

Supplemental Tables and Figures

Table S1: Comparison of TCGA projects and TUO classifier classes.

TCGA Project (Abbrv)	TUO Classifier Class
Adrenocortical Carcinoma (ACC)	Adrenocortical Carcinoma
Bladder Urothelial Carcinoma (BLCA)	Bladder
Brain Lower Grade Glioma (LGG)	Brain Non-Glioblastoma
Breast invasive carcinoma (BRCA)	Split into class Breast Group 1 and class Breast Group 2
Cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC)	Split into class Cervix Uteri and class Cervix Uteri Group 2
Cholangiocarcinoma (CHOL)	Intrahepatic Bile Duct (Cholangiocarcinoma)
Colon adenocarcinoma (COAD)	Split into class Colon and class Cecum
Esophageal carcinoma (ESCA)	Split into class Esophageal Adenocarcinoma, Esophageal Squamous Cell Carcinoma, and Stomach
Glioblastoma multiforme (GBM)	Glioblastoma
Head and Neck squamous cell carcinoma (HNSC)	Head and Neck
Kidney Chromophobe (KICH)	Kidney Renal Cell Carcinoma Chromophobe Type
Kidney renal clear cell carcinoma (KIRC)	Split into class Kidney Clear Cell Adenocarcinoma and Renal Cell Carcinoma Group 1 and class Kidney Clear Cell and Papillary Adenocarcinoma Group 2
Kidney renal papillary cell carcinoma (KIRP)	Split into class Kidney Clear Cell and Papillary Adenocarcinoma Group 2 and class Kidney Papillary Adenocarcinoma
Liver hepatocellular carcinoma (LIHC)	Hepatocellular Carcinoma
Lung adenocarcinoma (LUAD)	Lung Adenocarcinoma
Lung squamous cell carcinoma (LUSC)	Lung Squamous Cell Carcinoma
Lymphoid Neoplasm Diffuse Large B-cell Lymphoma (DLBC)	Lymph Nodes

Mesothelioma (MESO)	Lung Pleura (Mesothelioma)
Ovarian serous cystadenocarcinoma (OV)	Combined with Uterine Corpus Endometrial Carcinoma to create class Endo-Ovarian Serous Cystadenocarcinoma
Pancreatic adenocarcinoma (PAAD)	Split into class Pancreas, class Pancreas Group 3, and class Pancreas Neuroendocrine
Pheochromocytoma and Paraganglioma (PCPG)	Pheochromocytoma
Prostate adenocarcinoma (PRAD)	Prostate
Rectum adenocarcinoma (READ)	Rectum
Sarcoma	Split into class Soft Tissue Main, class Retroperitoneum, class Non-Uterine Leiomyosarcoma, and class Uterine Leiomyosarcoma
Skin Cutaneous Melanoma (SKCM)	Melanoma
Stomach adenocarcinoma (STAD)	Split into class Stomach and class Small Intestine
Testicular Germ Cell Tumors (TGCT)	Split into class Seminoma and class Testis Non-Seminoma
Thymoma (THYM)	Thymus and Chest
Thyroid carcinoma (THCA)	Split into class Thyroid Carcinoma and class Thyroid Follicular Neoplasm
Uterine Carcinosarcoma (UCS)	Combined with Uterine Corpus Endometrial Carcinoma to create class Endometrioid Adenocarcinoma
Uterine Corpus Endometrial Carcinoma (UCEC)	Combined with Uterine Carcinosarcoma to create class Endometrioid Adenocarcinoma and Ovarian serous cystadenocarcinoma to create class Endo-Ovarian Serous Cystadenocarcinoma
Uveal Melanoma (UVM)	Eye

Table S2: Class Accuracy

Class Abbrv	Class Name	Superclass	# Samples	# Correct (%)	# Match (%)	Average Score
AG_P	Adrenal Cortical Carcinoma	Adrenal Gland	14	13 (0.929)	12 (0.857)	0.975
BLD	Bladder	None	207	197 (0.952)	162 (0.783)	0.915
BNG	Brain Non-Glioblastoma	Brain	88	88 (1.000)	84 (0.955)	0.975
BRST1	Breast Group 1	Breast	122	121 (0.992)	117 (0.959)	0.986
BRST2	Breast Group 2	Breast	16	15 (0.938)	13 (0.813)	0.944
CEC	Cecum	Large Intestine	13	13 (1.000)	10 (0.769)	0.953
CVX_UT	Cervix Uteri	Gynecological	71	65 (0.915)	43 (0.606)	0.883
CVX_UT2	Cervix Uteri Group 2	Gynecological	7	7 (1.000)	4 (0.571)	0.877
COLON	Colon	Large Intestine	47	46 (0.979)	45 (0.957)	0.978
ENDO_ADC	Endometrioid Adenocarcinoma	Gynecological	16	16 (1.000)	16 (1.000)	0.987
ENDO_SCA	Endo-Ovarian Serous Cystadenocarcinoma	Gynecological	97	97 (1.000)	86 (0.887)	0.949
ESO_ADC	Esophageal Adenocarcinoma	Upper Gastrointestinal	20	19 (0.950)	16 (0.800)	0.925
ESO_SCC	Esophageal Squamous Cell Carcinoma	Squamous Cell Carcinoma	15	14 (0.933)	12 (0.800)	0.956
EYE	Eye	None	19	19 (1.000)	18 (0.947)	0.981
GBM	Glioblastoma	Brain	8	8 (1.000)	8 (1.000)	0.994

HN	Head and Neck	Squamous Cell Carcinoma	76	72 (0.947)	52 (0.684)	0.922
HCC	Hepatocellular Carcinoma	Liver	194	189 (0.974)	184 (0.948)	0.985
IHBD	Intrahepatic Bile Duct (Cholangiocarcinoma)	Liver	8	7 (0.875)	7 (0.875)	0.998
KCCA1	Kidney Clear Cell Adenocarcinoma and Renal Cell Carcinoma Group 1	Kidney	33	33 (1.000)	28 (0.848)	0.938
KCCA2	Kidney Clear Cell and Papillary Adenocarcinoma Group 2	Kidney	14	14 (1.000)	13 (0.929)	0.961
KPPA	Kidney Papillary Adenocarcinoma	Kidney	49	46 (0.939)	42 (0.857)	0.966
KRCCC	Kidney Renal Cell Carcinoma Chromophobe Type	Kidney	15	15 (1.000)	13 (0.867)	0.952
LUNG_ADC	Lung Adenocarcinoma	Lung	213	202 (0.948)	177 (0.831)	0.951
PLEURA	Lung Pleura (Mesothelioma)	Lung	15	14 (0.933)	11 (0.733)	0.918
LUNG_SC	Lung Squamous Cell Carcinoma	Lung/Squamous Cell Carcinoma	160	155 (0.969)	136 (0.85)	0.948
LYMPH	Lymph Nodes	None	6	6 (1.000)	6 (1.000)	0.987
NE_MED	Medullary Thyroid	Neuroendocrine	4	4 (1.000)	4 (1.000)	0.998
MEL	Melanoma	None	231	214 (0.926)	176 (0.762)	0.939
LMS	Non-Uterine Leiomyosarcoma	Soft Tissue	14	13 (0.929)	10 (0.714)	0.883
PANC	Pancreas	Pancreas	23	20 (0.870)	19 (0.826)	0.988

PANC3	Pancreas Group 3	Pancreas	3	3 (1.000)	3 (1.000)	0.970
NE_PANC	Pancreas Neuroendocrine	Neuroendocrine	11	11 (1.000)	10 (0.909)	0.978
AG_P	Pheochromocytoma	Adrenal Gland	35	35 (1.000)	32 (0.914)	0.979
PRST	Prostate	None	273	268 (0.982)	248 (0.908)	0.971
NE_PULM	Pulmonary Neuroendocrine	Neuroendocrine	4	4 (1.000)	3 (0.75)	0.854
RCTM	Rectum	Large Intestine	18	18 (1.000)	18 (1.000)	0.982
RTPT	Retroperitoneum	Soft Tissue	13	11 (0.846)	5 (0.385)	0.809
SEM	Seminoma	Testis	16	16 (1.000)	15 (0.938)	0.980
SMALL	Small Intestine	Upper Gastrointestinal	27	27 (1.000)	25 (0.926)	0.974
SOFT	Soft Tissue Main	Soft Tissue	17	16 (0.941)	11 (0.647)	0.830
STMCH	Stomach	Upper Gastrointestinal	48	47 (0.979)	40 (0.833)	0.938
TEST	Testis Non-Seminoma	Testis	17	17 (1.000)	14 (0.823)	0.937
THY_CHST	Thymus and Chest	None	29	28 (0.966)	24 (0.828)	0.944
THYC	Thyroid Carcinoma	Thyroid	207	205 (0.990)	196 (0.947)	0.985
THYFN	Thyroid Follicular Neoplasm	Thyroid	30	30 (1.000)	29 (0.967)	0.986
ULMS	Uterine Leiomyosarcoma	Gynecological	6	6 (1.000)	3 (0.5)	0.851

Table S3: Mutation differences among TUO classes.

Site	Classes in Comparison	Gene	Difference in Prevalence
Breast	BRST1 vs BRST2	TP53*	39%
		PIK3CA*	28%
Cervix	CVX_UT vs CVX_UT2	PIK3CA*	26%
		SYNE1*	16%
Esophagus	ESO_ADC vs ESO_SCC	SYNE1	25%
		TTN	23%
		MUC16	22%
Pancreas	PANC vs PANC3	TP53	39%
Gastrointestinal	SMALL vs STMCH	REV3L*	16%
		DNAH1*	13%
Testes	TEST vs SEM	KIT*	37%
		KRAS*	23%
		NRAS	10%
Thyroid	THYC vs THYFN	BRAF*	41%
		NRAS*	14%
Gynecological	CVX_UT vs CVX_UT2	PIK3CA	26%
	CVX_UT vs ENDO_ADC	PTEN*	56%
		CTTNB1*	32%
		ARID1A*	31%
	CVX_UT vs ENDO_SCA	TP53*	58%
		PPP2R1A*	38%
	CVX_UT2 vs ENDO_ADC	PTEN	43%
		ARID1A	34%
		CTTNB1	32%
	CVX_UT2 vs ENDO_SCA	TP53*	55%

		PPP2R1A	38%
		FBXW7	30%
	ENDO_ADC vs ENDO_SCA	PTEN	53%
		TP53	40%
		CTNNB1	32%
Kidney	KCCA1 vs KCCA2	TVP23C*	13%
		TTN	16%
	KCCA1 vs KPPA	VHL*	28%
		PBRM1*	20%
		MUC2*	17%
		TVP23C*	10%
		MTOR*	9%
	KCCA1 vs KRCCC	MUC4*	33%
		TP53*	31%
		MUC6*	29%
		VHL*	28%
		MUC2*	25%
		PBRM1*	21%
		TTN*	15%
		CDC27*	12%
		FRG1*	12%
		HLA-C*	11%
		MUC21*	10%
		RBMXL1*	10%
		TAS2R43*	10%
		CCDC144NL*	8%
		DSPP*	8%
		PCDHA8*	8%

	KCCA2 vs KPPA	PRSS3*	8%
		PBRM1*	24%
		VHL*	18%
	KCCA2 vs KRCCC	MUC6*	32%
		TP53*	31%
		MUC4*	27%
		PBRM1*	25%
		VHL*	18%
		TVP23C*	13%
	KPPA vs KRCCC	MUC4*	33%
		TP53*	31%
		MUC6*	29%
		FRG1*	14%
		CDC27*	12%
		HLA-C*	11%
		TVP23C*	10%
		PABPC3*	10%
		CCDC144NL*	8%
		HLA-A*	8%
		MAGEC1*	8%
		PCDHA8*	8%
		SLC35G5	8%
		SLC35G6*	8%
Soft Tissue	SOFT vs RTPT	RYR2	11%
		LRP1B	9%
	SOFT vs LMS	RYR2	11%
		LRP1B	9%
	RTPT vs LMS	TP53*	34%

		RB1*	15%
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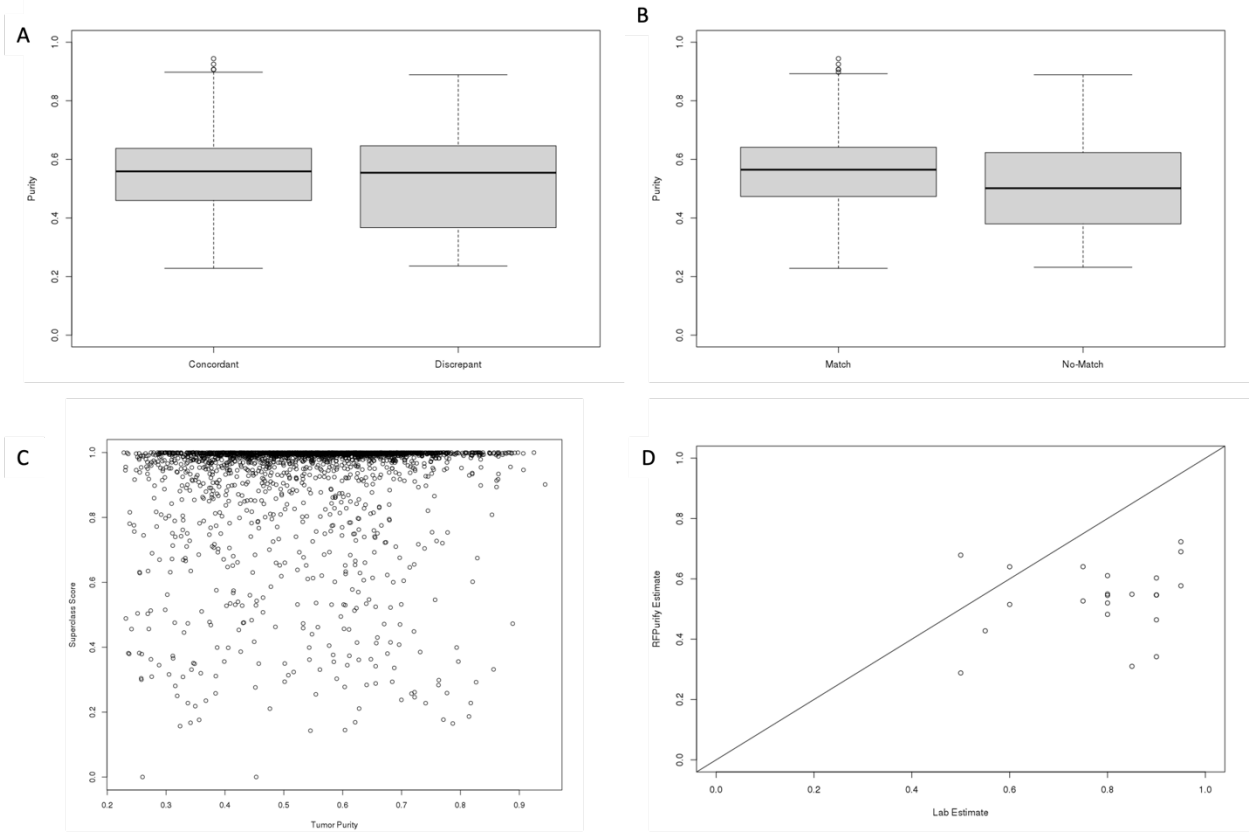


Figure S1: Effects of tumor purity on classifier performance. A. Purity of concordant versus discrepant samples. B. Purity of matching (score ≥ 0.9) versus non-matching samples. C. Purity versus superclass score. D. Comparison of internal sample purity estimated in the laboratory versus estimated computationally with RFPurify.

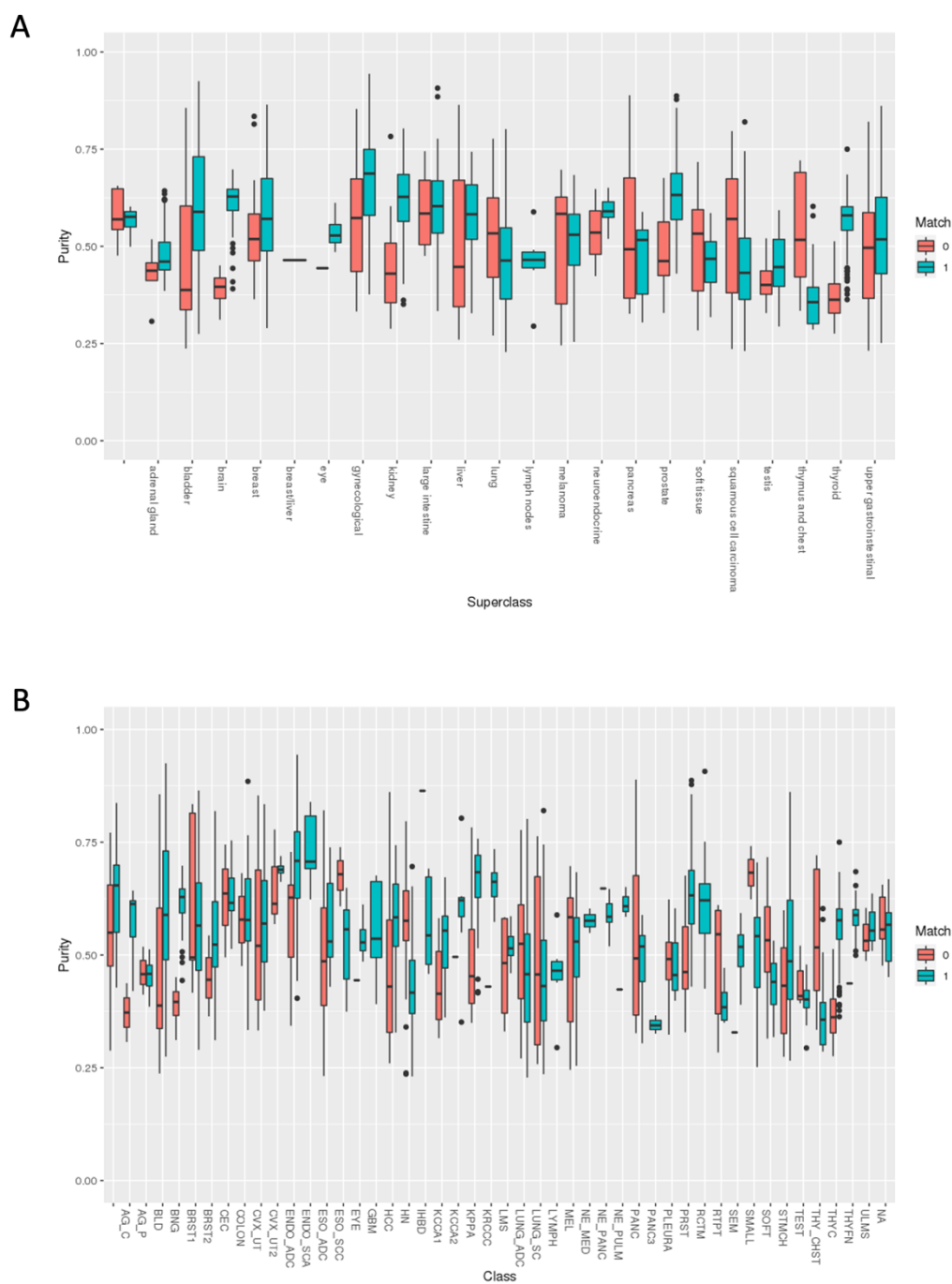


Figure S2: Tumor purity by superclass (A) and class (B). Green bars represent concordant samples with matching scores (≥ 0.9) while red bars represent discrepant samples and concordant samples with non-matching scores.

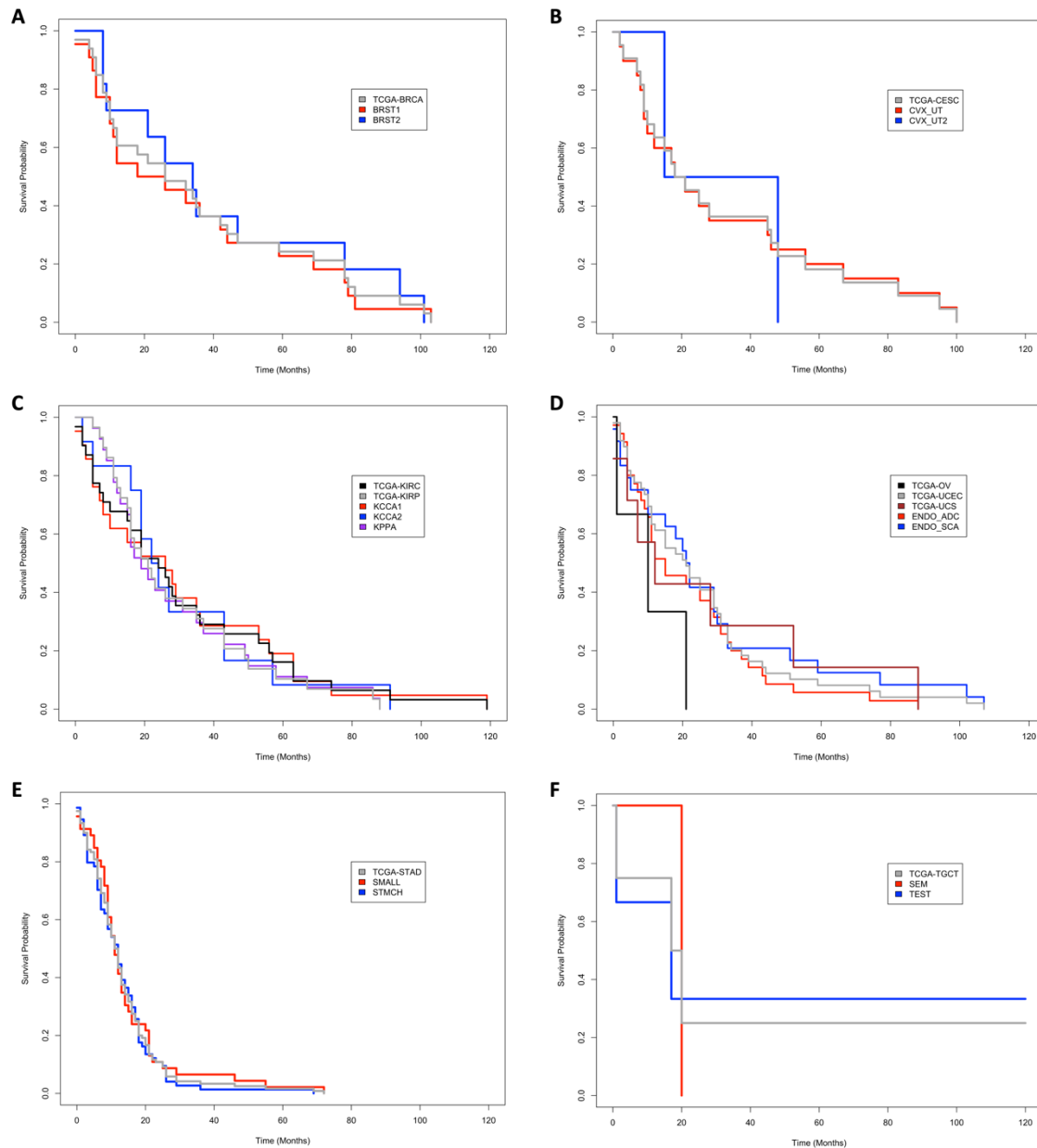


Figure S3: Overall survival of selected TUC classes. (A) Splitting TCGA project Breast Invasive Carcinoma (BRCA) into classes Breast group 1 (BRST1) and Breast group 2 (BRST2). (B) Splitting TCGA project Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma (CESC) into classes Cervix uteri (CVX_UT) and Cervix uteri group 2 (CVX_UT2). (C) Splitting TCGA projects Kidney Renal Clear Cell Carcinoma (KIRC) and Kidney Renal Papillary Cell Carcinoma (KIRP) into classes Kidney clear cell adenocarcinoma and renal cell carcinoma group 1 (KCCA1), Kidney clear cell and papillary carcinoma group 2 (KCCA2) and Kidney papillary adenocarcinoma (KPPA). (D) Splitting TCGA projects Ovarian Serous Cystadenocarcinoma (OV), Uterine Corpus Endometrial Carcinoma (UCEC), and Uterine Carcinosarcoma (UCS) into classes Endometrioid adenocarcinoma (ENDO_ADC) and Endo-ovarian serous

classes in the Kidney superclass: Kidney clear cell adenocarcinoma and renal cell carcinoma group 1 (KCCA1), Kidney clear cell and papillary adenocarcinoma group 2 (KCCA2), Kidney papillary adenocarcinoma (KPPA), and Kidney renal cell carcinoma chromophobe type (KRCCC). (D) Pancreas (PANC) compared to Pancreas group 3 (PANC3). (E) Comparisons among classes in the Soft Tissue superclass: Leiomyosarcoma (LMS), Retroperitoneum (RTPT), and Soft tissue main (SOFT). (F) Small intestine (SMALL) compared to Stomach (STMCH).