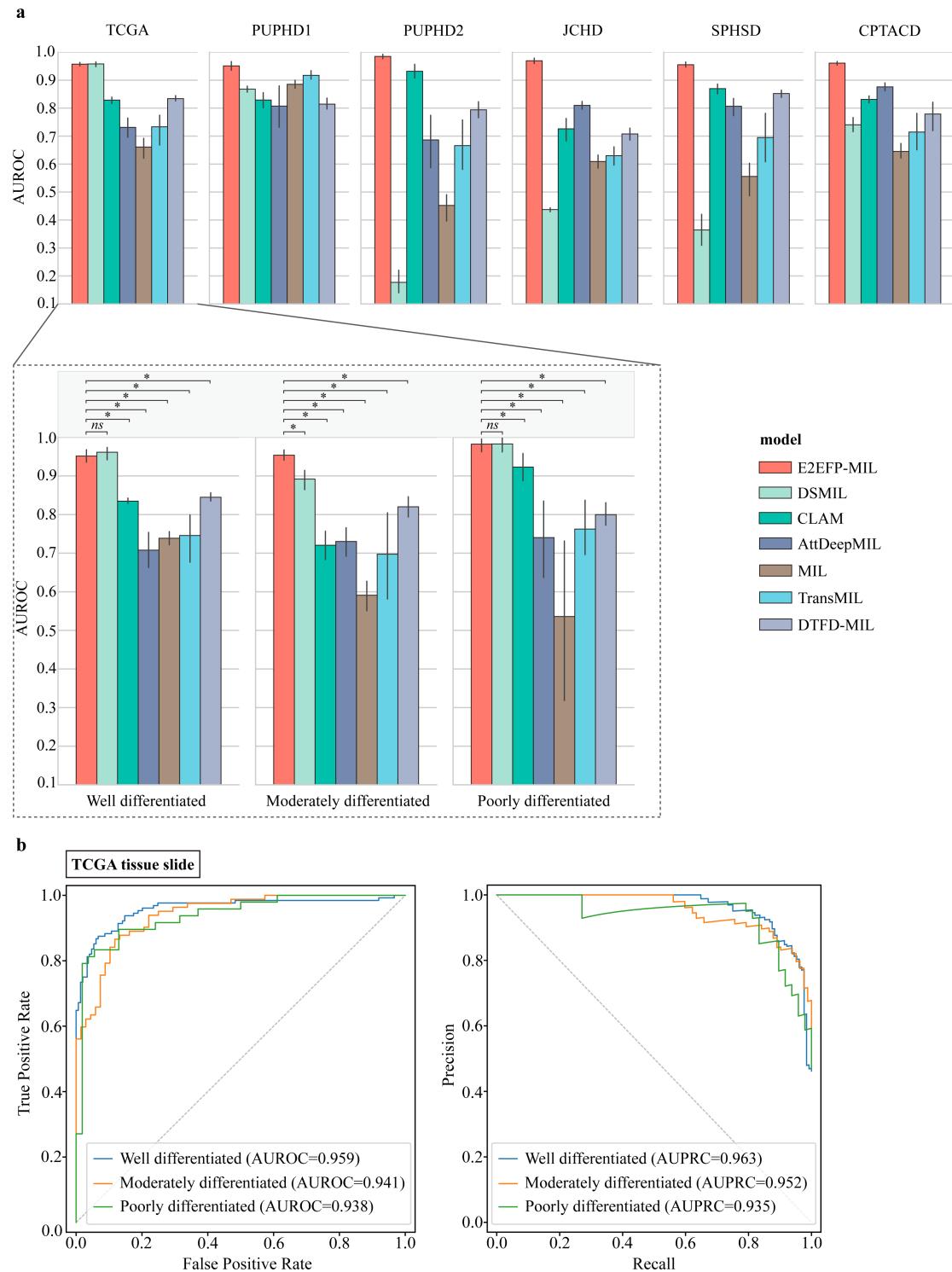


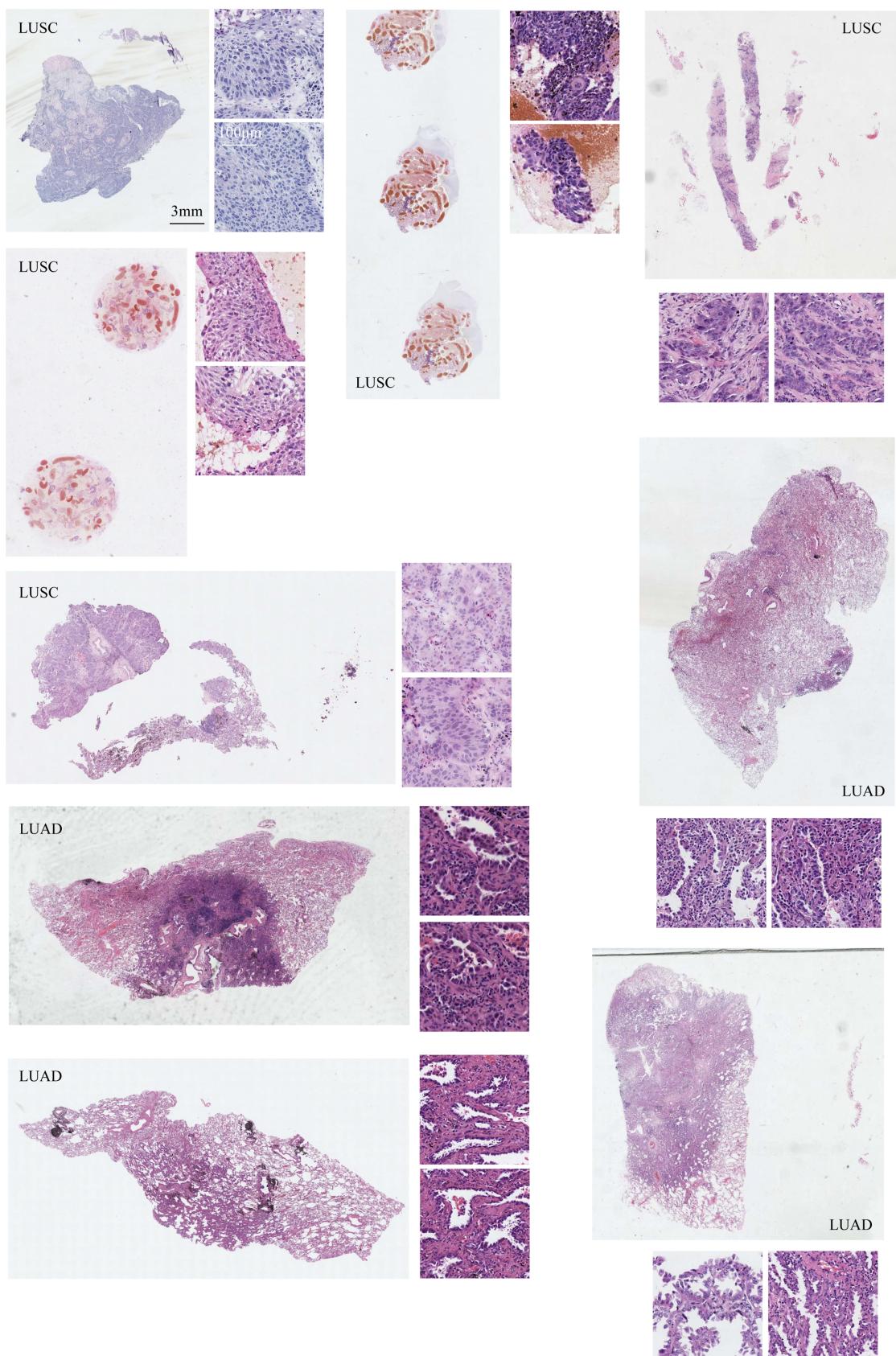
**Supplementary Figure 1** Reproduced results of Lu et al. (CLAM) and our method.

**Supplementary Table 1.** Comparative results between Lu et al. Nature Biomedical Engineering and our method.

	Lu et al. (origin)	Lu et al. (by us)	Lu et al. (by us)	Our method
Training set	TCGA+CPTAC	TCGA	TCGA	
Test AUC	0.975±0.007	0.963±0.009	0.854±0.040	0.955±0.008



**Supplementary Figure.2** Comparison of model performance in various differentiated tumors. (a) model performance on internal and external datasets, (b) performance of our method (E2EFP-MIL) on TCGA tissue slides stratified by tumor differentiation. \* represents statistical significant result, while ns represents non-significant result.



**Supplementary Figure.3** E2EFP-MIL learned histomorphological patterns important for the classification of LUAD and LUSC.

**Supplementary Table.2** Detailed description of models' performance on six heterogenous datasets.

AUROC	AUPRC	Model	Dataset
0.9662	0.9715	E2EFP-MIL	test
0.9517	0.9546	E2EFP-MIL	test
0.9494	0.9532	E2EFP-MIL	test
0.9517	0.9541	E2EFP-MIL	test
0.9662	0.969	E2EFP-MIL	test
0.9732	0.9821	E2EFP-MIL	beijing1
0.9271	0.9453	E2EFP-MIL	beijing1
0.9402	0.9639	E2EFP-MIL	beijing1
0.9418	0.9654	E2EFP-MIL	beijing1
0.9719	0.9801	E2EFP-MIL	beijing1
0.9876	0.9795	E2EFP-MIL	beijing2
0.9693	0.963	E2EFP-MIL	beijing2
0.9795	0.9655	E2EFP-MIL	beijing2
0.9919	0.9877	E2EFP-MIL	beijing2
0.9952	0.9931	E2EFP-MIL	beijing2
0.9703	0.9677	E2EFP-MIL	jiangsu
0.9775	0.9775	E2EFP-MIL	jiangsu
0.984	0.9845	E2EFP-MIL	jiangsu
0.9563	0.9494	E2EFP-MIL	jiangsu
0.9579	0.9577	E2EFP-MIL	jiangsu
0.9588	0.9452	E2EFP-MIL	shenzhen
0.9423	0.9215	E2EFP-MIL	shenzhen
0.9463	0.9252	E2EFP-MIL	shenzhen
0.9574	0.9413	E2EFP-MIL	shenzhen
0.9704	0.9576	E2EFP-MIL	shenzhen
0.967	0.9697	E2EFP-MIL	cptac
0.9629	0.9677	E2EFP-MIL	cptac
0.948	0.9511	E2EFP-MIL	cptac
0.9572	0.9608	E2EFP-MIL	cptac
0.9683	0.9709	E2EFP-MIL	cptac
0.8450	0.8293	CLAM	test
0.8336	0.8153	CLAM	test
0.8308	0.7771	CLAM	test
0.8273	0.7965	CLAM	test
0.8061	0.7308	CLAM	test
0.8127	0.8201	CLAM	beijing1
0.8639	0.8597	CLAM	beijing1
0.8709	0.8705	CLAM	beijing1
0.7928	0.7571	CLAM	beijing1
0.8039	0.8013	CLAM	beijing1
0.9623	0.9394	CLAM	beijing2

0.8885	0.8135	CLAM	beijing2
0.9359	0.8728	CLAM	beijing2
0.9612	0.9325	CLAM	beijing2
0.9116	0.8854	CLAM	beijing2
0.7089	0.5719	CLAM	jiangsu
0.6431	0.5103	CLAM	jiangsu
0.7426	0.6562	CLAM	jiangsu
0.7578	0.6391	CLAM	jiangsu
0.7783	0.7122	CLAM	jiangsu
0.8738	0.8231	CLAM	shenzhen
0.8385	0.6855	CLAM	shenzhen
0.8966	0.8274	CLAM	shenzhen
0.8663	0.7799	CLAM	shenzhen
0.8737	0.7791	CLAM	shenzhen
0.8159	0.7990	CLAM	cptac
0.8211	0.8104	CLAM	cptac
0.8518	0.8330	CLAM	cptac
0.8239	0.7958	CLAM	cptac
0.8428	0.8464	CLAM	cptac
0.7280	0.6493	DeepAttMIL	test
0.7147	0.7878	DeepAttMIL	test
0.7437	0.7507	DeepAttMIL	test
0.6737	0.6714	DeepAttMIL	test
0.7955	0.7994	DeepAttMIL	test
0.7125	0.7003	DeepAttMIL	beijing1
0.8784	0.8808	DeepAttMIL	beijing1
0.8152	0.8643	DeepAttMIL	beijing1
0.7098	0.7679	DeepAttMIL	beijing1
0.9210	0.9253	DeepAttMIL	beijing1
0.6654	0.6011	DeepAttMIL	beijing2
0.8254	0.7721	DeepAttMIL	beijing2
0.5113	0.5132	DeepAttMIL	beijing2
0.7004	0.6728	DeepAttMIL	beijing2
0.7295	0.6748	DeepAttMIL	beijing2
0.7939	0.7303	DeepAttMIL	jiangsu
0.8284	0.7093	DeepAttMIL	jiangsu
0.7983	0.6947	DeepAttMIL	jiangsu
0.7965	0.7279	DeepAttMIL	jiangsu
0.8322	0.7025	DeepAttMIL	jiangsu
0.7468	0.6727	DeepAttMIL	shenzhen
0.7931	0.7146	DeepAttMIL	shenzhen
0.8471	0.8420	DeepAttMIL	shenzhen
0.8316	0.7769	DeepAttMIL	shenzhen

0.8146	0.7867	DeepAttMIL	shenzhen
0.8803	0.8947	DeepAttMIL	cptac
0.8674	0.8805	DeepAttMIL	cptac
0.8968	0.9090	DeepAttMIL	cptac
0.8498	0.8824	DeepAttMIL	cptac
0.8855	0.9158	DeepAttMIL	cptac
0.5922	0.5678	MIL	test
0.6746	0.6419	MIL	test
0.6582	0.5883	MIL	test
0.6703	0.5909	MIL	test
0.7092	0.6556	MIL	test
0.9006	0.9168	MIL	beijing1
0.8722	0.8867	MIL	beijing1
0.8809	0.8801	MIL	beijing1
0.9082	0.9084	MIL	beijing1
0.8643	0.8875	MIL	beijing1
0.3448	0.2877	MIL	beijing2
0.4801	0.3712	MIL	beijing2
0.4865	0.4379	MIL	beijing2
0.4494	0.4589	MIL	beijing2
0.4995	0.4310	MIL	beijing2
0.6243	0.5312	MIL	jiangsu
0.5726	0.4650	MIL	jiangsu
0.5798	0.4947	MIL	jiangsu
0.6331	0.5231	MIL	jiangsu
0.6355	0.5804	MIL	jiangsu
0.4198	0.3274	MIL	shenzhen
0.5972	0.4231	MIL	shenzhen
0.6198	0.4624	MIL	shenzhen
0.5650	0.4435	MIL	shenzhen
0.5776	0.4489	MIL	shenzhen
0.6044	0.6026	MIL	cptac
0.6936	0.7159	MIL	cptac
0.6438	0.6418	MIL	cptac
0.6282	0.6334	MIL	cptac
0.6552	0.6861	MIL	cptac
0.9564	0.9062	DSMIL	test
0.938	0.8948	DSMIL	test
0.9635	0.9103	DSMIL	test
0.9682	0.9574	DSMIL	test
0.9635	0.9111	DSMIL	test
0.8685	0.8623	DSMIL	beijing1
0.8603	0.8667	DSMIL	beijing1

0.8756	0.8751	DSMIL	beijing1
0.8495	0.86	DSMIL	beijing1
0.8859	0.8709	DSMIL	beijing1
0.1417	0.2274	DSMIL	beijing2
0.173	0.231	DSMIL	beijing2
0.1245	0.2226	DSMIL	beijing2
0.2624	0.2517	DSMIL	beijing2
0.1843	0.2344	DSMIL	beijing2
0.4381	0.4385	DSMIL	jiangsu
0.4433	0.4243	DSMIL	jiangsu
0.446	0.4345	DSMIL	jiangsu
0.4377	0.4258	DSMIL	jiangsu
0.4224	0.4179	DSMIL	jiangsu
0.4059	0.2928	DSMIL	shenzhen
0.4644	0.3292	DSMIL	shenzhen
0.2935	0.2681	DSMIL	shenzhen
0.3554	0.2742	DSMIL	shenzhen
0.3032	0.2674	DSMIL	shenzhen
0.7426	0.7643	DSMIL	cptac
0.7116	0.6901	DSMIL	cptac
0.7718	0.8081	DSMIL	cptac
0.7026	0.6746	DSMIL	cptac
0.7733	0.8047	DSMIL	cptac
0.772	0.7864	TransMIL	test
0.7457	0.7543	TransMIL	test
0.7814	0.774	TransMIL	test
0.7671	0.7785	TransMIL	test
0.6005	0.6202	TransMIL	test
0.9018	0.8991	TransMIL	beijing1
0.9491	0.9476	TransMIL	beijing1
0.9121	0.9118	TransMIL	beijing1
0.9216	0.9242	TransMIL	beijing1
0.9013	0.8963	TransMIL	beijing1
0.8041	0.8181	TransMIL	beijing2
0.6137	0.6048	TransMIL	beijing2
0.5652	0.5737	TransMIL	beijing2
0.7613	0.7739	TransMIL	beijing2
0.5851	0.5925	TransMIL	beijing2
0.658	0.6478	TransMIL	jiangsu
0.6852	0.6766	TransMIL	jiangsu
0.5879	0.5823	TransMIL	jiangsu
0.6261	0.6269	TransMIL	jiangsu
0.5918	0.6195	TransMIL	jiangsu

0.758	0.7441	TransMIL	shenzhen
0.8223	0.783	TransMIL	shenzhen
0.5548	0.5489	TransMIL	shenzhen
0.7457	0.7052	TransMIL	shenzhen
0.593	0.5795	TransMIL	shenzhen
0.7403	0.7117	TransMIL	cptac
0.7809	0.768	TransMIL	cptac
0.6172	0.6071	TransMIL	cptac
0.8017	0.7896	TransMIL	cptac
0.6326	0.639	TransMIL	cptac
0.8265	0.816	DTFD-MIL	test
0.855	0.8476	DTFD-MIL	test
0.8346	0.8323	DTFD-MIL	test
0.8242	0.8016	DTFD-MIL	test
0.8293	0.7959	DTFD-MIL	test
0.8155	0.8582	DTFD-MIL	beijing1
0.8561	0.8721	DTFD-MIL	beijing1
0.7889	0.8192	DTFD-MIL	beijing1
0.7955	0.8262	DTFD-MIL	beijing1
0.8151	0.8264	DTFD-MIL	beijing1
0.7665	0.5997	DTFD-MIL	beijing2
0.7539	0.6085	DTFD-MIL	beijing2
0.7771	0.6573	DTFD-MIL	beijing2
0.8354	0.7611	DTFD-MIL	beijing2
0.837	0.7163	DTFD-MIL	beijing2
0.7198	0.6578	DTFD-MIL	jiangsu
0.7265	0.654	DTFD-MIL	jiangsu
0.7348	0.6985	DTFD-MIL	jiangsu
0.6724	0.6302	DTFD-MIL	jiangsu
0.6846	0.6445	DTFD-MIL	jiangsu
0.8293	0.632	DTFD-MIL	shenzhen
0.8457	0.6537	DTFD-MIL	shenzhen
0.8544	0.6733	DTFD-MIL	shenzhen
0.8573	0.6738	DTFD-MIL	shenzhen
0.8738	0.7017	DTFD-MIL	shenzhen
0.672	0.6985	DTFD-MIL	cptac
0.8341	0.8218	DTFD-MIL	cptac
0.807	0.8319	DTFD-MIL	cptac
0.7666	0.7766	DTFD-MIL	cptac
0.8147	0.8145	DTFD-MIL	cptac