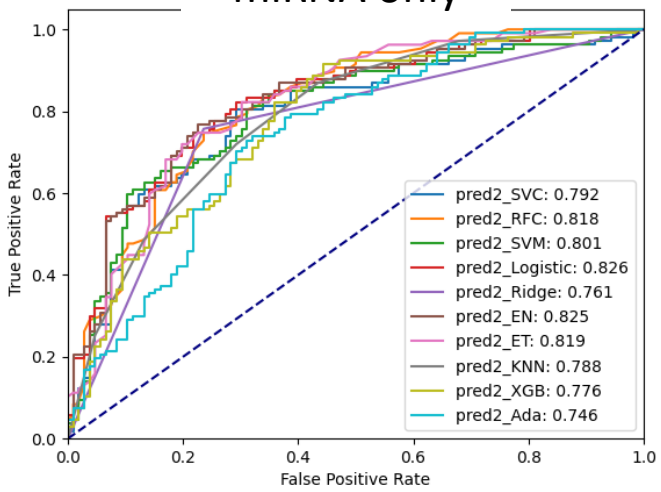
Alpha-hydroxybutyrate

Comparing single-omic predictors for PD-0325901 (Mirdametinib, MEK inhibitor)

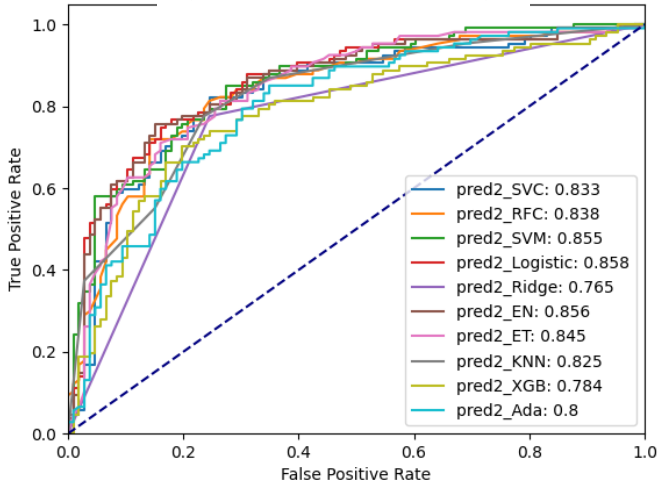
DNA only



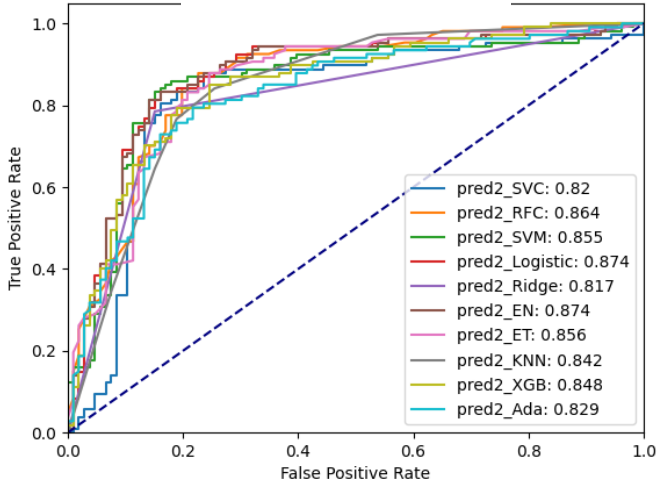
miRNA only



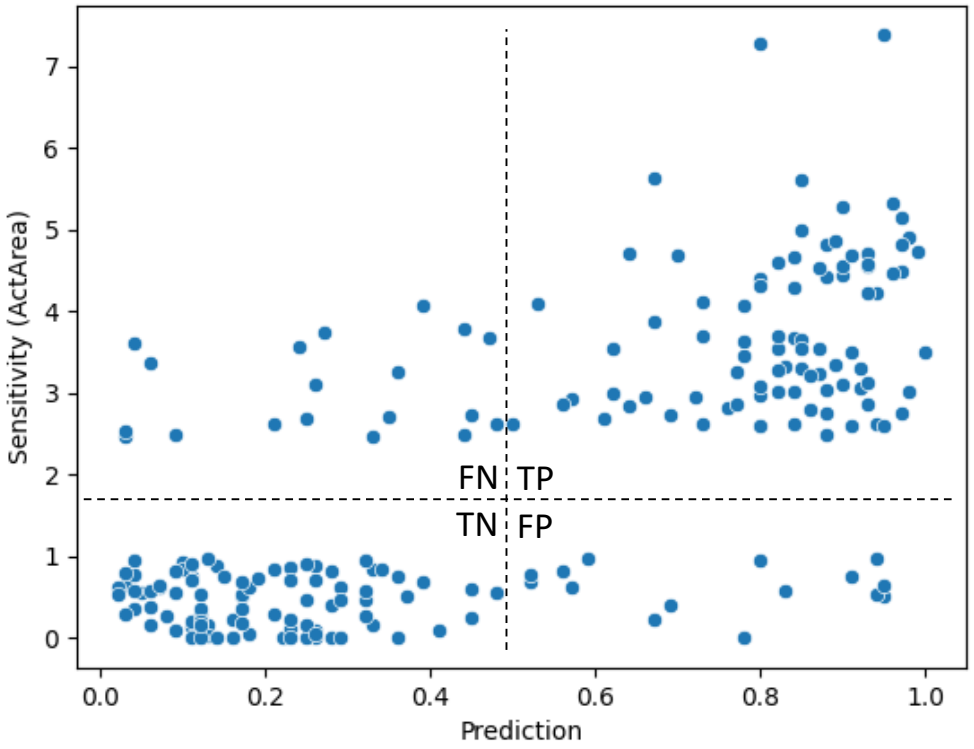
proteomics only



RNA only



Example of evaluation of diagnostic utility: PD-0325901 (Mirdametinib, MEK inhibitor)



	Sensitive		Resistant		PPV	NPV
	correct	wrong	correct	wrong		
Lung	13	3	23	2	**0.81**	**0.92**
Colon	13	0	1	0	**1.00**	**1.00**
Skin	15	2	0	0	**0.88**	
Hemato	14	0	13	2	**1.00**	**0.87**

NPV: 82.7%

PPV: 85.3%

Conclusions and perspectives

- Performance of predictors of sensitivity:
  - High (>75% ROCAUC): 7 drugs
  - Intermediate (>65% ROCAUC): 8 drugs
  - Low (<65% ROCAUC): 8 drugs
- High accuracy for specific cancer types
- Models point to both known and putative novel markers and/or targets
- Analysis of the contribution of specific omic types -> model shrinking

- => deeper analysis to lead to fully explainable models
- => experimental validation: causality of markers
- => clinical evaluation on patient data (organoids)

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