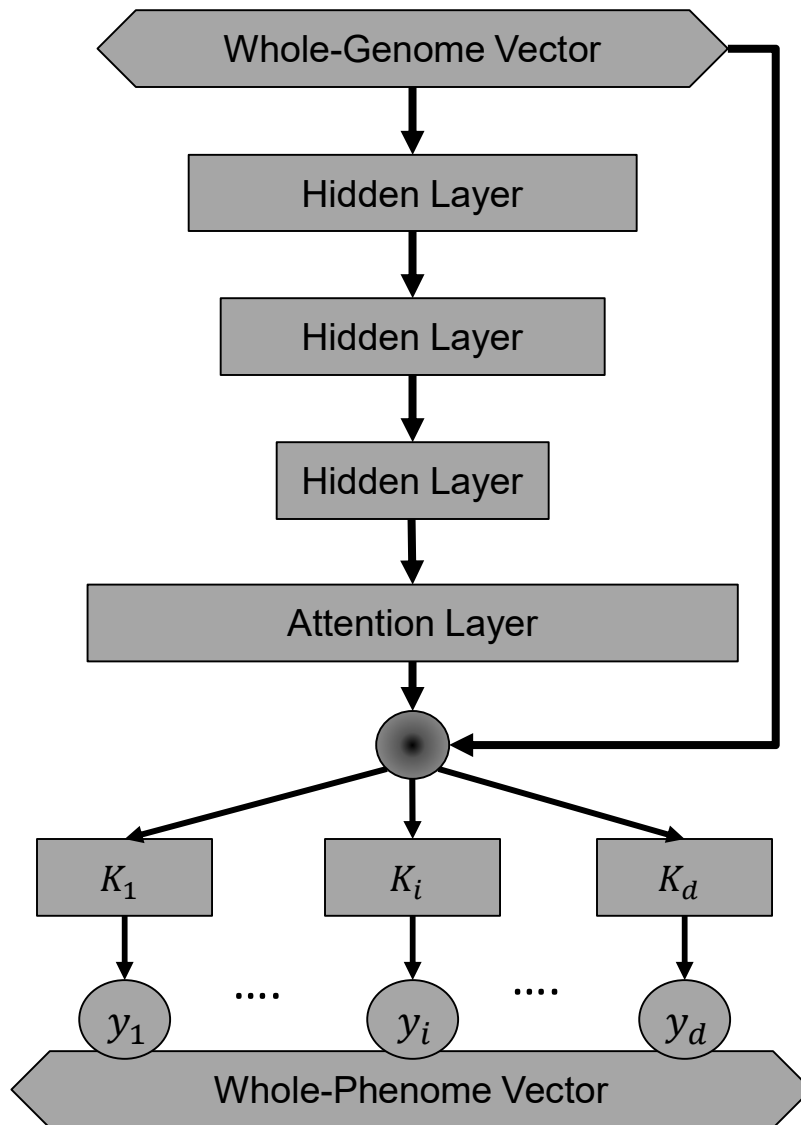




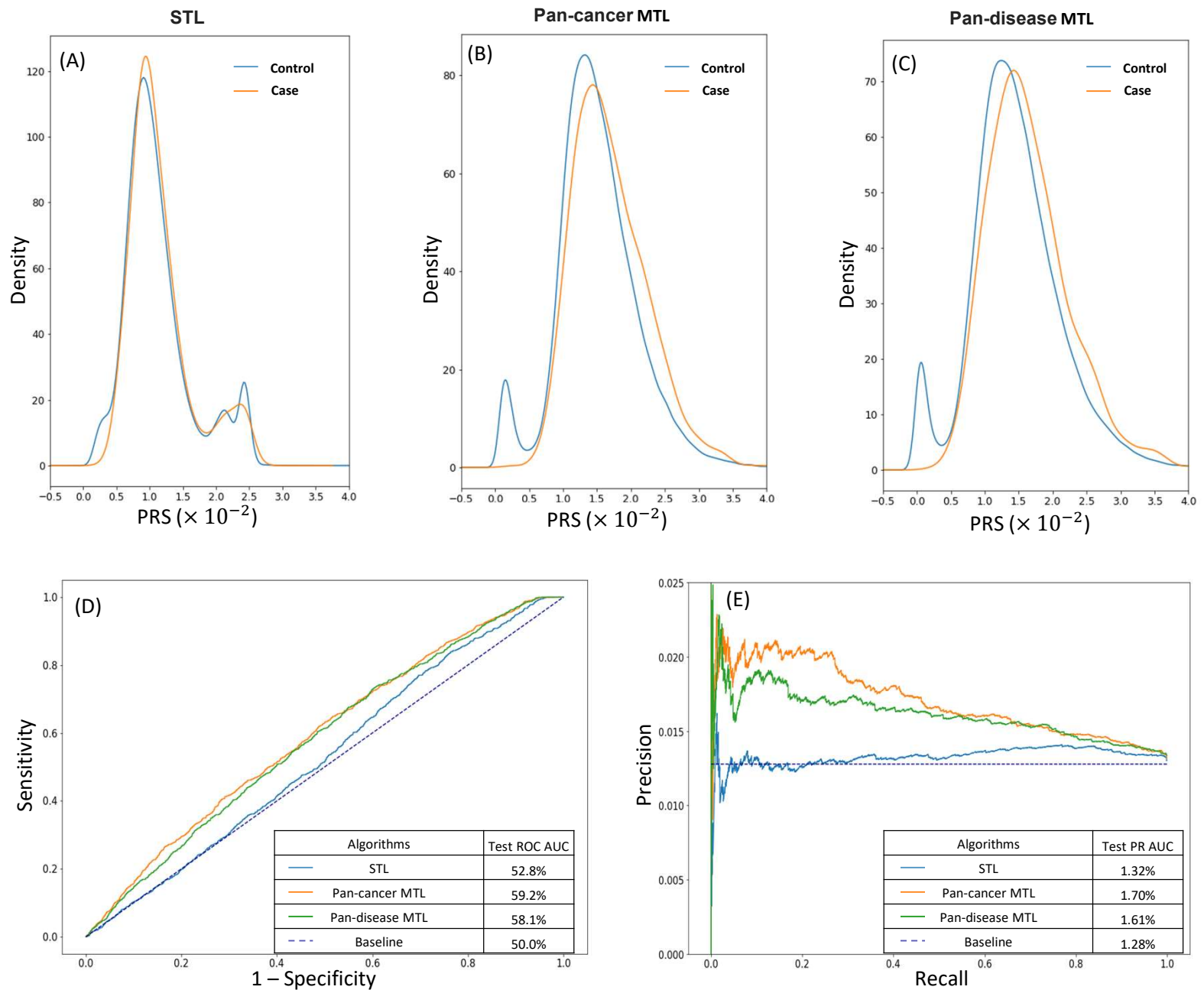


Figure 2: PRS estimation for malignant melanoma by STL and MTL. (A – C) Density plots of malignant melanoma PRS estimated by (A) STL, (B) pan-cancer MTL, and (C) pan-disease MTL. Each panel contains two overlapping density plots: a blue one for the control test cohort and an orange one for the case test cohort. The separation between the control and case density plots is greater in the two MTL panels than in the STL panel. (D) Receiver operating characteristic (ROC) curves of STL (blue), pan-cancer MTL (orange), and pan-disease MTL (green) for malignant melanoma PRS with the baseline (indigo dotted line). Both pan-cancer MTL and pan-disease MTL have larger ROC AUC than STL. (E) Precision-recall (PR) curves of STL (blue), pan-cancer MTL (orange), and pan-disease MTL (green) for malignant melanoma PRS with the disease prevalence as the baseline (indigo dotted line). The two MTL models also have larger PR AUC than STL.

Table 1: Comparison of STL, pan-cancer MTL, and pan-disease MTL by ROC AUC and PR AUC for 17 cancer types with >0.5% prevalence

Diseases	Receiver operating characteristics (ROC) AUC [#]					Precision-recall (PR) AUC [#]					
	STL ROC AUC	Pan-cancer MTL		Pan-disease MTL		STL PR AUC	Pan-cancer MTL		Pan-disease MTL		Prevalence (Baseline)
		ROC AUC	Relative increase*	ROC AUC	Relative increase*		PR AUC	Relative increase*	PR AUC	Relative increase*	
Malignant melanoma	52.80%	59.20%	234%	58.10%	194%	1.33%	1.70%	790%	1.61%	593%	1.28%
Non-melanoma skin cancer	61.50%	62.40%	8%	62.90%	12%	9.76%	10.03%	8%	10.21%	14%	6.65%
Skin cancer	61.00%	61.80%	7%	61.90%	8%	10.40%	10.73%	11%	10.86%	15%	7.32%
Lung cancer	59.10%	60.30%	14%	60.50%	16%	1.39%	1.44%	11%	1.51%	23%	0.90%
Intrathoracic cancer	59.10%	60.70%	18%	61.00%	21%	1.54%	1.58%	7%	1.65%	20%	1.01%
Colorectal cancer	54.40%	56.40%	46%	57.10%	60%	2.00%	2.21%	71%	2.29%	100%	1.72%
Colon cancer	53.90%	55.70%	47%	56.10%	59%	1.38%	1.49%	51%	1.49%	53%	1.17%
Rectal cancer	54.70%	57.90%	69%	59.30%	100%	0.77%	0.88%	98%	0.89%	116%	0.67%
Bladder cancer	64.50%	67.90%	24%	68.40%	27%	0.80%	0.87%	24%	0.92%	42%	0.51%
Uterine cancer	51.20%	53.20%	177%	51.80%	50%	1.08%	1.18%	224%	1.10%	49%	1.04%
Cervical cancer	55.20%	55.40%	4%	56.50%	24%	1.80%	1.88%	35%	1.97%	76%	1.58%
Prostate cancer	60.00%	59.70%	-3%	59.60%	-4%	8.33%	8.53%	9%	8.37%	2%	6.06%
Breast cancer	57.00%	58.30%	19%	58.10%	16%	9.38%	9.67%	13%	9.79%	20%	7.25%
Female genital tract cancer	54.00%	54.30%	7%	54.50%	11%	3.15%	3.27%	41%	3.39%	84%	2.86%
Male genital tract cancer	53.60%	56.10%	68%	54.50%	24%	2.57%	2.73%	57%	2.59%	9%	2.28%
Lymphoma	50.40%	56.80%	1442%	57.90%	1704%	0.73%	0.82%	102%	0.82%	98%	0.64%
Non-hodgkins lymphoma	52.10%	56.60%	220%	57.80%	278%	0.61%	0.68%	81%	0.69%	95%	0.53%

[#]Best AUC highlighted in bold

*Relative increase = $\frac{(MTL\ AUC - baseline\ AUC) - (STL\ AUC - baseline\ AUC)}{STL\ AUC - baseline\ AUC} \times 100\%$

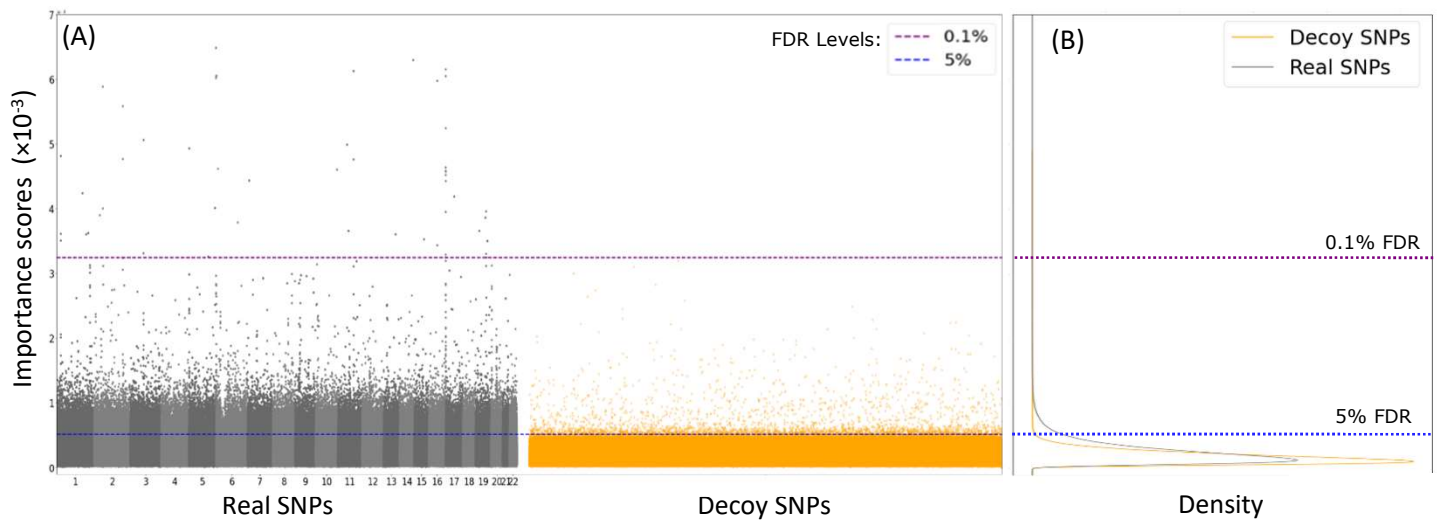
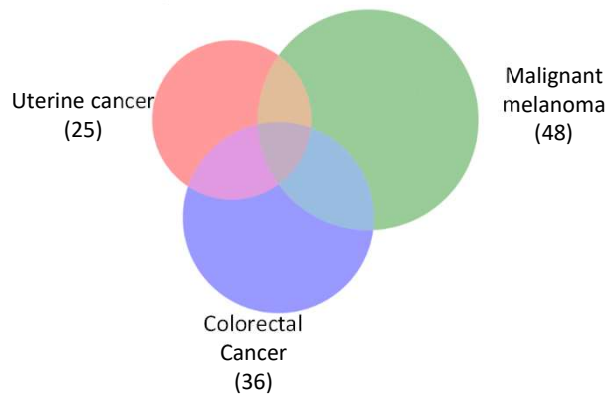


Figure 3: Importance scores of real and decoy SNPs for malignant melanoma PRS estimation by pan-cancer MTL. (A) Manhattan plots of real SNPs (black and grey dots) and decoy SNPs (orange dots) by their importance scores. (B) density plots of the importance scores of real SNPs (black curve) and decoy SNPs (orange curve). An estimated FDR of 5% (3091 decoy SNP to 59,350 real SNPs) was reached at the importance score threshold of 0.52×10^{-3} (blue dotted line). No decoy SNPs and 48 real SNPs have importance scores above the threshold of 3.25×10^{-3} for an estimated 0.1% FDR (purple dotted line).

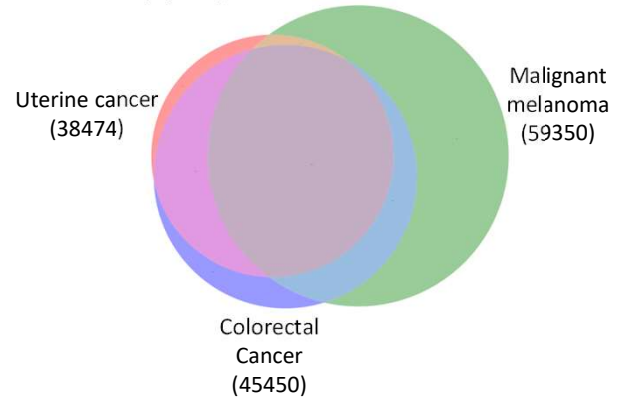
Table 2: Numbers of important SNPs used by pan-cancer MTL to estimate PRS of prevalent cancers

Disease	FDR levels	
	0.1%	5.0%
Malignant melanoma	48	59350
Non-melanoma skin cancer	132	48848
Skin cancer	106	48419
Lung cancer	4	41075
Intrathoracic cancer	3	40392
Colorectal cancer	36	45450
Colon cancer	22	37487
Rectal cancer	28	47904
Bladder cancer	8	37
Uterine cancer	25	38474
Cervical cancer	5	42068
Prostate cancer	23	94
Breast cancer	34	96
Female genital tract cancer	15	37083
Male genital tract cancer	5	40742
Lymphoma	0	43412
Non-hodgkins lymphoma	4	41889

(A) Important SNPs at 0.1% FDR



(B) Important SNPs at 5% FDR



(C) Genetic correlation between important SNPs at 5% FDR

Malignant melanoma	Non-melanoma skin cancer	Skin cancer	Lung cancer	Intrathoracic cancer	Colorectal cancer	Colon cancer	Rectal cancer	Bladder cancer	Uterine cancer	Cervical cancer	Prostate cancer	Breast cancer	Female genital tract cancer	Male genital tract cancer	Lymphoma	Non-hodgkins lymphoma	
	0.72	0.73	0.3	0.3	0.4	0.27	0.41	0.42	0.32	0.39	0.5	0.57	0.26	0.39	0.28	0.25	Malignant melanoma
		0.96	0.09	0.09	0.15	0.03	0.16	0.4	0.05	0.15	0.44	0.49	0.04	0.12	0.04	0.02	Non-melanoma skin cancer
			0.05	0.05	0.12	0	0.13	0.38	0.03	0.11	0.42	0.48	0	0.09	0.01	-0.01	Skin cancer
				0.99	0.86	0.86	0.86	0.74	0.78	0.84	0.91	0.87	0.86	0.8	0.89	0.89	Lung cancer
					0.85	0.84	0.85	0.76	0.75	0.83	0.91	0.86	0.86	0.78	0.88	0.87	Intrathoracic cancer
						0.9	0.93	0.65	0.81	0.87	0.84	0.87	0.81	0.86	0.86	0.84	Colorectal cancer
							0.83	0.69	0.83	0.81	0.87	0.87	0.85	0.81	0.9	0.9	Colon cancer
								0.66	0.82	0.88	0.85	0.86	0.81	0.87	0.86	0.84	Rectal cancer
									0.6	0.65	-0.43	-0.36	0.74	0.6	0.69	0.71	Bladder cancer
										0.8	0.77	0.88	0.78	0.82	0.85	0.84	Uterine cancer
											0.82	0.89	0.86	0.81	0.84	0.82	Cervical cancer
												-0.52	0.88	0.82	0.89	0.9	Prostate cancer
													0.88	0.82	0.89	0.88	Breast cancer
														0.75	0.87	0.88	Female genital tract cancer
															0.85	0.82	Male genital tract cancer
																0.98	Lymphoma
																	Non-hodgkins lymphoma

Figure 3: Genetic correlation between diseases in MTL. The Venn diagrams show the overlap among the important SNPs found for uterine cancer, malignant melanoma, and colorectal cancer at 0.1% FDR (A) and 5% FDR (B). The sizes of the circles and their overlaps are drawn proportionally. The important sets of SNPs for the three cancers have a small overlap at 0.1% FDR and a large overlap at 5% FDR. (C) Genetic correlations between every pair of prevalent cancers in pan-cancer MTL. The correlation coefficients are computed between the importance scores of the SNPs important for both or one of the two cancers at 5% FDR. The importance scores of many pairs of cancers have high correlation coefficients, which indicate shared genetic basis.