

SUPPLEMENTARY MATERIALS

Table S1. Baseline PathFX prediction results for 32 side effects sorted by TP values.

Side effect	Sensitivity	Specificity	Precision	# of associated drugs on the toxicity dataset	# of drugs predicted by PathFX	# of shared TP & FP genes	# of distinct TP genes	# of distinct FP genes
Hypertension	0.54	0.63	0.59	448	406	255	108	29
Myocardial infarction	0.55	0.61	0.45	325	396	219	20	104
Pancreatitis	0.39	0.63	0.32	276	336	282	43	128
Pneumonia	0.33	0.81	0.41	258	207	91	12	46
Edema	0.15	0.85	0.49	442	134	21	4	21
Thrombocytopenia	0.12	0.86	0.48	459	118	62	31	20
Gastric ulcer	0.61	0.56	0.12	80	403	45	2	27
Peripheral neuropathy	0.20	0.77	0.24	233	197	55	7	39
Sepsis	0.23	0.73	0.18	180	234	97	7	27
Hyperlipidemia	0.46	0.60	0.11	90	363	76	5	69
Sleep disorders	0.29	0.80	0.20	128	186	25	1	12
Anemia	0.20	0.77	0.18	181	196	56	8	46
Seizures	0.57	0.71	0.11	54	273	74	3	136
Stevens-Johnson syndrome	0.09	0.93	0.43	309	68	8	1	6
Tachycardia	0.23	0.80	0.15	122	181	19	0	7
Myopathy	0.32	0.67	0.09	81	296	34	1	95
Deep vein thrombosis	0.29	0.70	0.09	85	266	40	4	42
Delirium	0.19	0.85	0.17	128	139	11	0	11
Tardive dyskinesia	0.67	0.90	0.21	36	113	14	0	14

Cerebral infarction	0.44	0.60	0.04	34	356	98	3	172
Hemorrhage	0.04	0.98	0.65	381	23	8	5	4
Sleep apnea syndromes	0.31	0.81	0.06	35	172	14	0	12
Anaphylaxis	0.02	0.97	0.38	417	26	4	3	7
Pulmonary edema	0.06	0.96	0.24	154	37	14	4	6
Proteinuria	0.04	0.97	0.15	98	26	18	0	25
Cardiac arrest	0.01	0.99	0.18	184	11	0	1	32
Agranulocytosis	0.00	1.00	0.00	252	2	0	1	2
Lung cyst	0.00	1.00	0.00	101	0	1	0	0
Hepatic necrosis	0.00	1.00	0.00	111	0	1	0	0
Completed suicide	0.00	1.00	0.00	120	0	1	0	0
Neuroleptic malignant syndrome	0.00	1.00	0.00	72	0	1	0	0
Prolonged QT interval	0.00	1.00	0.00	71	0	1	0	0

Table S2. Enriched GO terms using TP distinct genes for hypertension along with the corresponding literature support.

GO term	Description	Literature support
GO:0010594	Regulation of endothelial cell migration	Several lines of evidence have suggested that endothelial function is impaired as blood pressure increases and that the degree of dysfunction is related to the magnitude of blood pressure elevation, indicating that endothelial dysfunction is a consequence of hypertension [R1].
GO:0030449	Regulation of complement activation	Accumulating evidence suggests that the complement system plays an active role in the pathogenesis of hypertension. Complement activation may drive the pathology of hypertension through its effects on innate and adaptive immune responses, aside from direct effects on the vasculature [R2].
GO:0007249	I-kappaB kinase/NF-kappaB signaling	NF-κB target genes involve in inflammation development and progression. Inflammation plays a pivotal role in the development and maintenance of hypertension. Both angiotensin II type 1 receptor (AT1R) and nuclear factor-kappa B (NF-κB) play significant roles in the pathogenesis of hypertension [R3, R4].
GO:0051092	Positive regulation of NF-kappaB transcription factor activity	
GO:0016477	Cell migration	One of the major proteins that regulate cell migration is focal adhesion kinase (FAK). FAK plays a critical role in pulmonary arterial hypertension pathogenesis by regulating proliferation, resistance to apoptosis, migration, and invasion of Human Pulmonary Artery Smooth Muscle Cells [R5].

Appendix References:

- [R1] Higashi, Yukihiro, Yasuki Kihara, and Kensuke Noma. "Endothelial dysfunction and hypertension in aging." *Hypertension Research* 35.11 (2012): 1039-1047.
- [R2] Chen, Xuejing, et al. "Potential Involvement of Complement Activation in Kidney Vascular Lesions of Arterionephrosclerosis." *Frontiers in medicine* (2022): 858.
- [R3] Solak, Yalcin, et al. "Hypertension as an autoimmune and inflammatory disease." *Hypertension Research* 39.8 (2016): 567-573.
- [R4] Patrick, David M., Justin P. Van Beusecum, and Annet Kirabo. "The role of inflammation in hypertension: novel concepts." *Current opinion in physiology* 19 (2021): 92-98.
- [R5] Paulin, Roxane, et al. "Targeting cell motility in pulmonary arterial hypertension." *European Respiratory Journal* 43.2 (2014): 531-544.

Table S3. GO enrichment analysis results using TP distinct genes for hypertension.

GO term	Description	P-value	FDR q-value	Genes
GO:0010594	regulation of endothelial cell migration	9.95E-04	1.68E-02	[EFNA1 - ephrin-a1, AKT1 - v-akt murine thymoma viral oncogene homolog 1, TGFB1 - transforming growth factor, beta 1, APOE - apolipoprotein e, FLT4 - fms-related tyrosine kinase 4, STAT5A - signal transducer and activator of transcription 5a]
GO:0045926	negative regulation of growth	9.97E-04	1.68E-02	[TP53 - tumor protein p53, ESR2 - estrogen receptor 2 (er beta), TGFB1 - transforming growth factor, beta 1, SMAD3 - smad family member 3, CDKN1A - cyclin-dependent kinase inhibitor 1a (p21, cip1), TGFB2 - transforming growth factor, beta receptor ii (70/80kda), ENO1 - enolase 1, (alpha)]
GO:0062012	regulation of small molecule metabolic process	9.73E-04	1.65E-02	[TP53 - tumor protein p53, GHSR - growth hormone secretagogue receptor, EP300 - e1a binding protein p300, AKT1 - v-akt murine thymoma viral oncogene homolog 1, TGFB1 - transforming growth factor, beta 1, APOE - apolipoprotein e, NOS2 - nitric oxide synthase 2, inducible, BRCA1 - breast cancer 1, early onset, MTOR - mechanistic target of rapamycin (serine/threonine kinase), ENO1 - enolase 1, (alpha)]
GO:0030449	regulation of complement activation	9.59E-04	1.63E-02	[CFH - complement factor h, C4BPA - complement component 4 binding protein, alpha, CD59 - cd59 molecule, complement regulatory protein, C4BPB - complement component 4 binding protein, beta, C1QB - complement component 1, q subcomponent, b chain]

GO:0050871	positive regulation of B cell activation	9.59E-04	1.63E-02	[VAV3 - vav 3 guanine nucleotide exchange factor, TGFB1 - transforming growth factor, beta 1, TLR4 - toll-like receptor 4, CDKN1A - cyclin-dependent kinase inhibitor 1a (p21, cip1), TP53BP1 - tumor protein p53 binding protein 1]
GO:0045787	positive regulation of cell cycle	9.41E-04	1.60E-02	[CHEK2 - checkpoint kinase 2, TP53 - tumor protein p53, BECN1 - beclin 1, autophagy related, AKT1 - v-akt murine thymoma viral oncogene homolog 1, PRKACA - protein kinase, camp-dependent, catalytic, alpha, EP300 - e1a binding protein p300, TGFA - transforming growth factor, alpha, BRCA1 - breast cancer 1, early onset, CDKN1A - cyclin-dependent kinase inhibitor 1a (p21, cip1)]
GO:1902679	negative regulation of RNA biosynthetic process	9.43E-04	1.60E-02	[EFNA1 - ephrin-a1, H2AFX - h2a histone family, member x, TGFB1 - transforming growth factor, beta 1, XRCC6 - x-ray repair complementing defective repair in chinese hamster cells 6, CD36 - cd36 molecule (thrombospondin receptor), SMAD2 - smad family member 2, CCNE1 - cyclin e1, BRCA1 - breast cancer 1, early onset, STAT3 - signal transducer and activator of transcription 3 (acute-phase response factor), KDM4A - lysine (k)-specific demethylase 4a, TP53 - tumor protein p53, POU5F1 - pou class 5 homeobox 1, ESR2 - estrogen receptor 2 (er beta), EP300 - e1a binding protein p300, SMAD3 - smad family member 3, HDAC1 - histone deacetylase 1, SMAD7 - smad family member 7, ENO1 - enolase 1, (alpha)]
GO:0030888	regulation of B cell proliferation	9.32E-04	1.59E-02	[VAV3 - vav 3 guanine nucleotide exchange factor, LYN - v-yes-1 yamaguchi sarcoma viral related oncogene homolog, TLR4 - toll-like receptor 4, CDKN1A - cyclin-dependent kinase inhibitor 1a (p21, cip1)]
GO:0007249	I-kappaB kinase/NF-kappaB signaling	9.32E-04	1.59E-02	[AKT1 - v-akt murine thymoma viral oncogene homolog 1, TLR3 - toll-like receptor 3, NFKBIA - nuclear factor of kappa light polypeptide gene enhancer in b-cells inhibitor, alpha, TLR4 - toll-like receptor 4]
GO:0060420	regulation of heart growth	9.32E-04	1.59E-02	[TGFB1 - transforming growth factor, beta receptor 1, MAPK1 - mitogen-activated protein kinase 1, MTOR - mechanistic target of rapamycin (serine/threonine kinase), TGFB2 - transforming growth factor, beta receptor ii (70/80kda)]

GO:1903507	negative regulation of nucleic acid-templated transcription	9.24E-04	1.58E-02	[EFNA1 - ephrin-a1, H2AFX - h2a histone family, member x, TGFB1 - transforming growth factor, beta 1, XRCC6 - x-ray repair complementing defective repair in chinese hamster cells 6, CD36 - cd36 molecule (thrombospondin receptor), SMAD2 - smad family member 2, CCNE1 - cyclin e1, BRCA1 - breast cancer 1, early onset, STAT3 - signal transducer and activator of transcription 3 (acute-phase response factor), KDM4A - lysine (k)-specific demethylase 4a, TP53 - tumor protein p53, POU5F1 - pou class 5 homeobox 1, ESR2 - estrogen receptor 2 (er beta), EP300 - e1a binding protein p300, SMAD3 - smad family member 3, HDAC1 - histone deacetylase 1, SMAD7 - smad family member 7, ENO1 - enolase 1, (alpha)]
GO:0045892	negative regulation of transcription, DNA-templated	9.05E-04	1.55E-02	[EFNA1 - ephrin-a1, H2AFX - h2a histone family, member x, TGFB1 - transforming growth factor, beta 1, XRCC6 - x-ray repair complementing defective repair in chinese hamster cells 6, CD36 - cd36 molecule (thrombospondin receptor), SMAD2 - smad family member 2, CCNE1 - cyclin e1, BRCA1 - breast cancer 1, early onset, STAT3 - signal transducer and activator of transcription 3 (acute-phase response factor), KDM4A - lysine (k)-specific demethylase 4a, TP53 - tumor protein p53, POU5F1 - pou class 5 homeobox 1, ESR2 - estrogen receptor 2 (er beta), EP300 - e1a binding protein p300, SMAD3 - smad family member 3, HDAC1 - histone deacetylase 1, SMAD7 - smad family member 7, ENO1 - enolase 1, (alpha)]
GO:0010954	positive regulation of protein processing	9.09E-04	1.55E-02	[F12 - coagulation factor xii (hageman factor), KLKB1 - kallikrein b, plasma (fletcher factor) 1, ENO1 - enolase 1, (alpha)]
GO:0045930	negative regulation of mitotic cell cycle	8.98E-04	1.54E-02	[CHEK2 - checkpoint kinase 2, TP53 - tumor protein p53, EP300 - e1a binding protein p300, TGFB1 - transforming growth factor, beta 1, SMAD3 - smad family member 3, TOPBP1 - topoisomerase (dna) ii binding protein 1, BRCA1 - breast cancer 1, early onset, CDKN1A - cyclin-dependent kinase inhibitor 1a (p21, cip1)]
GO:0016477	cell migration	8.67E-04	1.50E-02	[TGFB1 - transforming growth factor, beta receptor 1, EFNA1 - ephrin-a1, EPHA3 - eph receptor a3, VAV3 - vav 3 guanine nucleotide exchange factor,

				AKT1 - v-akt murine thymoma viral oncogene homolog 1, FN1 - fibronectin 1, TGFB1 - transforming growth factor, beta 1, PPIA - peptidylprolyl isomerase a (cyclophilin a), EPHB1 - eph receptor b1, IL12B - interleukin 12b (natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2, p40), PLAT - plasminogen activator, tissue, SDCCAG8 - serologically defined colon cancer antigen 8, LYN - v-yes-1 yamaguchi sarcoma viral related oncogene homolog, VAV2 - vav 2 guanine nucleotide exchange factor, F2RL1 - coagulation factor ii (thrombin) receptor-like 1]
GO:0032970	regulation of actin filament-based process	8.69E-04	1.50E-02	[TGFB1 - transforming growth factor, beta receptor 1, EPHA3 - eph receptor a3, RAC2 - ras-related c3 botulinum toxin substrate 2 (rho family, small gtp binding protein rac2), LRP1 - low density lipoprotein receptor-related protein 1, SMAD3 - smad family member 3, PDE4D - phosphodiesterase 4d, camp-specific, F2RL1 - coagulation factor ii (thrombin) receptor-like 1, MTOR - mechanistic target of rapamycin (serine/threonine kinase), ALMS1 - alstrom syndrome 1]
GO:0048598	embryonic morphogenesis	8.69E-04	1.50E-02	[TGFB1 - transforming growth factor, beta receptor 1, TP53 - tumor protein p53, SMAD2 - smad family member 2, MAPK3 - mitogen-activated protein kinase 3, MAPK1 - mitogen-activated protein kinase 1, EPHB2 - eph receptor b2, SMAD3 - smad family member 3, HDAC1 - histone deacetylase 1, TGFB2 - transforming growth factor, beta receptor ii (70/80kda)]
GO:0070304	positive regulation of stress-activated protein kinase signaling cascade	8.72E-04	1.50E-02	[LYN - v-yes-1 yamaguchi sarcoma viral related oncogene homolog, TLR3 - toll-like receptor 3, MYD88 - myeloid differentiation primary response 88, TLR4 - toll-like receptor 4, F2RL1 - coagulation factor ii (thrombin) receptor-like 1, FLT4 - fms-related tyrosine kinase 4]
GO:0051092	positive regulation of NF-kappaB transcription factor activity	8.72E-04	1.50E-02	[TLR3 - toll-like receptor 3, MYD88 - myeloid differentiation primary response 88, PPIA - peptidylprolyl isomerase a (cyclophilin a), CD36 - cd36 molecule (thrombospondin receptor), TLR4 - toll-like receptor 4, STAT3 - signal transducer and activator of transcription 3 (acute-phase response factor)]
GO:0035295	tube development	8.72E-04	1.50E-02	[TGFB1 - transforming growth factor, beta 1, SMAD2 - smad family member

				2, SMAD3 - smad family member 3, SMAD7 - smad family member 7, OXTR - oxytocin receptor, TGFBR2 - transforming growth factor, beta receptor ii (70/80kda)]
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Table S4. 24 pathway phenotypes and their corresponding pathway numbers (for 8 side effects having the highest number of distinct TP genes in the baseline analysis).

Pathway phenotype names	Pathway numbers
phen_sig_tp_myocardial infarction	6787
phen_sig_tp_thrombocytopenia	6537
phen_sig_knockout_myocardial infarction	5769
phen_sig_knockout_thrombocytopenia	5556
phen_sig_tp_hypertension	5502
phen_sig_tp_pancreatitis	4935
phen_sig_knockout_hypertension	4677
phen_sig_tp_peripheral neuropathy	4467
phen_sig_tp_pneumonia	4365
phen_sig_knockout_pancreatitis	4195
phen_sig_knockout_peripheral neuropathy	3797
phen_sig_knockout_pneumonia	3710
phen_sig_tp_sepsis	3265
phen_sig_knockout_sepsis	2775
phen_sig_tp_anemia	1886
phen_sig_noise_hypertension	1640
phen_sig_knockout_anemia	1603
phen_sig_noise_pancreatitis	1601
phen_sig_noise_myocardial infarction	1545
phen_sig_noise_pneumonia	1008
phen_sig_noise_sepsis	906
phen_sig_noise_anemia	872
phen_sig_noise_peripheral neuropathy	787
phen_sig_noise_thrombocytopenia	250

Table S5. Engineered pathways discovered similar and distinct drugs. phen_sig_tp_noFP_Sig_hypertension discovered more drug pathways, but only 16 shared with phen_tp_hypertension.

Pathway phenotype (from Table 5)	Description	Total identified drug pathways	New identified drug pathways when we added the signature data
phen_tp_hypertension	The associated pathway phenotype when we engineered pathways including only distinct TP genes	31	-
phen_sig_tp_noFP_Sig_hypertension	The associated pathway phenotype when we engineered pathways including both TP baseline and signature genes but removed the FP signature examples	198	15

Table S6. Per pathway phenotype performance metrics and comparison with animal testing results for myocardial infarction.

Side effect	Pathway phenotype	TP	TN	FP	FN	Sensitivity	Specificity
myocardial infarction	myocardial infarction 1	0	565	0	325	0.00	1.00
myocardial infarction	myocardial infarction susceptibility to, 1 (finding)	0	565	0	325	0.00	1.00
myocardial infarction	myocardial ischemia	0	565	0	325	0.00	1.00
myocardial infarction	myocardial failure	0	565	0	325	0.00	1.00
myocardial infarction	phen_tp_myocardial infarction	0	565	0	325	0.00	1.00
myocardial infarction	phen_sig_tp_noFP_Dis_myocardial infarction	0	565	0	325	0.00	1.00
myocardial infarction	myocardial infarction	3	557	8	322	0.01	0.99
myocardial infarction	acute myocardial infarction	14	548	17	311	0.04	0.97
cardiovascular organ category (Rodent)						0.03	0.94
cardiovascular organ category (Nonhuman primate)						0.20	0.84
myocardial infarction	old myocardial infarction	112	432	133	213	0.34	0.76
myocardial infarction	phen_sig_tp_noFP_Sig_myocardial infarction	126	420	145	199	0.39	0.74
cardiovascular organ category (Dog)						0.87	0.62

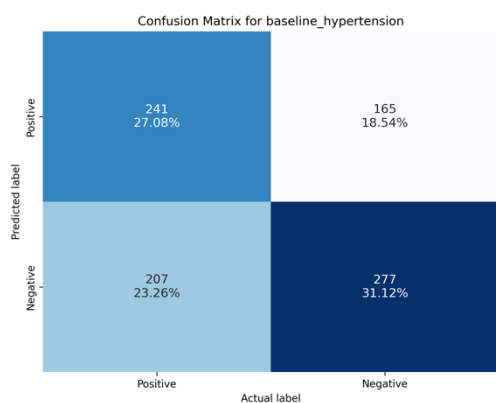
Table S7. Per pathway phenotype performance metrics and comparison with animal testing results for thrombocytopenia.

Side effect	Pathway phenotype	TP	TN	FP	FN	Sensitivity	Specificity
thrombocytopenia	thrombocytopenia	0	431	0	459	0.00	1.00
thrombocytopenia	autoimmune thrombocytopenia	0	431	0	459	0.00	1.00
thrombocytopenia	thrombocythemia, essential	0	431	0	459	0.00	1.00
thrombocytopenia	phen_sig_tp_noFP_Dis_thrombocytopenia	0	431	0	459	0.00	1.00
thrombocytopenia	phen_tp_thrombocytopenia	24	430	1	435	0.05	1.00
thrombocytopenia	macrothrombocytopenia	8	424	7	451	0.02	0.98
cardiovascular organ category (Rodent)						0.03	0.94
thrombocytopenia	thrombocytopenia 5			86	379	0.19	0.88
thrombocytopenia	phen_sig_tp_noFP_Sig_thrombocytopenia	72	374	57	387	0.16	0.87
cardiovascular organ category (Nonhuman primate)						0.20	0.84
thrombocytopenia	thrombocytopenia due to platelet alloimmunization	77	337	94	382	0.17	0.78
thrombocytopenia	idiopathic thrombocytopenia	159	285	146	300	0.35	0.66
thrombocytopenia	thrombocytopenia 6	126	281	150	333	0.27	0.65
cardiovascular organ category (Dog)						0.87	0.62

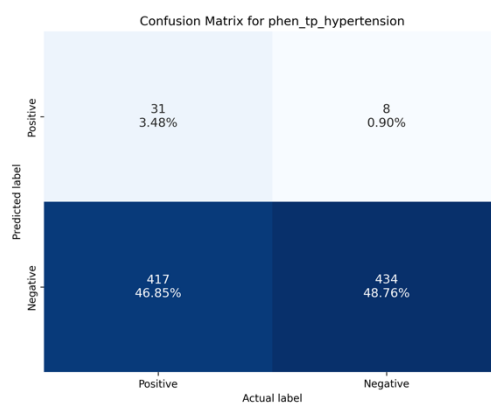
Table S8. Per pathway phenotype performance metrics and comparison with animal testing results for pancreatitis.

Side effect	Pathway phenotype	TP	TN	FP	FN	Sensitivity	Specificity
pancreatitis	carcinoma of pancreas	0	614	0	276	0.00	1.00
pancreatitis	pancreatitis, chronic	0	614	0	276	0.00	1.00
pancreatitis	pancreatitis, alcoholic	0	614	0	276	0.00	1.00
pancreatitis	phen_sig_tp_noFP_Dis_pancreatitis	14	613	1	262	0.05	1.00
pancreatitis	phen_tp_pancreatitis	12	612	2	264	0.04	1.00
gastrointestinal organ category (Nonhuman primate)						0.48	0.97
pancreatitis	adenocarcinoma of pancreas	26	588	26	250	0.09	0.96
pancreatitis	pancreatitis	28	561	53	248	0.10	0.91
pancreatitis	acute pancreatitis	45	522	92	231	0.16	0.85

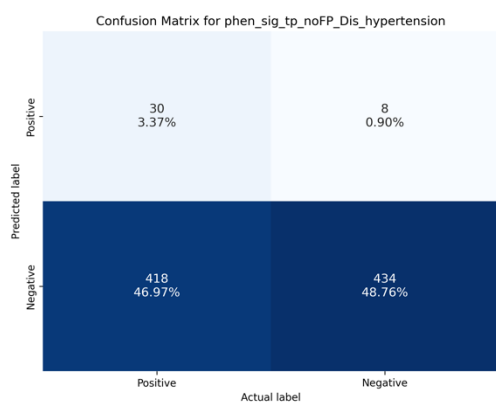
gastrointestinal organ category (Rodent)						0.25	0.84
pancreatitis	pancreatitis idiopathic	44	508	106	232	0.16	0.83
gastrointestinal organ category (Dog)						0.54	0.74
pancreatitis	phen_sig_tp_noFP_Sig_pancreatitis	142	379	235	134	0.51	0.62



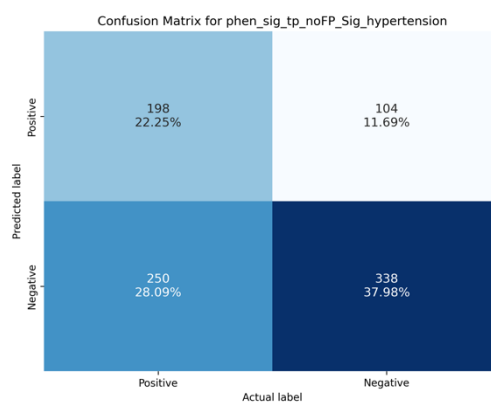
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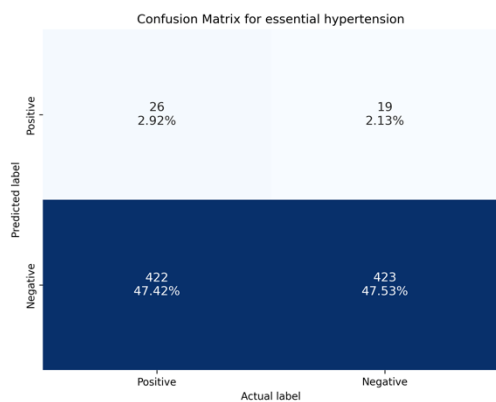
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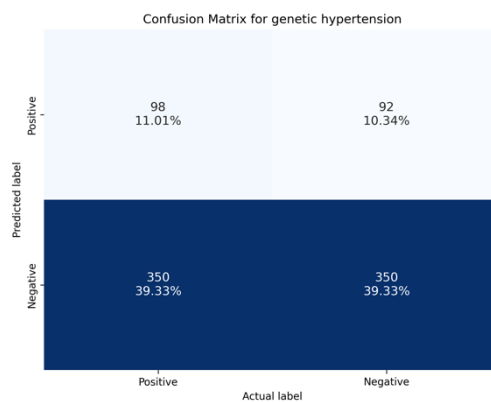
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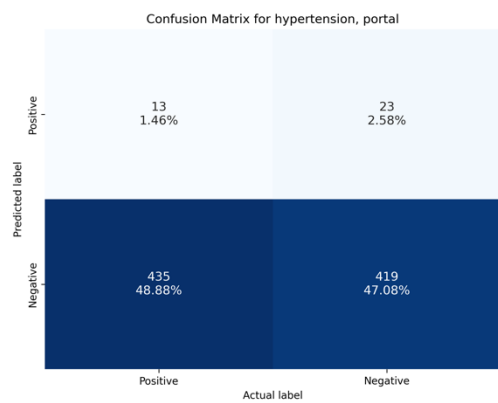
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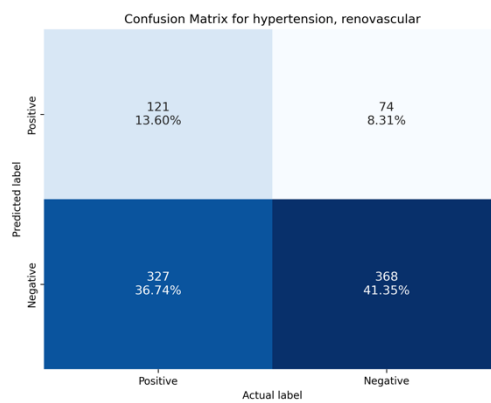
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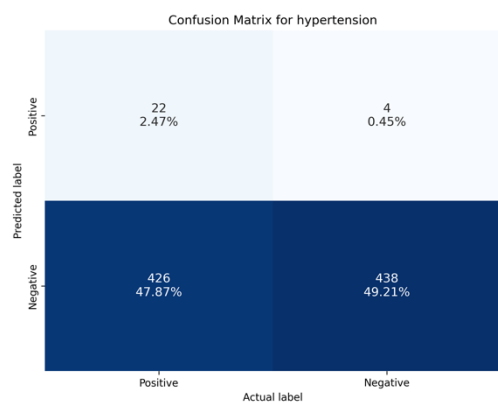
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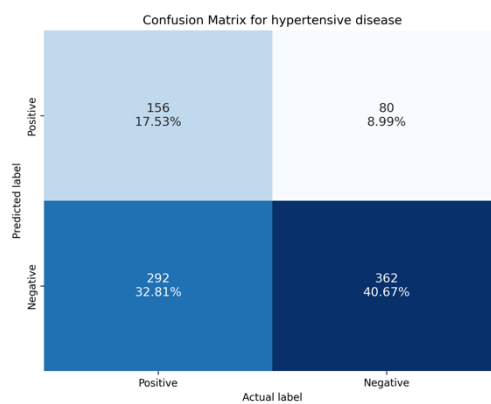
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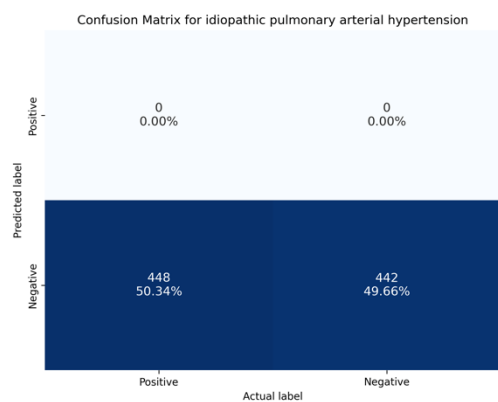
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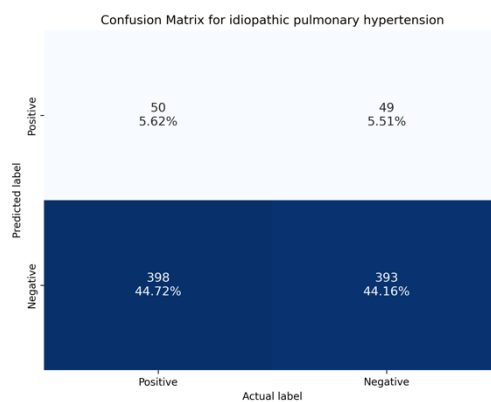
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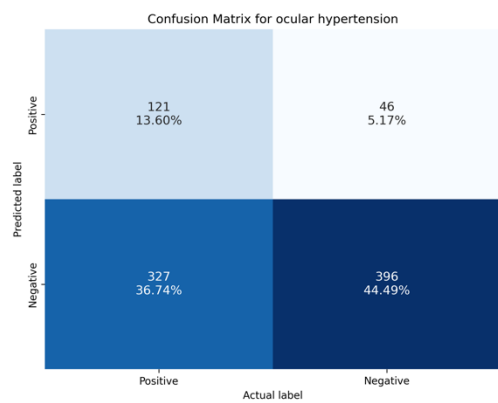
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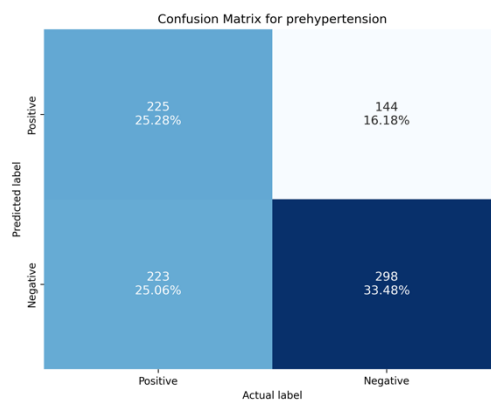
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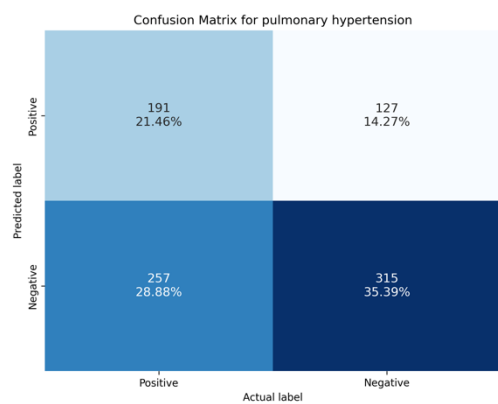
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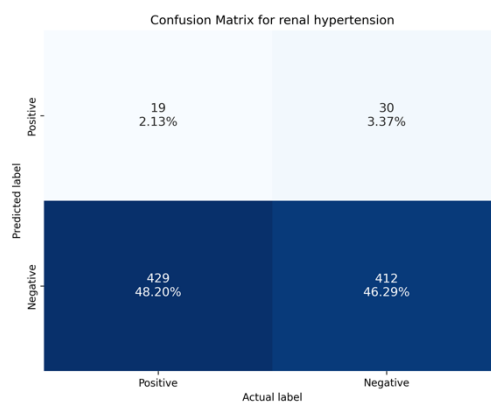
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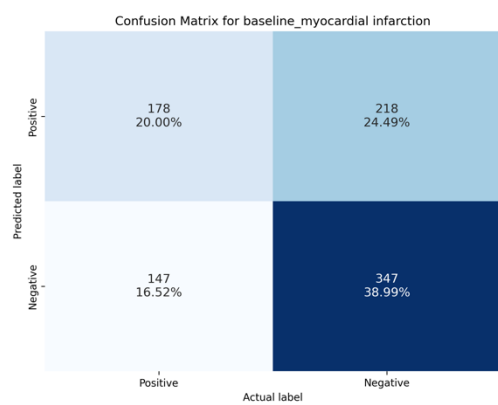


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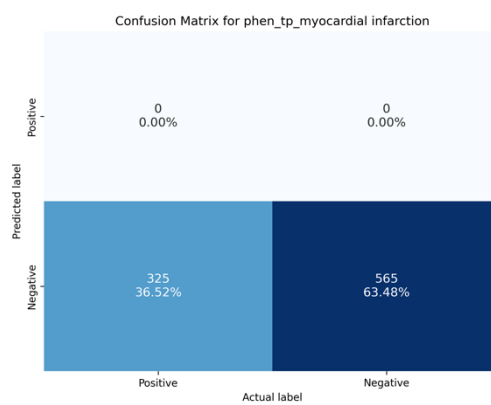


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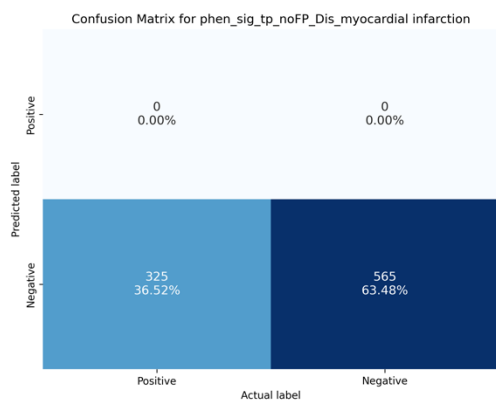
Figure S1. Confusion matrices for hypertension pathway phenotypes.



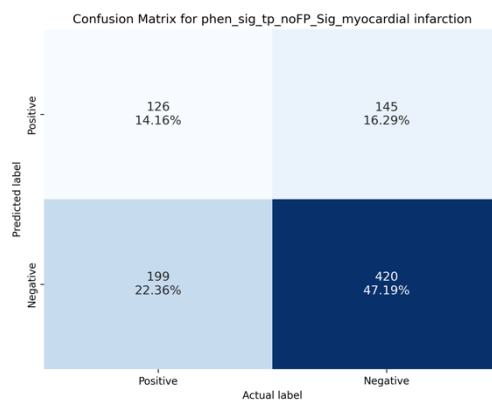
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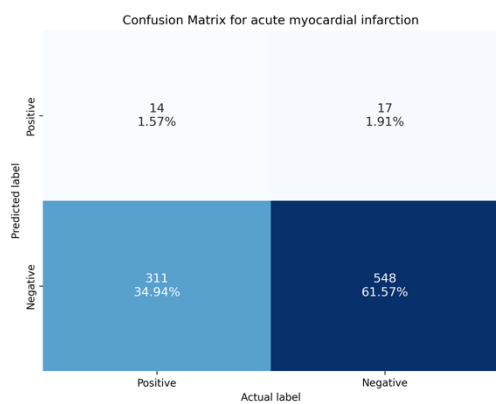
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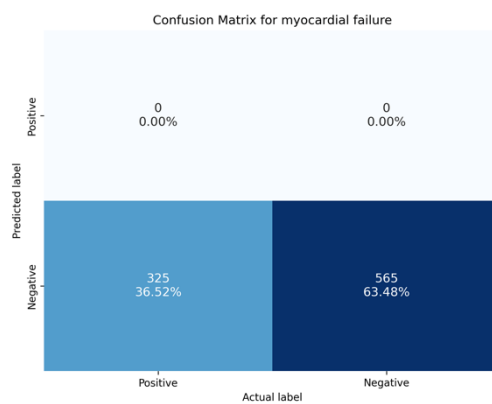
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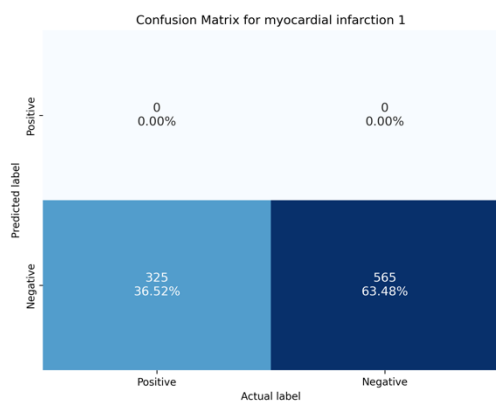
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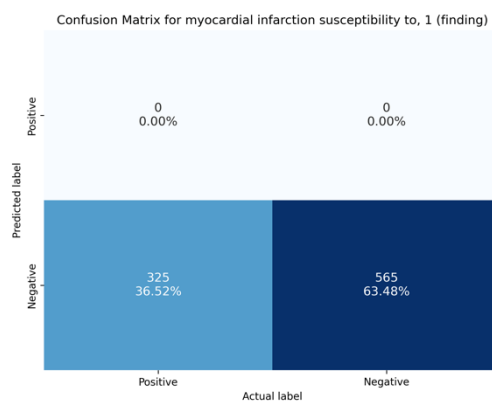
e)



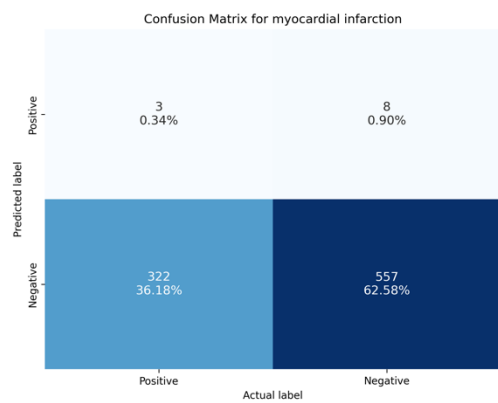
f)



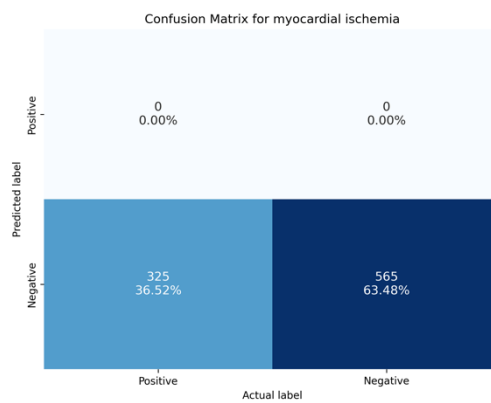
g)



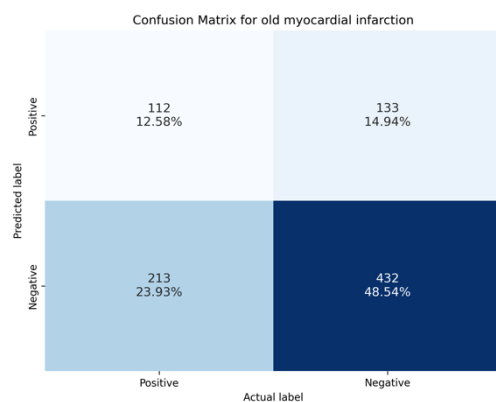
h)



i)

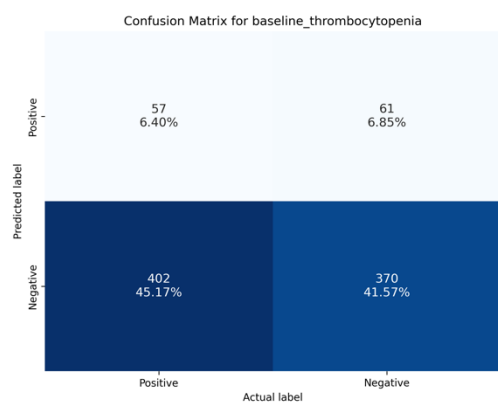


j)

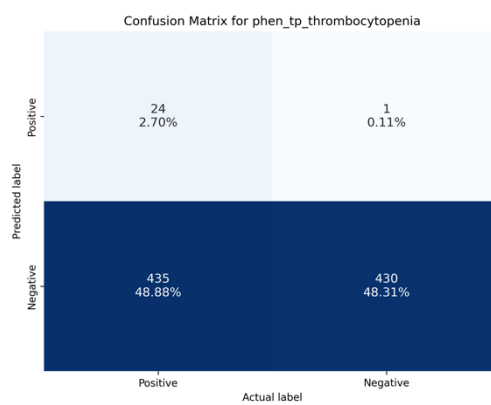


k)

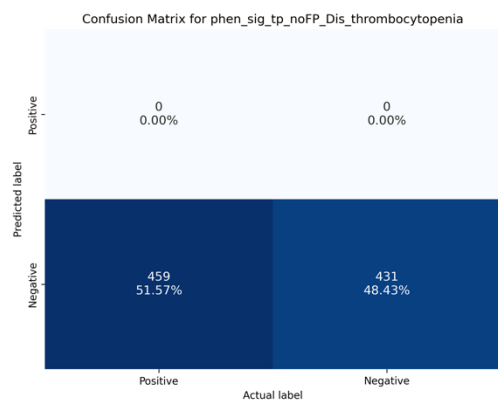
Figure S2. Confusion matrices for myocardial infarction pathway phenotypes.



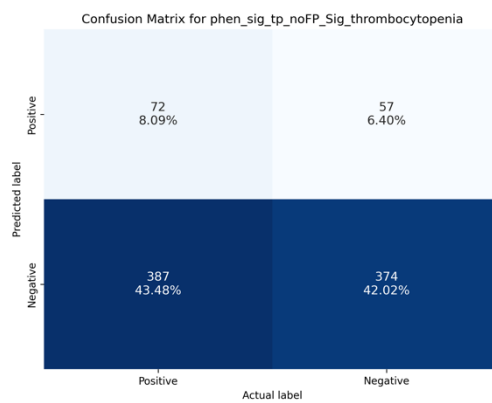
a)



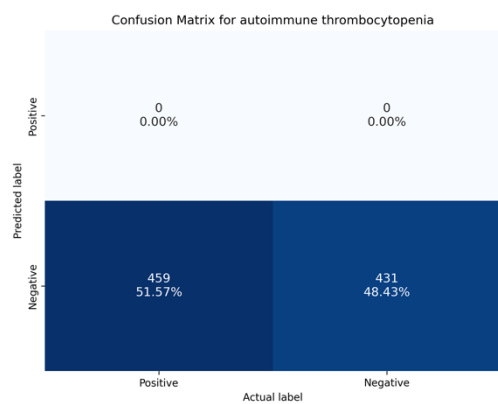
b)



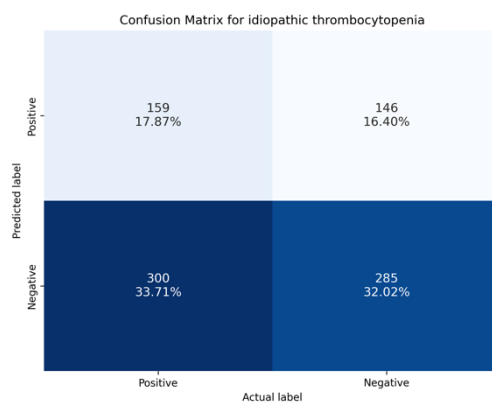
c)



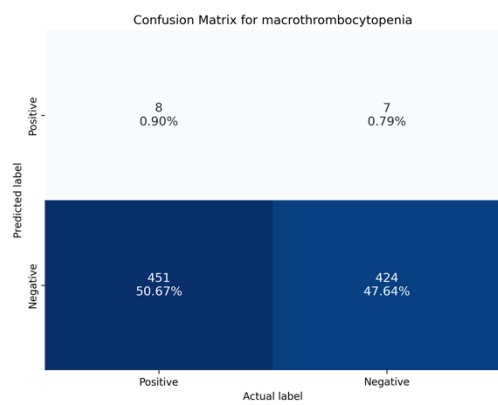
d)



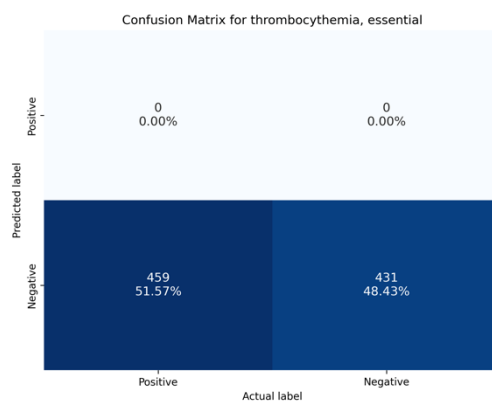
e)



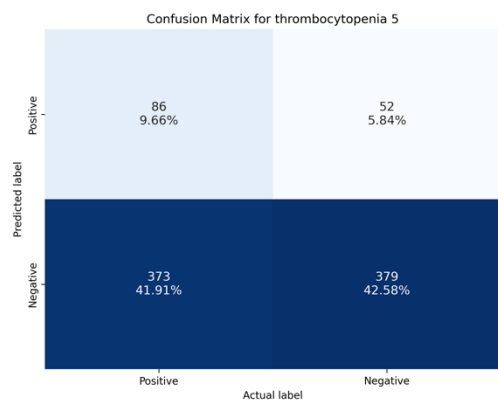
f)



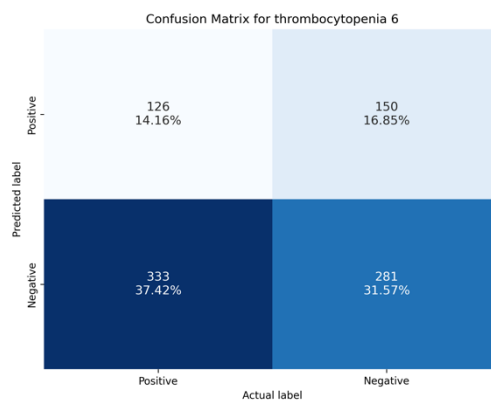
g)



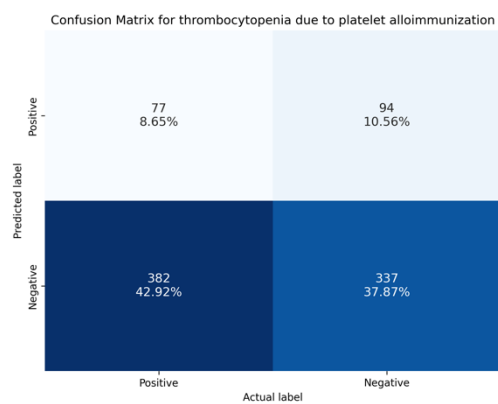
h)



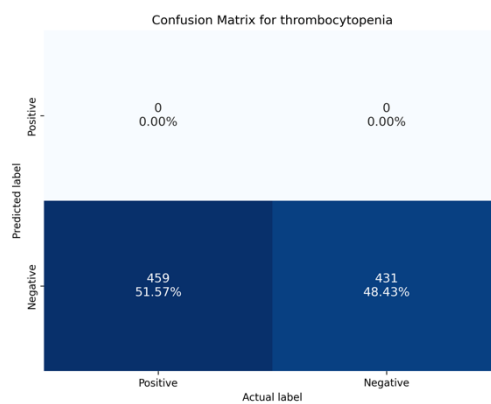
i)



j)

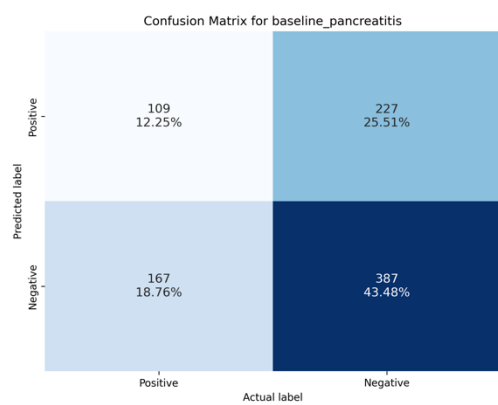


k)

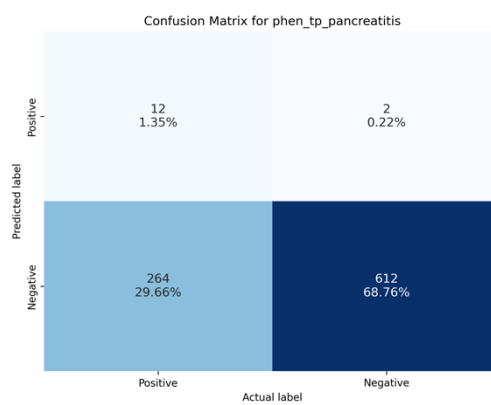


l)

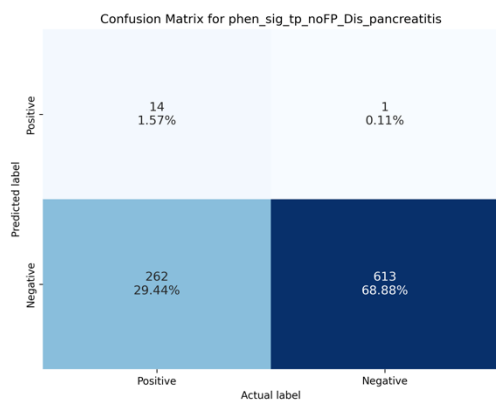
Figure S3. Confusion matrices for thrombocytopenia pathway phenotypes.



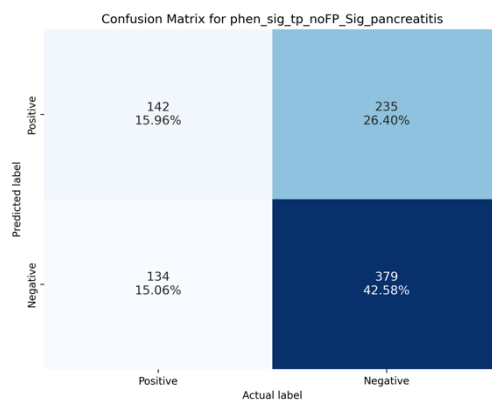
a)



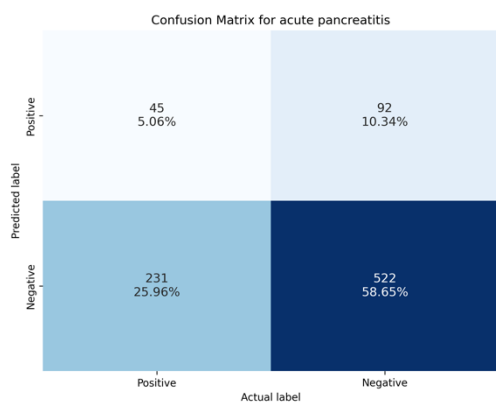
b)



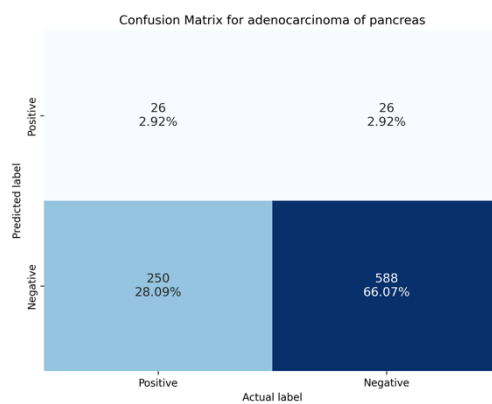
c)



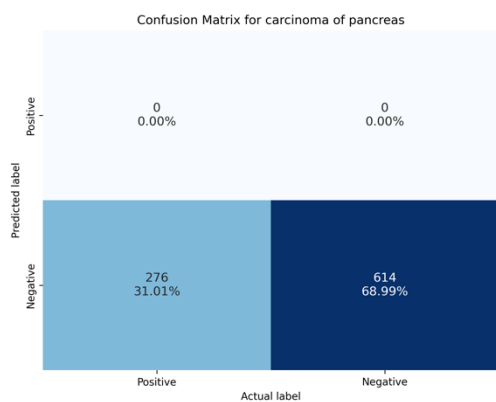
d)



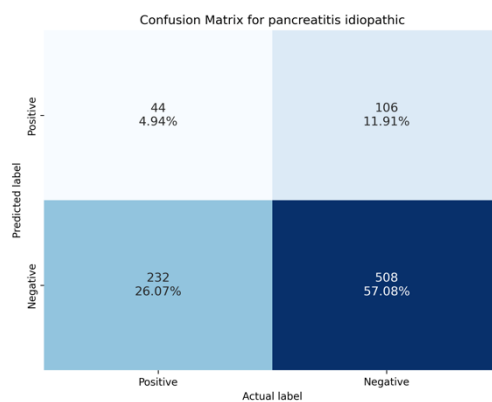
e)



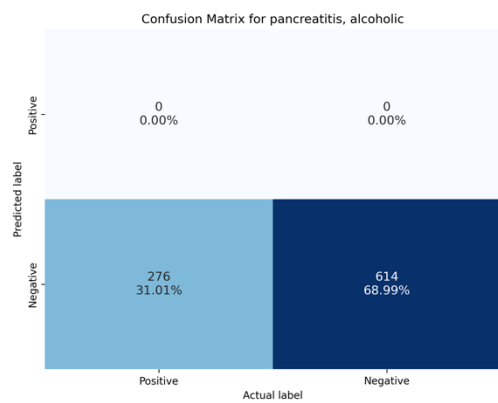
f)



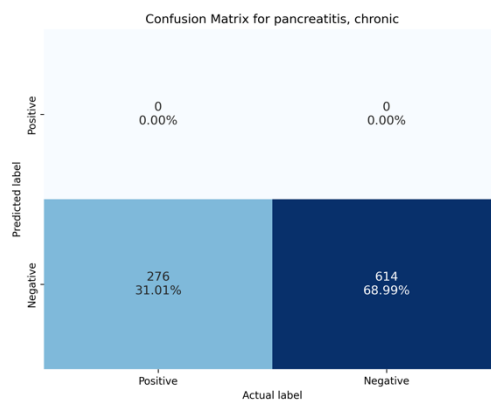
g)



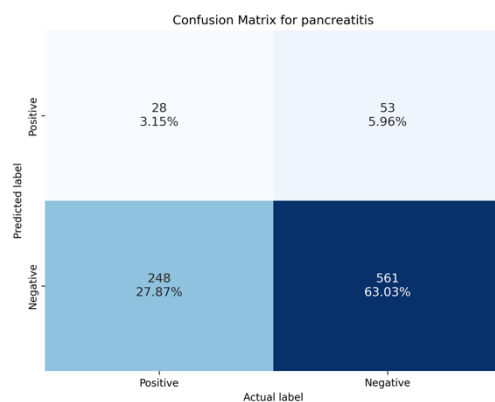
h)



i)



j)



k)

Figure S4. Confusion matrices for pancreatitis pathway phenotypes.