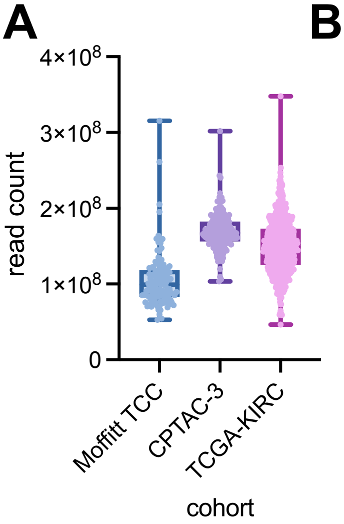
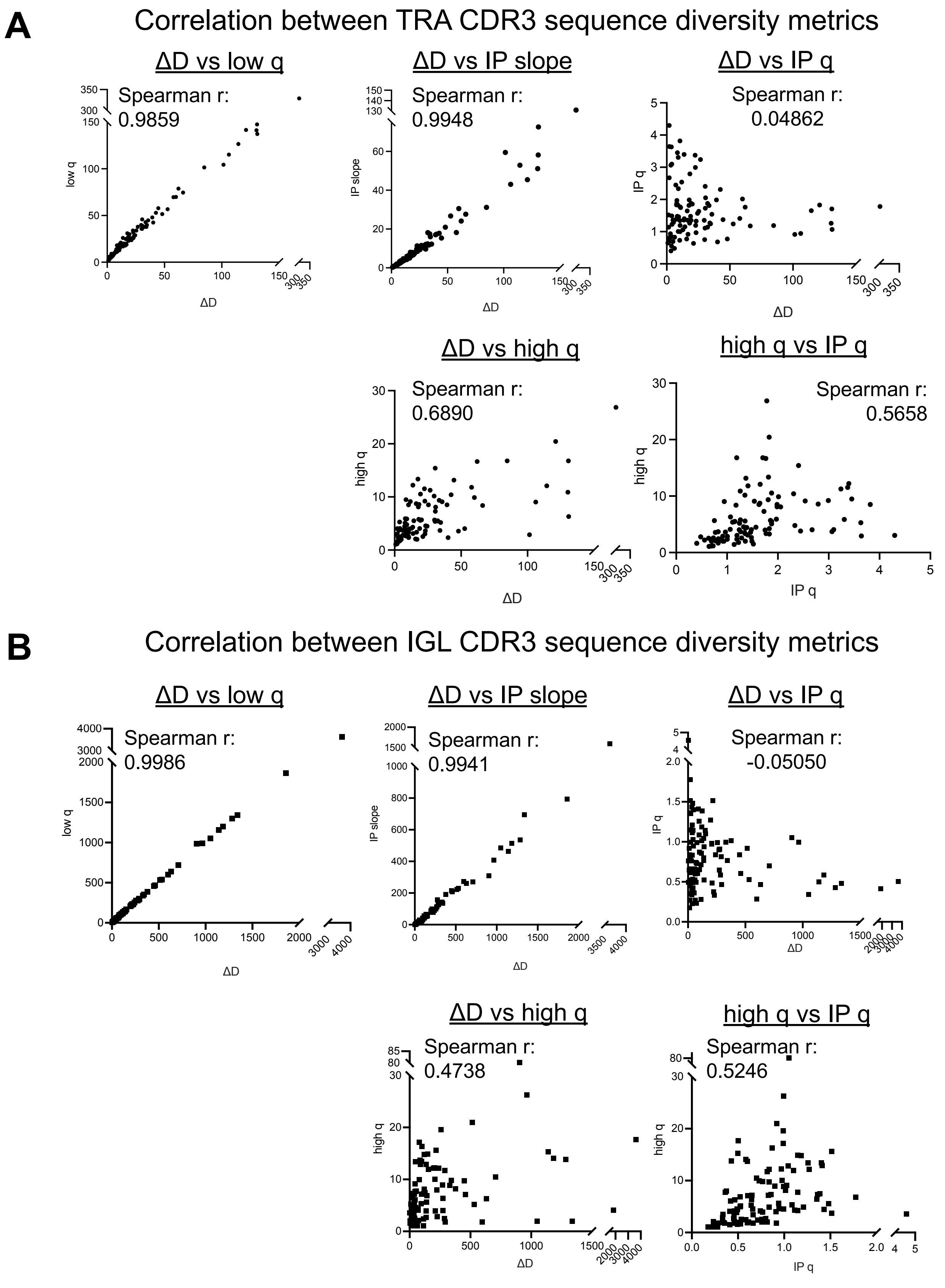


B

READ COUNT PER PATIENT SUMMARY

	Moffitt TCC	CPTAC-3	TCGA-KIRC
Minimum	52,681,974	103,511,778	46,385,620
Median	99,130,487	167,532,845	149,172,293
Mean	105,428,221	169,287,091	149,988,431
Maximum	315,438,680	301,887,952	347,818,908

Supplementary Figure S1: Distributions of read counts per sample across all three cohorts. (A) Distribution of individual reads counts per patient across the Moffitt TCC Cohort, CPTAC-3 Cohort, and the TCGA-KIRC Cohort. (B) Summary table of the minimum, median, mean, and maximum number of read counts across all three cohorts.

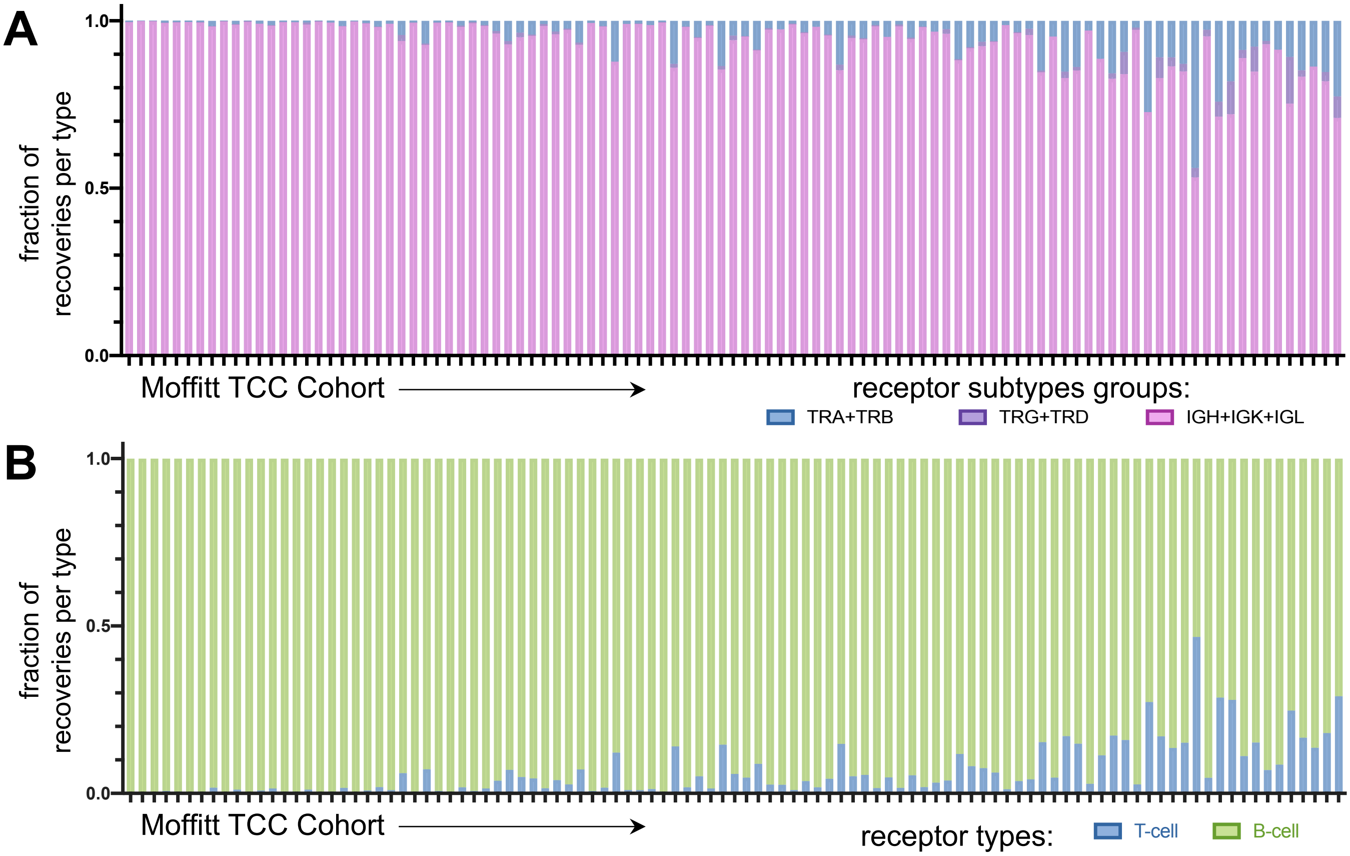


A Correlation between TRA CDR3 sequence diversity metrics

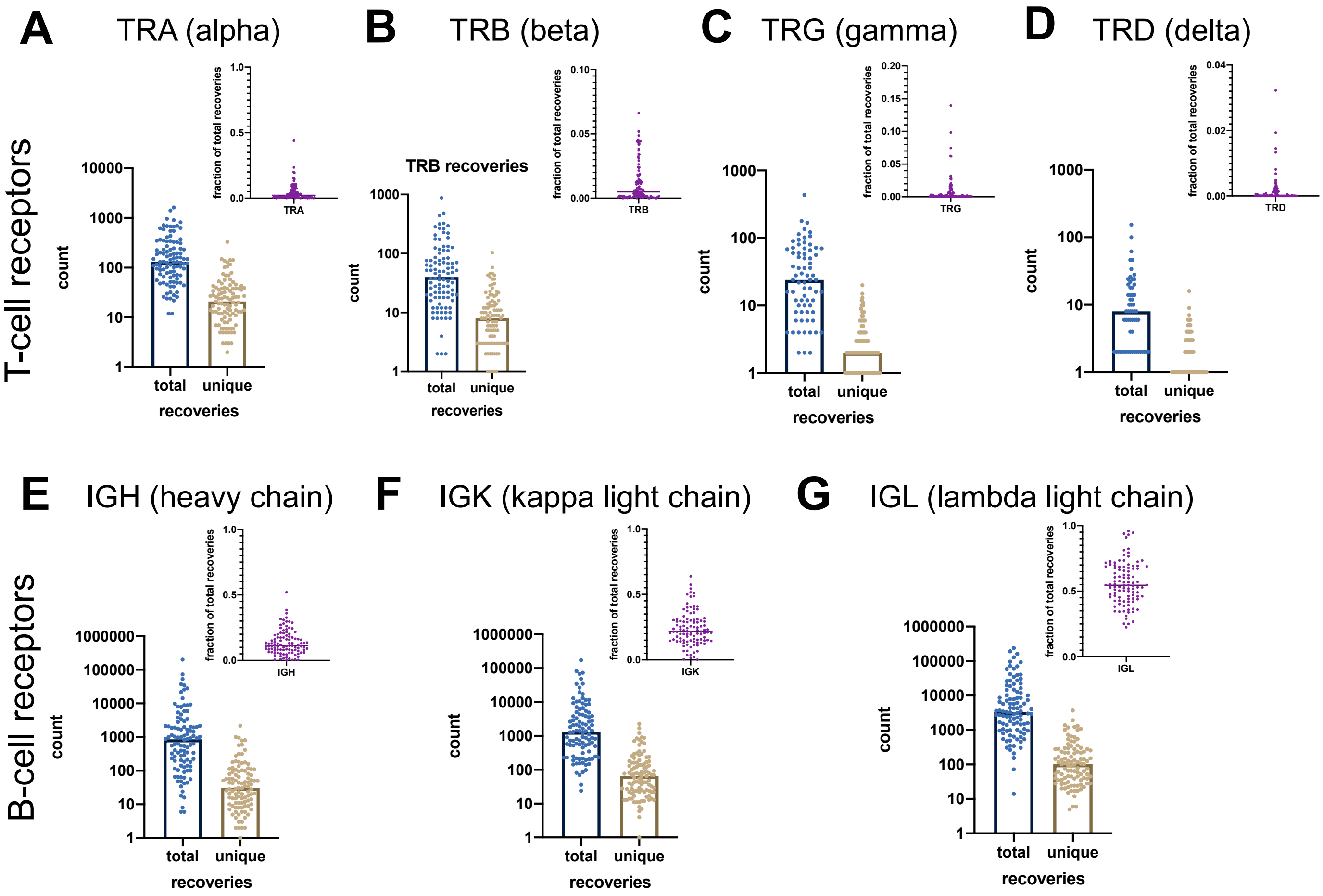
B Correlation between IGL CDR3 sequence diversity metrics

Supplementary Figure S2: Correlation analysis showing the low q, ΔD, and inflection point slope diversity metrics are highly correlated and give the same information. Correlations were assessed using a Spearman correlation coefficient (r) across all samples in the cohort segregated by receptor type, highlighting TRA & IGL CDR3 sequence diversities here.

MOFFITT TCC COHORT RECOVERY LANDSCAPE

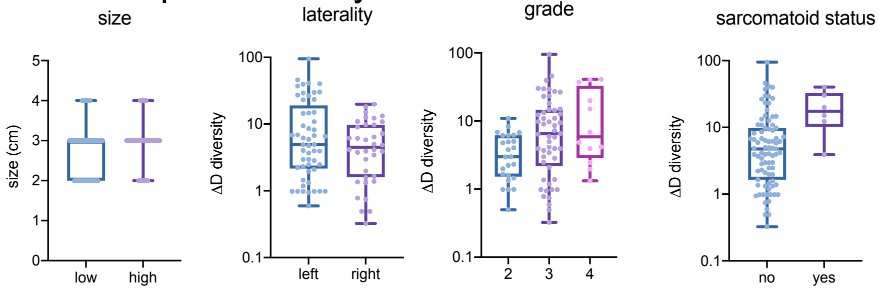


Supplemental Figure S3: Tumor infiltrating lymphocyte receptor recovery landscape the Moffitt TCC Cohort of clear cell renal cell carcinoma. Patient tumors undergo bulk RNA sequencing and then CDR3 sequences from TCR and BCR receptors were recovered. Then for each patient, CDR3s are segregated by receptor class. **Fig. 1B** shows total recoveries per patient was reported in a bar plot with each bar reflecting the total number of recoveries from each patient and the proportion of each recovery type per patient was reported for individual T-cell and B-cell receptor types. The proportion of each recovery type per patient grouped by common receptor combinations (C) and per cell type combinations (D) are reflected in the bar charts above.



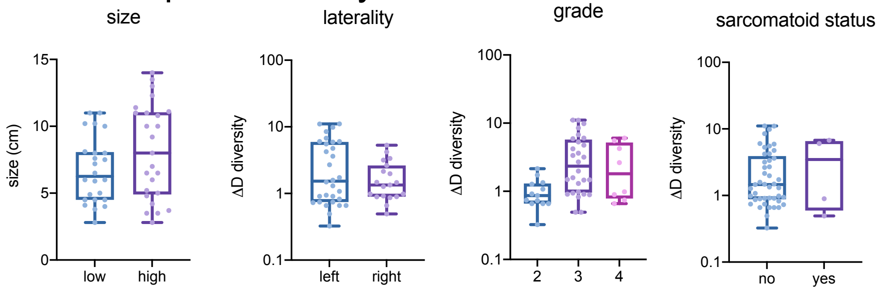
Supplemental Figure S4: Recovery counts per patient across all seven tumor-infiltrating lymphocyte receptor subtypes in the Moffitt TCC Cohort of clear cell renal cell carcinoma patients. Patient tumors undergo bulk RNA sequencing and then CDR3 sequences from TCR and BCR receptors were recovered. Then for each patient, CDR3 sequences were segregated by receptor class. Total and unique recovery counts per patient as well as the fraction of those recoveries out of all recoveries for each patient were reported for T-cell receptors (TR) type (A) alpha, (B) beta, (C) gamma, and (D), delta, as well as B-cell receptors immunoglobulin (IG) type (E) heavy chain, (F) kappa light chain, and (G) lambda light chain.

A TRB receptor diversity



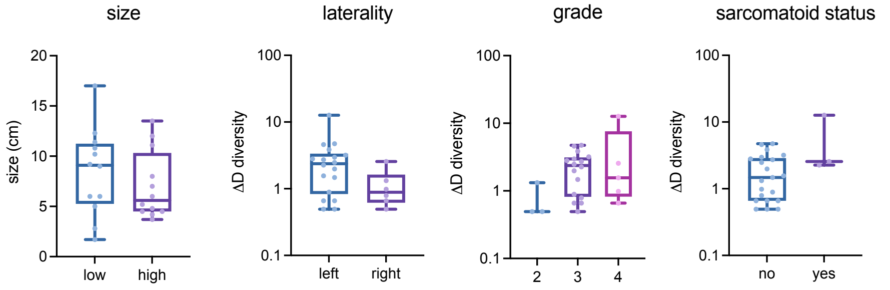
	p-value
Size	0.2324
Laterality	0.0307 *
Grade	0.0243 *
Sarcomatoid status	0.0649

B TRG receptor diversity



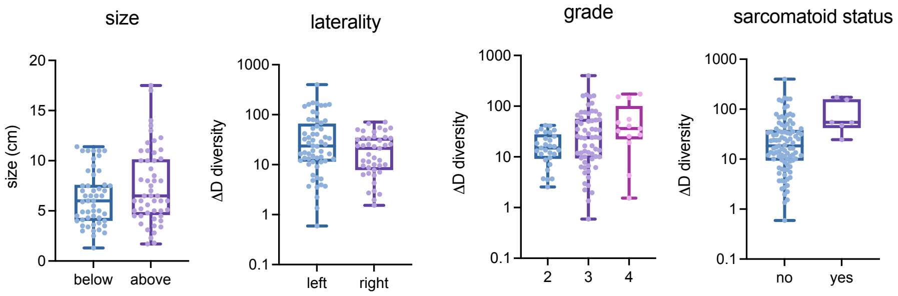
	p-value
Size	0.1072
Laterality	0.0628
Grade	0.0191 *
Sarcomatoid status	0.5857

C TRD receptor diversity



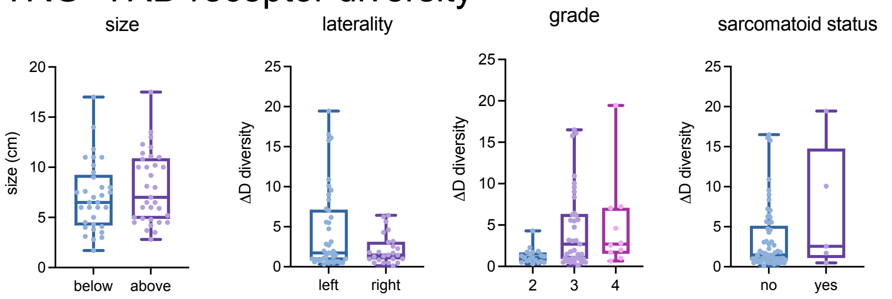
	p-value
Size	0.3847
Laterality	0.1681
Grade	0.2928
Sarcomatoid status	0.0088 **

D TRA+TRB receptor diversity



	p-value
Size	0.0615
Laterality	0.0139 *
Grade	0.0329 *
Sarcomatoid status	0.0324 *

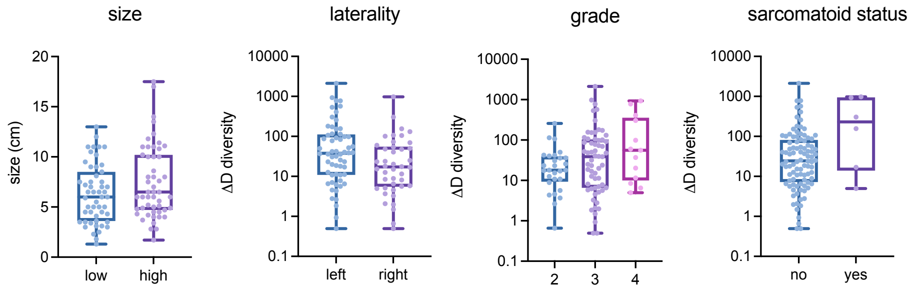
E TRG+TRD receptor diversity



	p-value
Size	0.3052
Laterality	0.0393 *
Grade	0.0172 *
Sarcomatoid status	0.0847

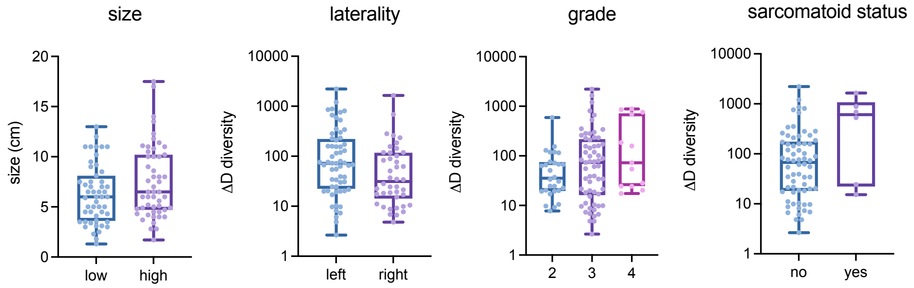
Supplementary Figure S5. (continued on next page)

F IGH receptor diversity



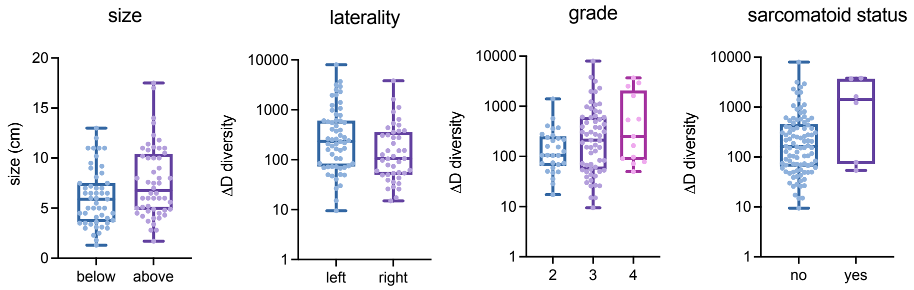
	p-value
Size	0.0839
Laterality	0.1088
Grade	0.1272
Sarcomatoid status	0.0080 **

G IGK receptor diversity



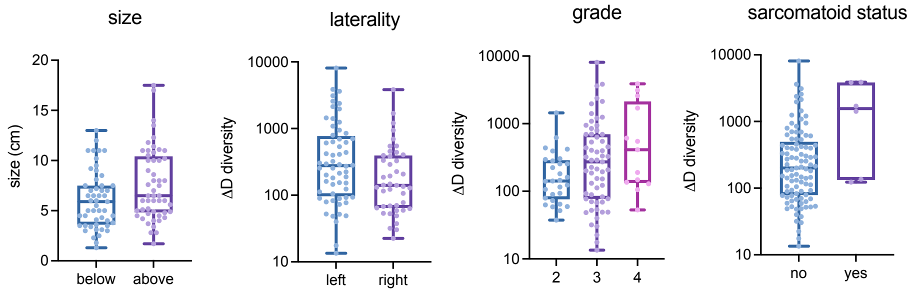
	p-value
Size	0.0602
Laterality	0.1392
Grade	0.1056
Sarcomatoid status	0.0053 **

H IGH+IGK+IGL receptor diversity



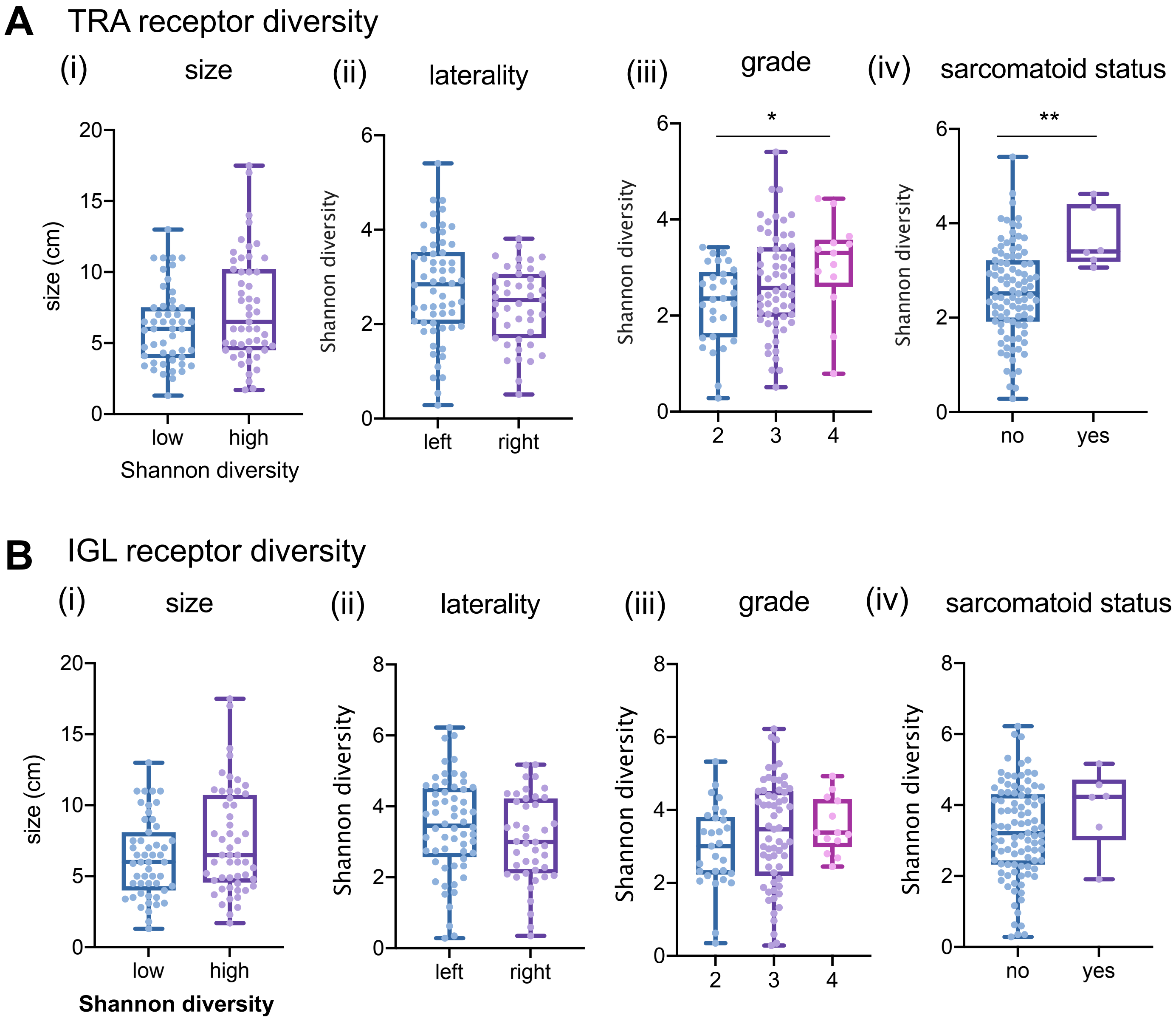
	p-value
Size	0.0165 *
Laterality	0.0708
Grade	0.0684
Sarcomatoid status	0.0042 **

I TRs+IGs receptor diversity

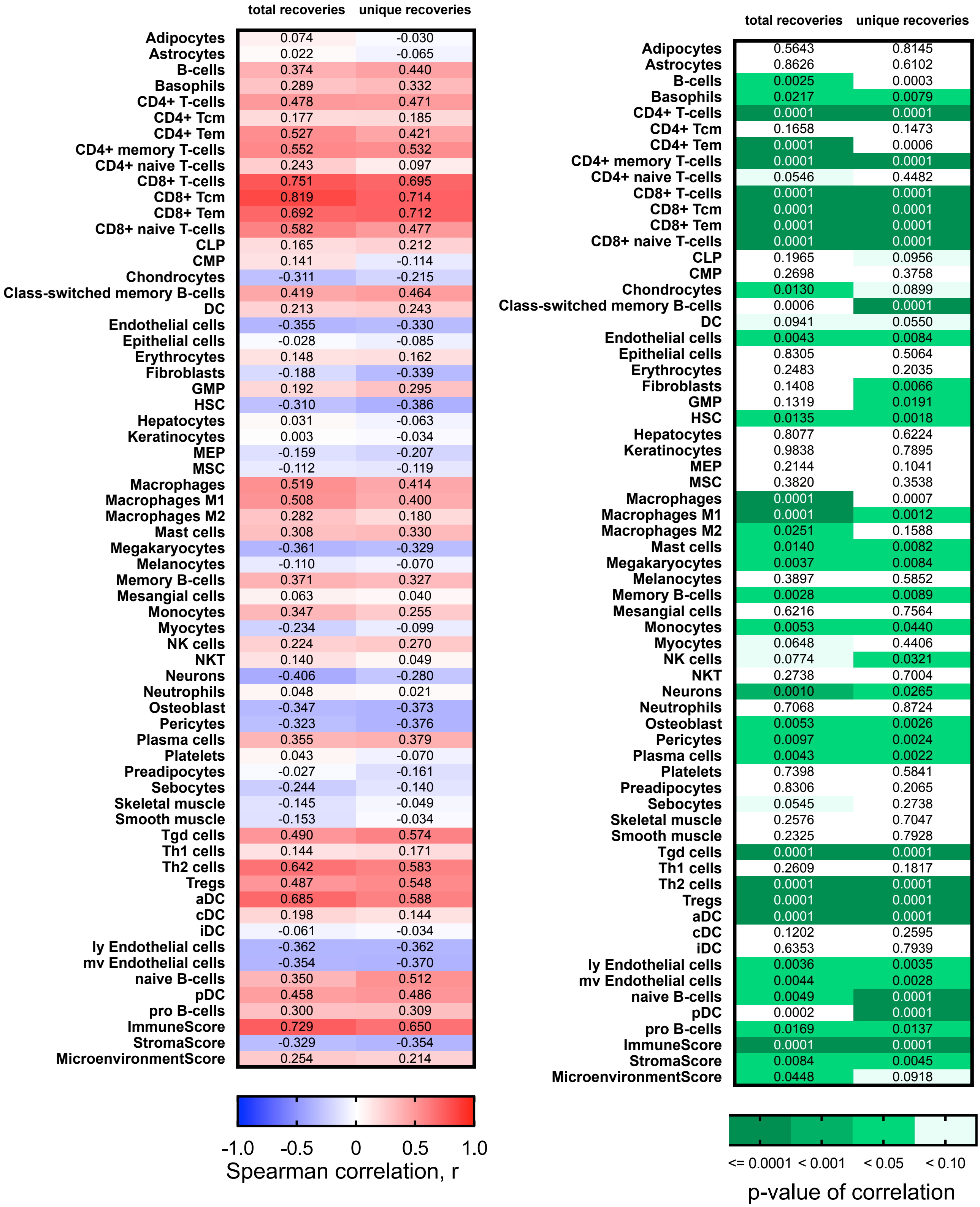


	p-value
Size	0.0195 *
Laterality	0.0584
Grade	0.0574
Sarcomatoid status	0.0036 **

Supplementary Figure S5. Species richness associated with larger and worse tumors across other receptor combinations. Receptor diversity with respect to largest diameter (size, cm), laterality, grade, and sarcomatoid status for (A) TRB recoveries, (B) TRG recoveries, (C) TRD recoveries, (D) TRA and TRB recoveries, (E) TRG and TRD recoveries, (F) IGH recoveries, (G) IGK recoveries, (H) IGH, IGK, IGL (or B-cell) recoveries, and (I) total (TRs+IGs) recoveries. Similar plots for TRA recoveries and IGL recoveries are in Fig 2. p-value significance represented by * < 0.05, ** < 0.01, *** < 0.001



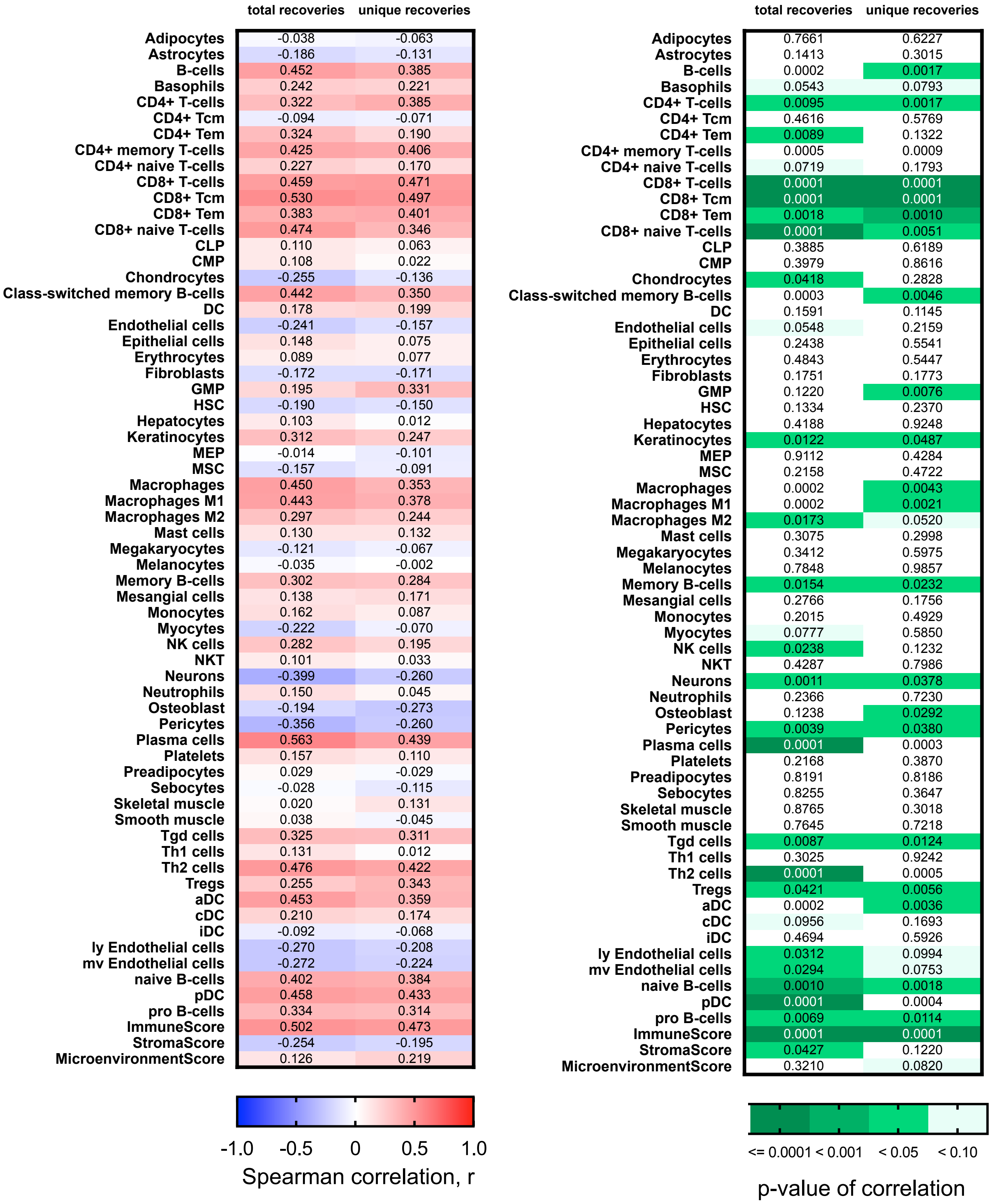
Supplemental Figure S6: Shannon diversity does not capture the same clinical information in TRA and IGL receptors. (A) TRA receptor CDR3 sequence Shannon diversity across the Moffitt TCC Cohort trends in (i) largest diameter tumors (low diversity had mean diameter of 6.2 cm and high diversity had a mean diameter for 7.5 cm; p-value: 0.0506), (ii) tumor laterality (score of 2.762 on left vs 2.401 on right; p-value: 0.0729), (iii) grade (mean score from grade 2 was 2.262, mean score from grade 3 was 2.682, and mean score from grade 4 was 3.049; p-value: 0.0414), and (v) sarcomatoid status (no mean score of 2.541 vs yes mean score of 3.675; p-value 0.0065). (B) IGL receptor CDR3 sequence Shannon diversity no significant trends for (i) size (low diversity had mean diameter of 6.3 cm and high diversity had a mean diameter for 7.5 cm; p-value: 0.0676), (ii) laterality (score of 3.436 vs 3.063; p-value: 0.1548), (iii) grade (mean score from grade 2 was 2.979, mean score from grade 3 was 3.363, and mean score from grade 4 was 3.564; p-value: 0.3060), and (iv) sarcomatoid status (no had a mean score of 3.241 vs yes with a mean score of 3.917; p-value: 0.2216). Unpaired t-tests were used to compare two group data and ANOVA was used to compare grade, three group data. p-value significance represented by * < 0.05, ** < 0.01, *** < 0.001



	total recoveries	unique recoveries
Adipocytes	0.074	-0.030
Astrocytes	0.022	-0.065
B-cells	0.374	0.440
Basophils	0.289	0.332
CD4+ T-cells	0.478	0.471
CD4+ Tcm	0.177	0.185
CD4+ Tem	0.527	0.421
CD4+ memory T-cells	0.552	0.532
CD4+ naive T-cells	0.243	0.097
CD8+ T-cells	0.751	0.695
CD8+ Tcm	0.819	0.714
CD8+ Tem	0.692	0.712
CD8+ naive T-cells	0.582	0.477
CLP	0.165	0.212
CMP	0.141	-0.114
Chondrocytes	-0.311	-0.215
Class-switched memory B-cells	0.419	0.464
DC	0.213	0.243
Endothelial cells	-0.355	-0.330
Epithelial cells	-0.028	-0.085
Erythrocytes	0.148	0.162
Fibroblasts	-0.188	-0.339
GMP	0.192	0.295
HSC	-0.310	-0.386
Hepatocytes	0.031	-0.063
Keratinocytes	0.003	-0.034
MEP	-0.159	-0.207
MSC	-0.112	-0.119
Macrophages	0.519	0.414
Macrophages M1	0.508	0.400
Macrophages M2	0.282	0.180
Mast cells	0.308	0.330
Megakaryocytes	-0.361	-0.329
Melanocytes	-0.110	-0.070
Memory B-cells	0.371	0.327
Mesangial cells	0.063	0.040
Monocytes	0.347	0.255
Myocytes	-0.234	-0.099
NK cells	0.224	0.270
NKT	0.140	0.049
Neurons	-0.406	-0.280
Neutrophils	0.048	0.021
Osteoblast	-0.347	-0.373
Pericytes	-0.323	-0.376
Plasma cells	0.355	0.379
Platelets	0.043	-0.070
Preadipocytes	-0.027	-0.161
Sebocytes	-0.244	-0.140
Skeletal muscle	-0.145	-0.049
Smooth muscle	-0.153	-0.034
Tgd cells	0.490	0.574
Th1 cells	0.144	0.171
Th2 cells	0.642	0.583
Tregs	0.487	0.548
aDC	0.685	0.588
cDC	0.198	0.144
iDC	-0.061	-0.034
ly Endothelial cells	-0.362	-0.362
mv Endothelial cells	-0.354	-0.370
naive B-cells	0.350	0.512
pDC	0.458	0.486
pro B-cells	0.300	0.309
ImmuneScore	0.729	0.650
StromaScore	-0.329	-0.354
MicroenvironmentScore	0.254	0.214

	total recoveries	unique recoveries
Adipocytes	0.5643	0.8145
Astrocytes	0.8626	0.6102
B-cells	0.0025	0.0003
Basophils	0.0217	0.0079
CD4+ T-cells	0.0001	0.0001
CD4+ Tcm	0.1658	0.1473
CD4+ Tem	0.0001	0.0006
CD4+ memory T-cells	0.0001	0.0001
CD4+ naive T-cells	0.0546	0.4482
CD8+ T-cells	0.0001	0.0001
CD8+ Tcm	0.0001	0.0001
CD8+ Tem	0.0001	0.0001
CD8+ naive T-cells	0.0001	0.0001
CLP	0.1965	0.0956
CMP	0.2698	0.3758
Chondrocytes	0.0130	0.0899
Class-switched memory B-cells	0.0006	0.0001
DC	0.0941	0.0550
Endothelial cells	0.0043	0.0084
Epithelial cells	0.8305	0.5064
Erythrocytes	0.2483	0.2035
Fibroblasts	0.1408	0.0066
GMP	0.1319	0.0191
HSC	0.0135	0.0018
Hepatocytes	0.8077	0.6224
Keratinocytes	0.9838	0.7895
MEP	0.2144	0.1041
MSC	0.3820	0.3538
Macrophages	0.0001	0.0007
Macrophages M1	0.0001	0.0012
Macrophages M2	0.0251	0.1588
Mast cells	0.0140	0.0082
Megakaryocytes	0.0037	0.0084
Melanocytes	0.3897	0.5852
Memory B-cells	0.0028	0.0089
Mesangial cells	0.6216	0.7564
Monocytes	0.0053	0.0440
Myocytes	0.0648	0.4406
NK cells	0.0774	0.0321
NKT	0.2738	0.7004
Neurons	0.0010	0.0265
Neutrophils	0.7068	0.8724
Osteoblast	0.0053	0.0026
Pericytes	0.0097	0.0024
Plasma cells	0.0043	0.0022
Platelets	0.7398	0.5841
Preadipocytes	0.8306	0.2065
Sebocytes	0.0545	0.2738
Skeletal muscle	0.2576	0.7047
Smooth muscle	0.2325	0.7928
Tgd cells	0.0001	0.0001
Th1 cells	0.2609	0.1817
Th2 cells	0.0001	0.0001
Tregs	0.0001	0.0001
aDC	0.0001	0.0001
cDC	0.1202	0.2595
iDC	0.6353	0.7939
ly Endothelial cells	0.0036	0.0035
mv Endothelial cells	0.0044	0.0028
naive B-cells	0.0049	0.0001
pDC	0.0002	0.0001
pro B-cells	0.0169	0.0137
ImmuneScore	0.0001	0.0001
StromaScore	0.0084	0.0045
MicroenvironmentScore	0.0448	0.0918

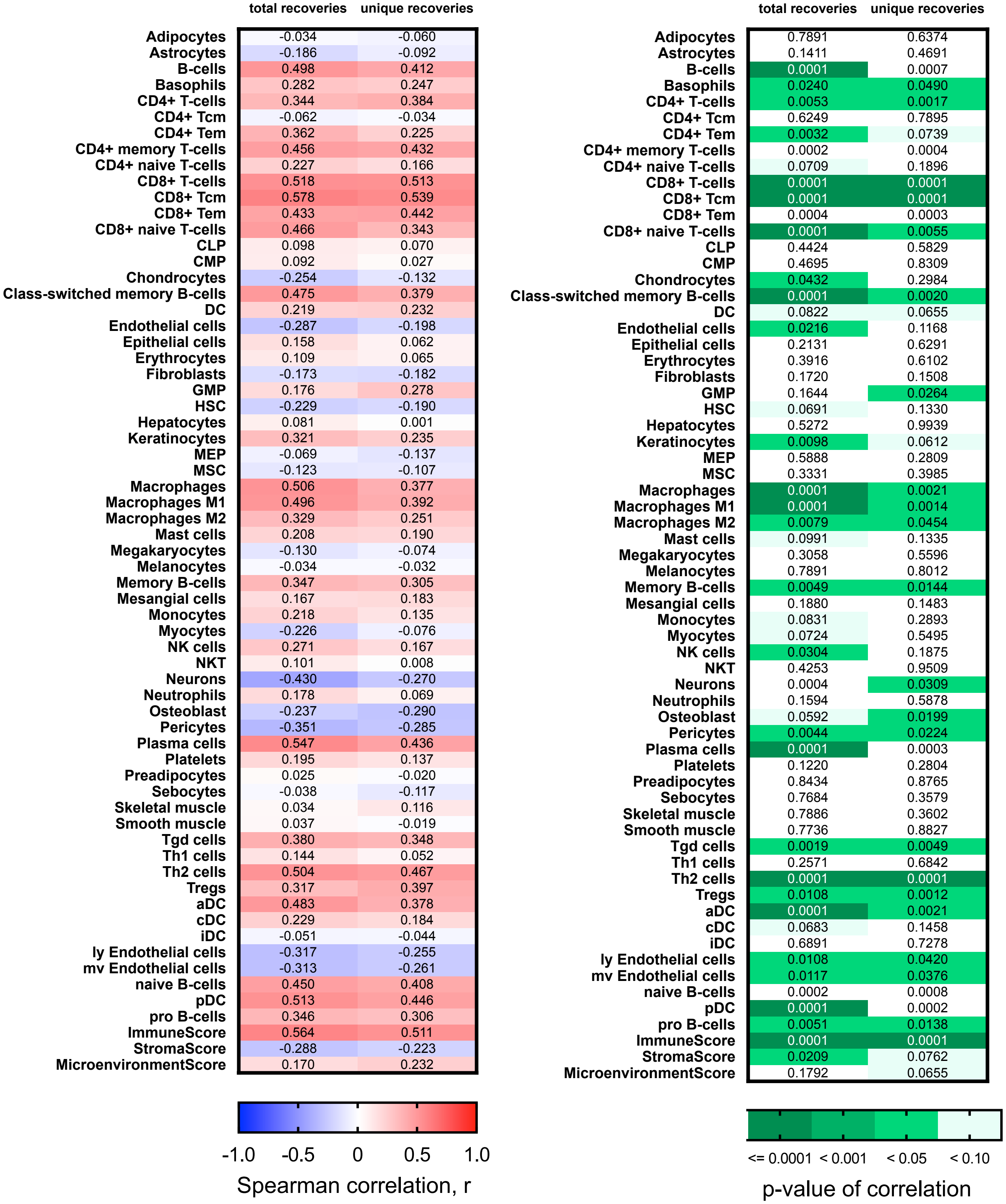
Supplemental Figure S7: TRA receptor full xCELL score Spearman correlation heatmaps and associated p-values.



	total recoveries	unique recoveries
Adipocytes	-0.038	-0.063
Astrocytes	-0.186	-0.131
B-cells	0.452	0.385
Basophils	0.242	0.221
CD4+ T-cells	0.322	0.385
CD4+ Tcm	-0.094	-0.071
CD4+ Tem	0.324	0.190
CD4+ memory T-cells	0.425	0.406
CD4+ naive T-cells	0.227	0.170
CD8+ T-cells	0.459	0.471
CD8+ Tcm	0.530	0.497
CD8+ Tem	0.383	0.401
CD8+ naive T-cells	0.474	0.346
CLP	0.110	0.063
CMP	0.108	0.022
Chondrocytes	-0.255	-0.136
Class-switched memory B-cells	0.442	0.350
DC	0.178	0.199
Endothelial cells	-0.241	-0.157
Epithelial cells	0.148	0.075
Erythrocytes	0.089	0.077
Fibroblasts	-0.172	-0.171
GMP	0.195	0.331
HSC	-0.190	-0.150
Hepatocytes	0.103	0.012
Keratinocytes	0.312	0.247
MEP	-0.014	-0.101
MSC	-0.157	-0.091
Macrophages	0.450	0.353
Macrophages M1	0.443	0.378
Macrophages M2	0.297	0.244
Mast cells	0.130	0.132
Megakaryocytes	-0.121	-0.067
Melanocytes	-0.035	-0.002
Memory B-cells	0.302	0.284
Mesangial cells	0.138	0.171
Monocytes	0.162	0.087
Myocytes	-0.222	-0.070
NK cells	0.282	0.195
NKT	0.101	0.033
Neurons	-0.399	-0.260
Neutrophils	0.150	0.045
Osteoblast	-0.194	-0.273
Pericytes	-0.356	-0.260
Plasma cells	0.563	0.439
Platelets	0.157	0.110
Preadipocytes	0.029	-0.029
Sebocytes	-0.028	-0.115
Skeletal muscle	0.020	0.131
Smooth muscle	0.038	-0.045
Tgd cells	0.325	0.311
Th1 cells	0.131	0.012
Th2 cells	0.476	0.422
Tregs	0.255	0.343
aDC	0.453	0.359
cDC	0.210	0.174
iDC	-0.092	-0.068
ly Endothelial cells	-0.270	-0.208
mv Endothelial cells	-0.272	-0.224
naive B-cells	0.402	0.384
pDC	0.458	0.433
pro B-cells	0.334	0.314
ImmuneScore	0.502	0.473
StromaScore	-0.254	-0.195
MicroenvironmentScore	0.126	0.219

	total recoveries	unique recoveries
Adipocytes	0.7661	0.6227
Astrocytes	0.1413	0.3015
B-cells	0.0002	0.0017
Basophils	0.0543	0.0793
CD4+ T-cells	0.0095	0.0017
CD4+ Tcm	0.4616	0.5769
CD4+ Tem	0.0089	0.1322
CD4+ memory T-cells	0.0005	0.0009
CD4+ naive T-cells	0.0719	0.1793
CD8+ T-cells	0.0001	0.0001
CD8+ Tcm	0.0001	0.0001
CD8+ Tem	0.0018	0.0010
CD8+ naive T-cells	0.0001	0.0051
CLP	0.3885	0.6189
CMP	0.3979	0.8616
Chondrocytes	0.0418	0.2828
Class-switched memory B-cells	0.0003	0.0046
DC	0.1591	0.1145
Endothelial cells	0.0548	0.2159
Epithelial cells	0.2438	0.5541
Erythrocytes	0.4843	0.5447
Fibroblasts	0.1751	0.1773
GMP	0.1220	0.0076
HSC	0.1334	0.2370
Hepatocytes	0.4188	0.9248
Keratinocytes	0.0122	0.0487
MEP	0.9112	0.4284
MSC	0.2158	0.4722
Macrophages	0.0002	0.0043
Macrophages M1	0.0002	0.0021
Macrophages M2	0.0173	0.0520
Mast cells	0.3075	0.2998
Megakaryocytes	0.3412	0.5975
Melanocytes	0.7848	0.9857
Memory B-cells	0.0154	0.0232
Mesangial cells	0.2766	0.1756
Monocytes	0.2015	0.4929
Myocytes	0.0777	0.5850
NK cells	0.0238	0.1232
NKT	0.4287	0.7986
Neurons	0.0011	0.0378
Neutrophils	0.2366	0.7230
Osteoblast	0.1238	0.0292
Pericytes	0.0039	0.0380
Plasma cells	0.0001	0.0003
Platelets	0.2168	0.3870
Preadipocytes	0.8191	0.8186
Sebocytes	0.8255	0.3647
Skeletal muscle	0.8765	0.3018
Smooth muscle	0.7645	0.7218
Tgd cells	0.0087	0.0124
Th1 cells	0.3025	0.9242
Th2 cells	0.0001	0.0005
Tregs	0.0421	0.0056
aDC	0.0002	0.0036
cDC	0.0956	0.1693
iDC	0.4694	0.5926
ly Endothelial cells	0.0312	0.0994
mv Endothelial cells	0.0294	0.0753
naive B-cells	0.0010	0.0018
pDC	0.0001	0.0004
pro B-cells	0.0069	0.0114
ImmuneScore	0.0001	0.0001
StromaScore	0.0427	0.1220
MicroenvironmentScore	0.3210	0.0820

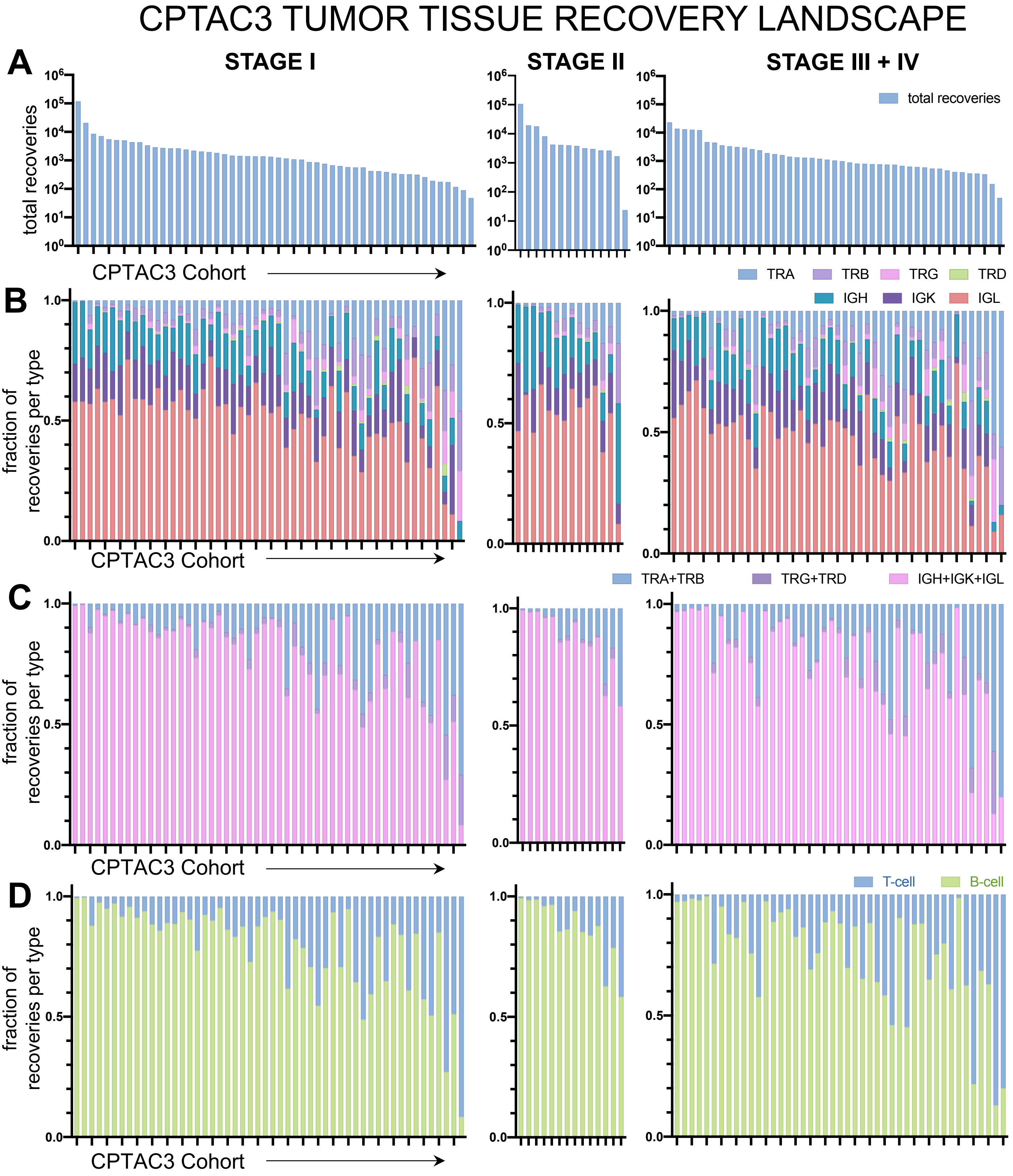
Supplemental Figure S8: IGL receptor full xCELL score Spearman correlation heatmaps and associated p-values.



	total recoveries	unique recoveries
Adipocytes	-0.034	-0.060
Astrocytes	-0.186	-0.092
B-cells	0.498	0.412
Basophils	0.282	0.247
CD4+ T-cells	0.344	0.384
CD4+ Tcm	-0.062	-0.034
CD4+ Tem	0.362	0.225
CD4+ memory T-cells	0.456	0.432
CD4+ naive T-cells	0.227	0.166
CD8+ T-cells	0.518	0.513
CD8+ Tcm	0.578	0.539
CD8+ Tem	0.433	0.442
CD8+ naive T-cells	0.466	0.343
CLP	0.098	0.070
CMP	0.092	0.027
Chondrocytes	-0.254	-0.132
Class-switched memory B-cells	0.475	0.379
DC	0.219	0.232
Endothelial cells	-0.287	-0.198
Epithelial cells	0.158	0.062
Erythrocytes	0.109	0.065
Fibroblasts	-0.173	-0.182
GMP	0.176	0.278
HSC	-0.229	-0.190
Hepatocytes	0.081	0.001
Keratinocytes	0.321	0.235
MEP	-0.069	-0.137
MSC	-0.123	-0.107
Macrophages	0.506	0.377
Macrophages M1	0.496	0.392
Macrophages M2	0.329	0.251
Mast cells	0.208	0.190
Megakaryocytes	-0.130	-0.074
Melanocytes	-0.034	-0.032
Memory B-cells	0.347	0.305
Mesangial cells	0.167	0.183
Monocytes	0.218	0.135
Myocytes	-0.226	-0.076
NK cells	0.271	0.167
NKT	0.101	0.008
Neurons	-0.430	-0.270
Neutrophils	0.178	0.069
Osteoblast	-0.237	-0.290
Pericytes	-0.351	-0.285
Plasma cells	0.547	0.436
Platelets	0.195	0.137
Preadipocytes	0.025	-0.020
Sebocytes	-0.038	-0.117
Skeletal muscle	0.034	0.116
Smooth muscle	0.037	-0.019
Tgd cells	0.380	0.348
Th1 cells	0.144	0.052
Th2 cells	0.504	0.467
Tregs	0.317	0.397
aDC	0.483	0.378
cDC	0.229	0.184
iDC	-0.051	-0.044
ly Endothelial cells	-0.317	-0.255
mv Endothelial cells	-0.313	-0.261
naive B-cells	0.450	0.408
pDC	0.513	0.446
pro B-cells	0.346	0.306
ImmuneScore	0.564	0.511
StromaScore	-0.288	-0.223
MicroenvironmentScore	0.170	0.232

	total recoveries	unique recoveries
Adipocytes	0.7891	0.6374
Astrocytes	0.1411	0.4691
B-cells	0.0001	0.0007
Basophils	0.0240	0.0490
CD4+ T-cells	0.0053	0.0017
CD4+ Tcm	0.6249	0.7895
CD4+ Tem	0.0032	0.0739
CD4+ memory T-cells	0.0002	0.0004
CD4+ naive T-cells	0.0709	0.1896
CD8+ T-cells	0.0001	0.0001
CD8+ Tcm	0.0001	0.0001
CD8+ Tem	0.0004	0.0003
CD8+ naive T-cells	0.0001	0.0055
CLP	0.4424	0.5829
CMP	0.4695	0.8309
Chondrocytes	0.0432	0.2984
Class-switched memory B-cells	0.0001	0.0020
DC	0.0822	0.0655
Endothelial cells	0.0216	0.1168
Epithelial cells	0.2131	0.6291
Erythrocytes	0.3916	0.6102
Fibroblasts	0.1720	0.1508
GMP	0.1644	0.0264
HSC	0.0691	0.1330
Hepatocytes	0.5272	0.9939
Keratinocytes	0.0098	0.0612
MEP	0.5888	0.2809
MSC	0.3331	0.3985
Macrophages	0.0001	0.0021
Macrophages M1	0.0001	0.0014
Macrophages M2	0.0079	0.0454
Mast cells	0.0991	0.1335
Megakaryocytes	0.3058	0.5596
Melanocytes	0.7891	0.8012
Memory B-cells	0.0049	0.0144
Mesangial cells	0.1880	0.1483
Monocytes	0.0831	0.2893
Myocytes	0.0724	0.5495
NK cells	0.0304	0.1875
NKT	0.4253	0.9509
Neurons	0.0004	0.0309
Neutrophils	0.1594	0.5878
Osteoblast	0.0592	0.0199
Pericytes	0.0044	0.0224
Plasma cells	0.0001	0.0003
Platelets	0.1220	0.2804
Preadipocytes	0.8434	0.8765
Sebocytes	0.7684	0.3579
Skeletal muscle	0.7886	0.3602
Smooth muscle	0.7736	0.8827
Tgd cells	0.0019	0.0049
Th1 cells	0.2571	0.6842
Th2 cells	0.0001	0.0001
Tregs	0.0108	0.0012
aDC	0.0001	0.0021
cDC	0.0683	0.1458
iDC	0.6891	0.7278
ly Endothelial cells	0.0108	0.0420
mv Endothelial cells	0.0117	0.0376
naive B-cells	0.0002	0.0008
pDC	0.0001	0.0002
pro B-cells	0.0051	0.0138
ImmuneScore	0.0001	0.0001
StromaScore	0.0209	0.0762
MicroenvironmentScore	0.1792	0.0655

Supplemental Figure S9: TRs+IGs receptors full xCELL score Spearman correlation heatmaps and associated p-values.



Supplemental Figure S10: Tumor infiltrating lymphocyte receptor recovery landscape the tumor tissue from the CTPAC3 clear cell renal cell carcinoma cohort. Patient tumors undergo bulk RNA sequencing and then CDR3 sequences from TCR and BCR receptors were recovered. Then for each patient, CDR3s are segregated by receptor class. (A) Total recoveries per patient was reported in a bar plot with each bar reflecting the total number of recoveries from each patient. The proportion of each recovery type per patient was reported for individual T-cell and B-cell receptor types (B), common receptor combinations (C), and per cell type combinations (D).

MOFFITT TCC COHORT

	Stage I	Stage II	Stage III + IV	Overall
Number of patients (n)	31	3	68	103
T-cell % mean (median)	0.06383 (0.04803)	0.06421 (0.01471)	0.06787 (0.02659)	0.06595 (0.03677)
T-cell % range	0.0040044, 0.1707	0.01125, 0.1667	0.0004771, 0.4671	0.0004771, 0.4676
B-cell % mean (median)	0.9362 (0.9520)	0.9358 (0.9853)	0.9321 (0.9734)	0.9341 (0.9632)
B-cell % range	0.8293, 0.9960	0.8333, 0.9888	0.5324, 0.9995	0.5324, 0.4671

ANOVA: p-value: 0.9736 (of % T-cells by Stage)

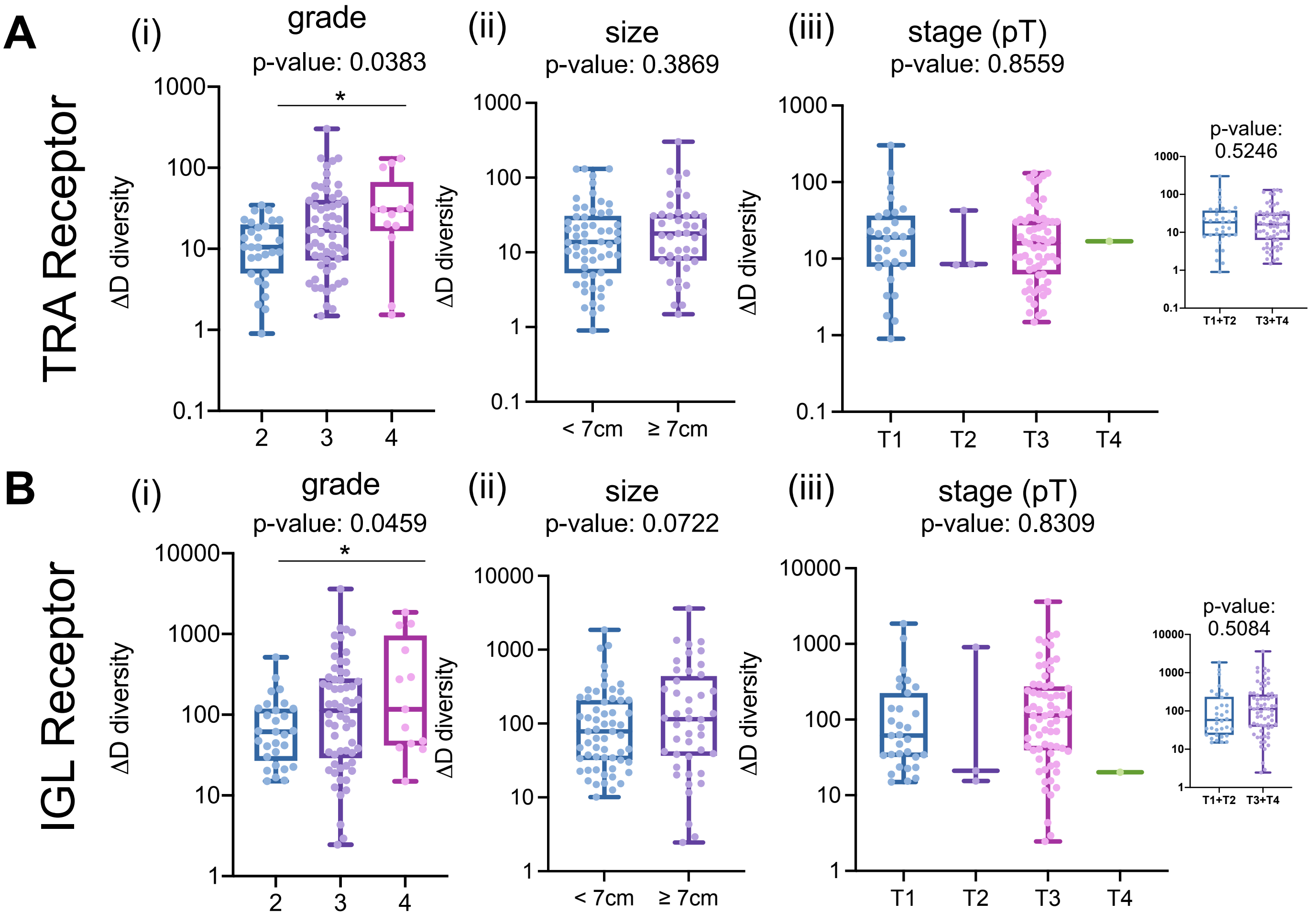
CPTAC-3 COHORT

	Stage I	Stage II	Stage III + IV	Overall
Number of patients (n)	52	14	45	111
T-cell % mean (median)	0.2061 (0.1315)	0.1349 (0.1297)	0.2388 (0.1751)	0.2104 (0.1386)
T-cell % range	0.003466, 0.9167	0.007548, 0.4167	0.008270, 0.8701	0.003466, 0.9167
B-cell % mean (median)	0.7939 (0.8685)	0.8651 (0.8703)	0.7612 (0.8249)	0.7896 (0.8614)
B-cell % range	0.08333, 0.9965	0.5883, 0.9925	0.1299, 0.9917	0.08333, 0.9965

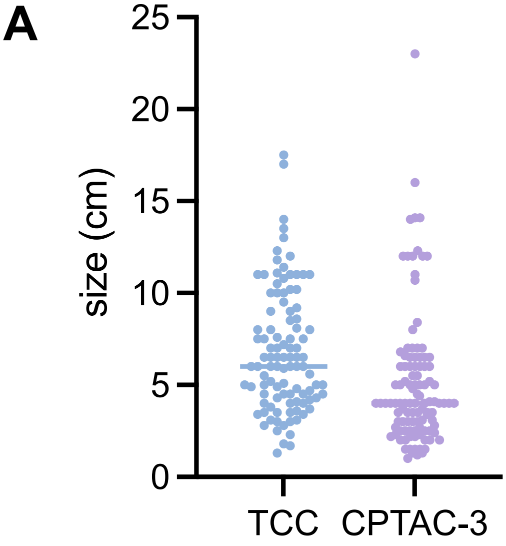
ANOVA: p-value: 0.2145 (of % T-cells by Stage)

Supplemental Figure S11: Comparison of T-cell and B-cell contributions to recovery landscape in the Moffitt TCC and CTPAC-3 clear cell renal cell carcinoma cohorts.

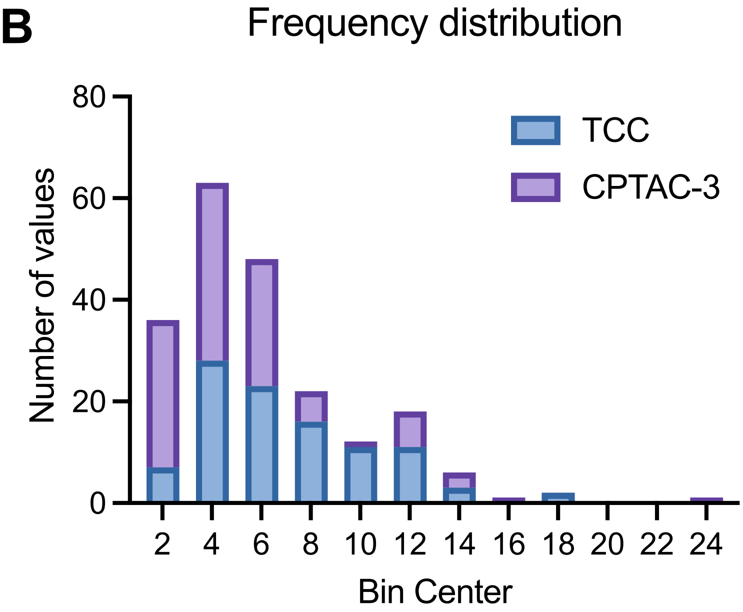
Figure 3 B Comparable Plots in Moffitt TCC Cohort



Supplemental Figure S12: Comparable size, grade, and stage (pT) plots of ΔD diversity in TRA and IGL receptors of the Moffitt TCC cohort. Based on the clinical data available, some of the comparisons between the Moffitt TCC cohort and CPTAC-3 cohort are a little different. The panels in this figure show the same grouping of data from the Moffitt TCC cohort as shown in the validation CPTAC-3 cohort data shown in **Fig. 3B**. (A) TRA receptor CDR3 sequence ΔD diversity was increased diversity in (i) with higher grade tumors (replicate of figure panel **Fig. 2A iii**), (ii) larger diameter tumors (tumors with a largest tumor diameter above 7cm had a mean ΔD diversity of 32.67, tumors with a diameter below 7cm had a mean ΔD diversity of 25.47; p-value: 0.03869), and (iii) stage (mean score for T1 tumors was 33.84, mean score for T2 tumors was 19.77, mean score for T3 tumors was 27.11, and mean score for T4 tumors was 16.87, p-value 0.8559; mean score for T1+T2 tumors was 32.56 and for T3+T4 tumors was 26.95, p-value: 0.5246). (B) IGL receptor CDR3 sequence ΔD diversity showed similar trends as TRA receptor CDR3 sequence diversity for (i) grade (replicate of figure panel **Fig. 2B iii**), (ii) size (tumors with a largest tumor diameter above 7cm had a mean ΔD diversity of 349.0, tumors with a diameter below 7cm had a mean ΔD diversity of 179.4; p-value: 0.0722), and (iii) stage (mean score for T1 tumors was 198.8, mean score for T2 tumors was 314.1, mean score for T3 tumors was 279.3, and mean score for T4 tumors was 20.20, p-value 0.8309; mean score for T1+T2 tumors was 209.0 and for T3+T4 tumors was 275.5, p-value: 0.5084). Unpaired t-tests were used to compare two group data and ANOVA was used to compare grade, three group data. p-value significance represented by * < 0.05, ** < 0.01, *** < 0.001

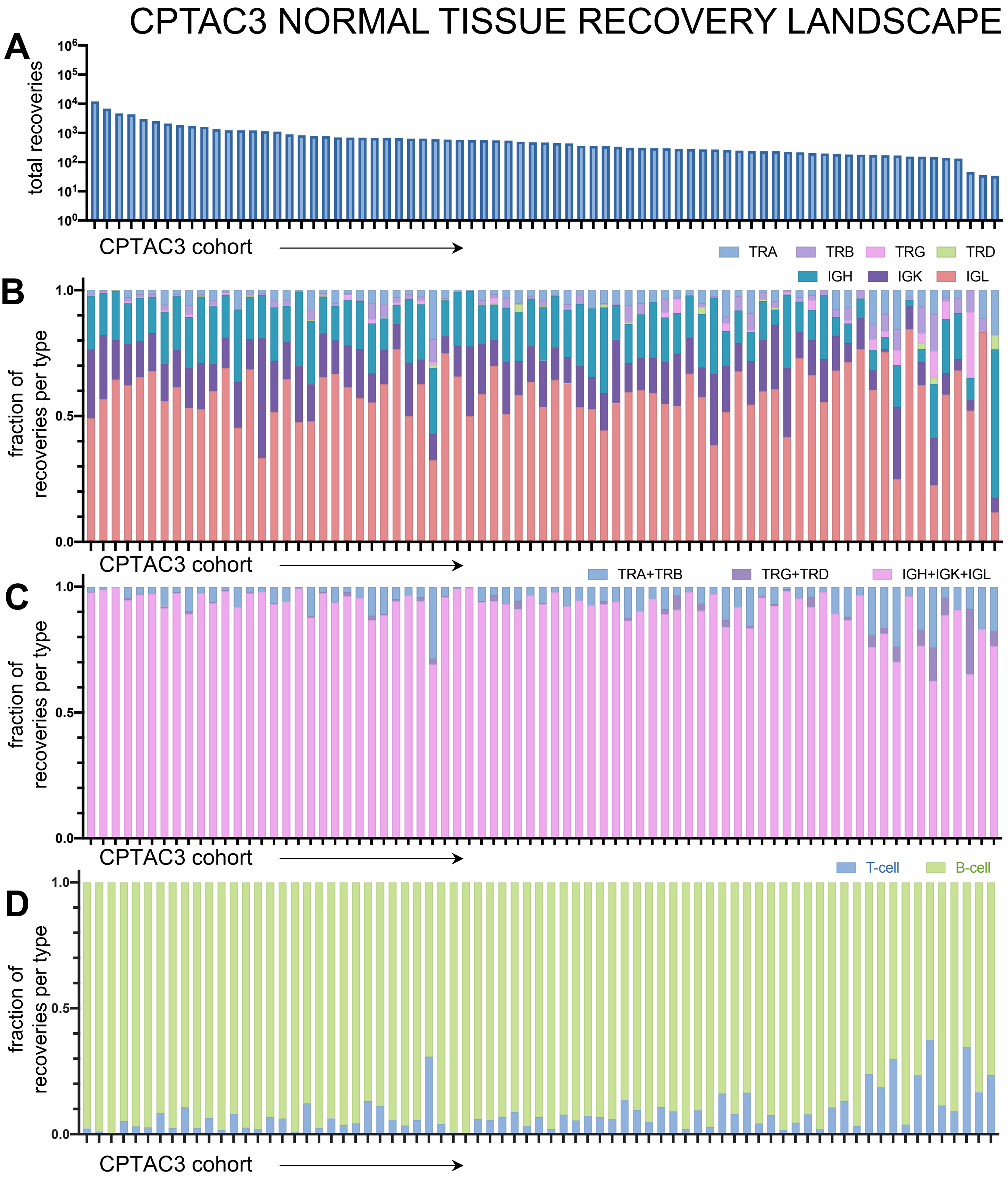


	TCC	CPTAC-3
Median	6	4
Mean	6.8	5.1
Std Dev	3.3	3.7
Range	1.3 – 17.5	1 - 23



Distribution comparison with Kolmogorov-Smirnov test
p-value: < 0.0001 ***
KS distance: 0.3371

Supplemental Figure S13: Comparison of the largest diameter size distribution of the Moffitt TCC and CPTAC-3 renal cell carcinoma cohorts. (A) Distribution of largest diameter sizes (in cm) of tumors from the Moffitt TCC and CPTAC-3 Cohort with descriptive statistics showing that mean and median diameter of CPTAC-3 tumors is smaller than the mean and median diameter of Moffitt TCC tumors. (B) Histogram of the frequency distribution of tumors that show the distribution of Moffitt TCC and CPTAC-3 tumors are statistically significantly different (Kolmogorov-Smirnov test, distance of 0.3371 and p-value < 0.0001).

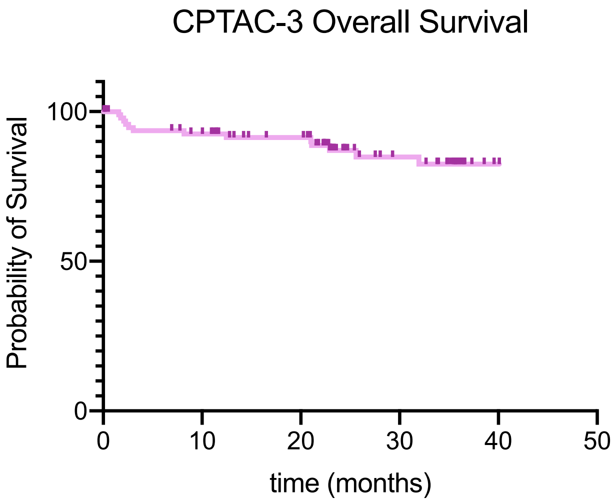


Supplemental Figure S14: Tumor infiltrating lymphocyte receptor recovery landscape the normal tissue from CPTAC3 clear cell renal cell carcinoma cohort. Patient tumors undergo bulk RNA sequencing and then CDR3 sequences from TCR and BCR receptors were recovered. Then for each patient, CDR3s are segregated by receptor class. (A) Total recoveries per patient was reported in a bar plot with each bar reflecting the total number of recoveries from each patient. The proportion of each recovery type per patient was reported for individual T-cell and B-cell receptor types (B), common receptor combinations (C), and per cell type combinations (D).

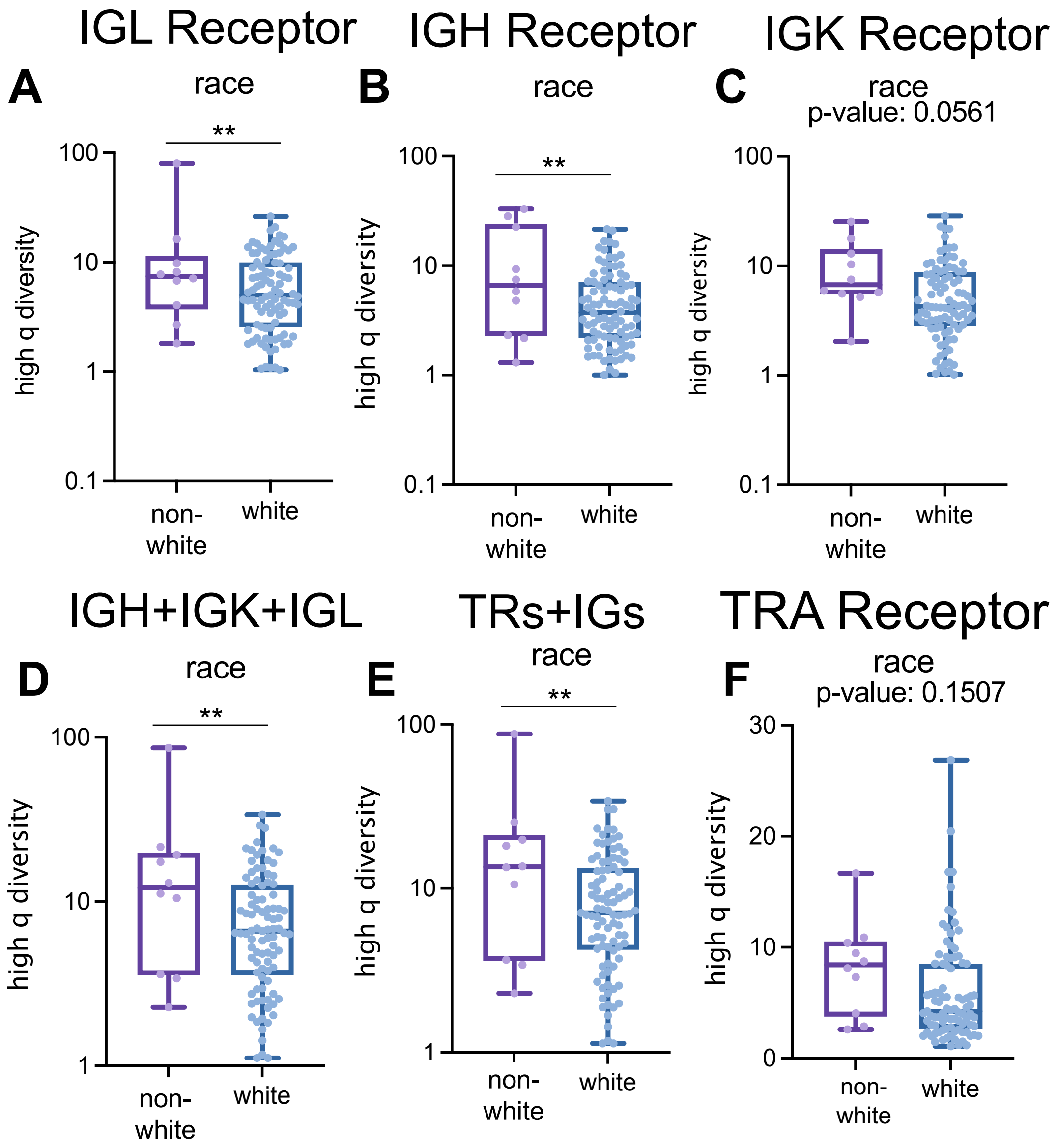
CPTAC-3 cohort low q diversity				
grouping	clinical variable	p-value	test	result
TRA	normal vs tumor (matched)	<0.0001	paired t-test	mean difference between tumor-normal: 29.55 (95% CI: 21.97, 37.12)
TRB	normal vs tumor (matched)	<0.0001	paired t-test	mean difference between tumor-normal: 19.51 (95% CI: 14.76, 24.26)
TRG	normal vs tumor (matched)	<0.0001	paired t-test	mean difference between tumor-normal: 4.633 (95% CI: 3.039, 6.227)
TRD	normal vs tumor (matched)	0.0282	paired t-test	mean difference between tumor-normal: 0.9988 (95% CI: 0.1198, 1.878)
IGH	normal vs tumor (matched)	0.0041	paired t-test	mean difference between tumor-normal: 39.39 (95% CI: 12.87, 65.91)
IGK	normal vs tumor (matched)	0.0013	paired t-test	mean difference between tumor-normal: 64.49 (95% CI: 26.00, 103.0)
IGL	normal vs tumor (matched)	0.0003	paired t-test	mean difference between tumor-normal: 77.63 (95% CI: 36.97, 118.3)
TRA+TRB	normal vs tumor (matched)	<0.0001	paired t-test	mean difference between tumor-normal: 50.84 (95% CI: 39.13, 62.54)
TRG+TRD	normal vs tumor (matched)	<0.0001	paired t-test	mean difference between tumor-normal: 6.628 (95% CI: 4.462, 8.795)
IGH+IGK+IGL	normal vs tumor (matched)	0.0008	paired t-test	mean difference between tumor-normal: 177.4 (95% CI: 76.62, 278.3)
TRs+IGs	normal vs tumor (matched)	<0.0001	paired t-test	mean difference between tumor-normal: 233.2 (95% CI: 125.8, 340.5)

CPTAC-3 cohort high q diversity				
grouping	clinical variable	p-value	test	result
TRA	normal vs tumor (matched)	<0.0001	paired t-test	mean difference between tumor-normal: 4.655 (95% CI: 2.883, 6.426)
TRB	normal vs tumor (matched)	<0.0001	paired t-test	mean difference between tumor-normal: 4.195 (95% CI: 2.863, 5.527)
TRG	normal vs tumor (matched)	<0.0001	paired t-test	mean difference between tumor-normal: 1.754 (95% CI: 1.091, 2.416)
TRD	normal vs tumor (matched)	0.0291	paired t-test	mean difference between tumor-normal: 0.5970 (95% CI: 0.06811, 1.126)
IGH	normal vs tumor (matched)	0.0052	paired t-test	mean difference between tumor-normal: 2.538 (95% CI: 0.7827, 4.293)
IGK	normal vs tumor (matched)	0.0368	paired t-test	mean difference between tumor-normal: 2.991 (95% CI: 0.1885, 5.793)
IGL	normal vs tumor (matched)	0.3074	paired t-test	mean difference between tumor-normal: 1.022 (95% CI: -0.9598, 3.005)
TRA+TRB	normal vs tumor (matched)	<0.0001	paired t-test	mean difference between tumor-normal: 7.593 (95% CI: 5.237, 9.949)
TRG+TRD	normal vs tumor (matched)	<0.0001	paired t-test	mean difference between tumor-normal: 2.320 (95% CI: 1.520, 3.121)
IGH+IGK+IGL	normal vs tumor (matched)	0.1299	paired t-test	mean difference between tumor-normal: 2.287 (95% CI: -0.6887, 5.262)
TRs+IGs	normal vs tumor (matched)	0.0041	paired t-test	mean difference between tumor-normal: 4.902 (95% CI: 1.608, 8.196)

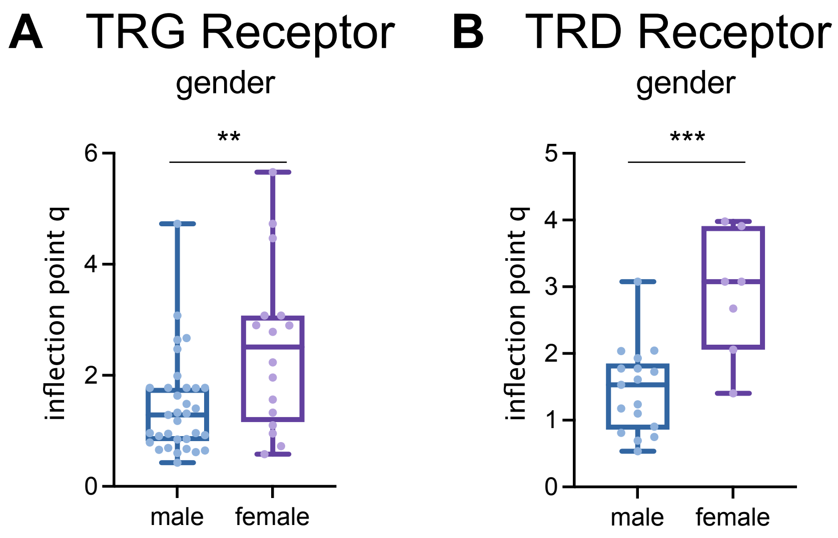
Supplemental Figure S15: Statistical comparison of low q (richness) and high q (evenness) across all receptor subtypes and combinations in the CPTAC-3 cohort.



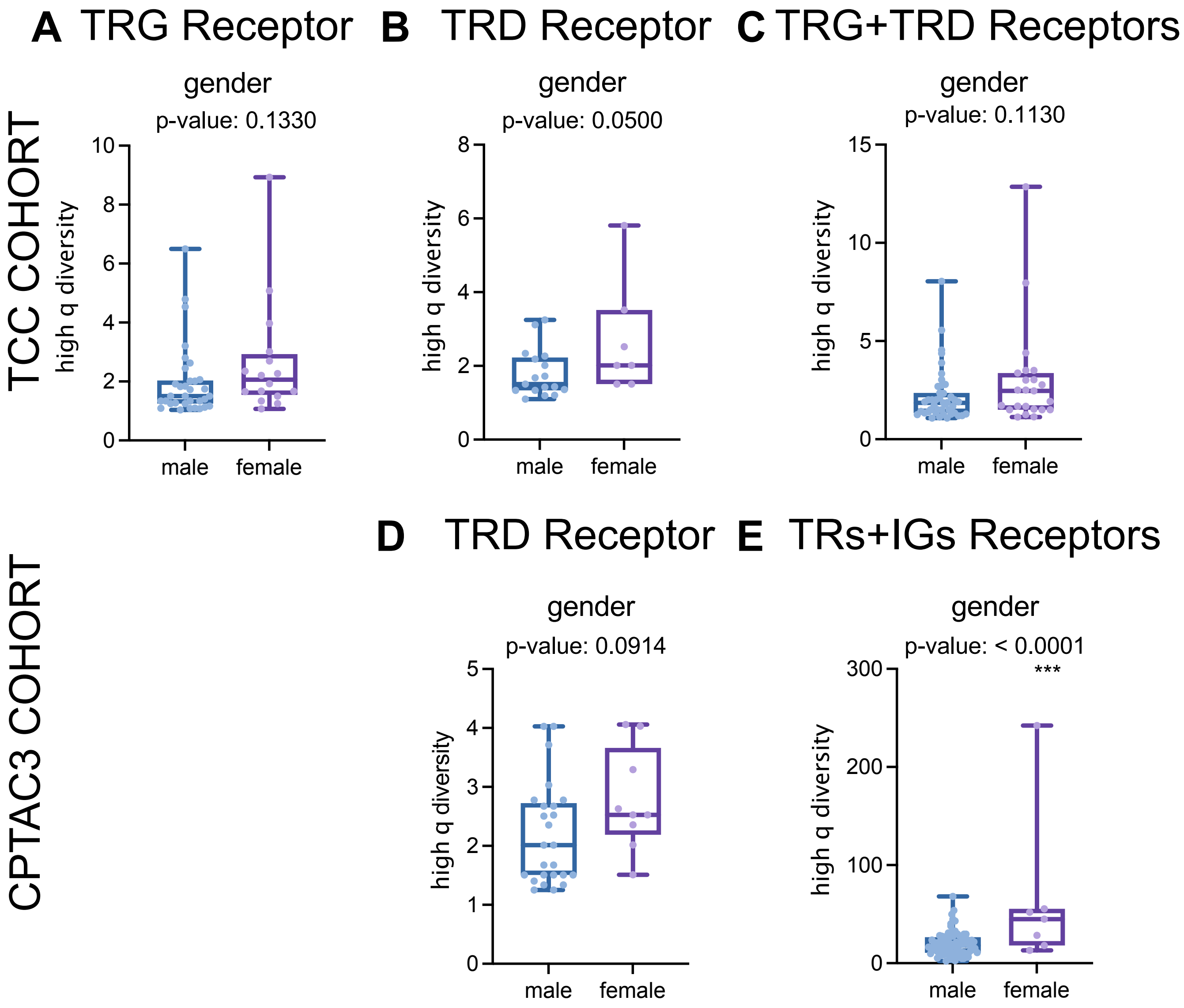
Supplemental Figure S16: CPTAC-3 Cohort overall survival could not confirm the Moffitt TCC survival trend because over 85% of patients were censored.



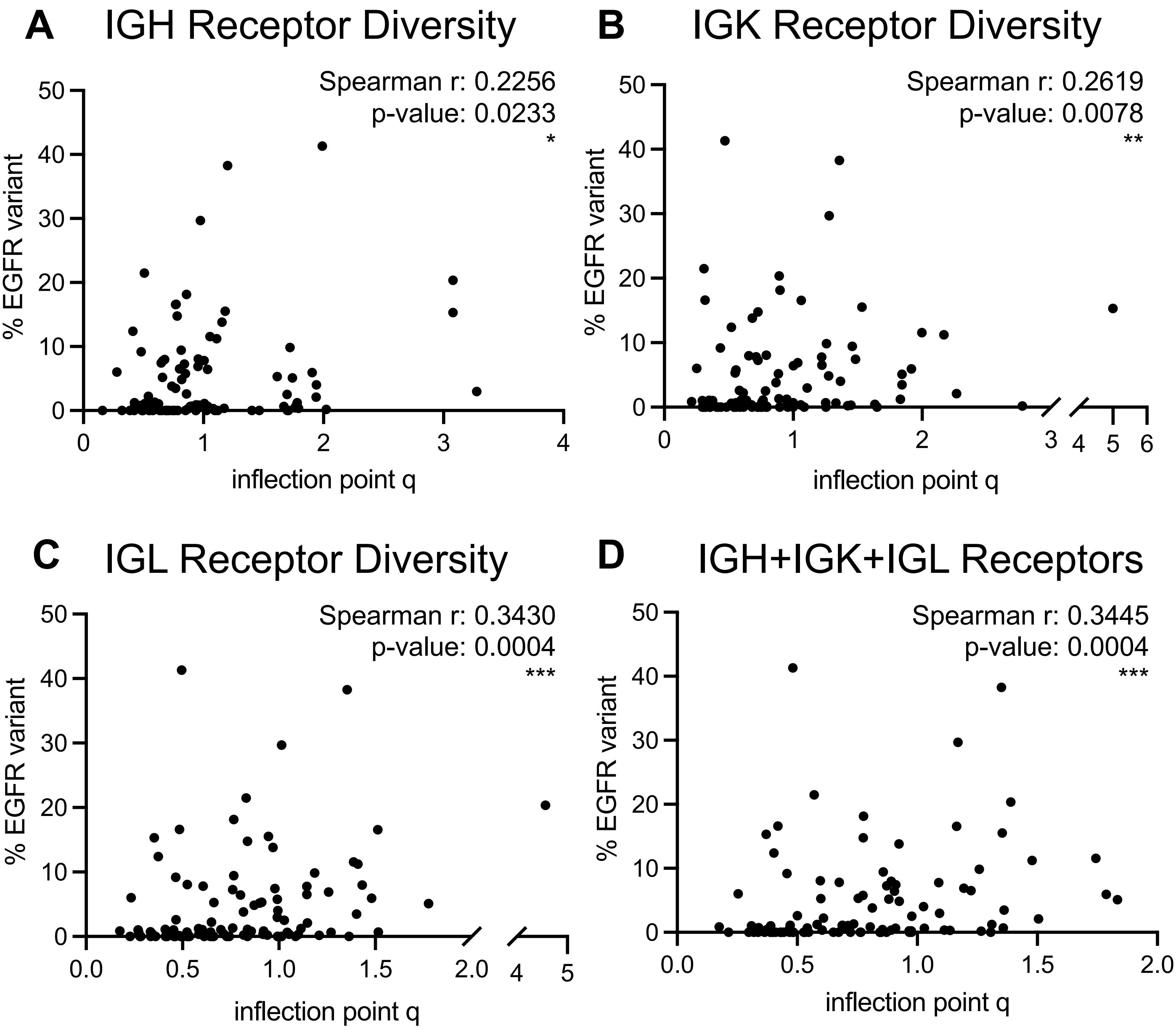
Supplemental Figure S17: Generalized diversity index can capture race-based difference in B-cell receptor CDR3 recoveries in the Moffitt TCC cohort. High q diversity differences in the Moffitt TCC Cohort based on race in (A) IGL receptor (score of 6.883 in white vs score of 14.47 in non-white, p-value: 0.0095), (B) IGH receptor (score of 5.376 in white vs score of 11.69 in non-white, p-value: 0.0026), (C) IGK receptor (score of 6.282 in white vs score of 9.832 in non-white, p-value: 0.0561), (D) IGH+IGK+IGL receptors (score of 8.712 in white vs score of 18.86 in non-white, p-value: 0.0026), (E) all receptors (score of 9.336 in white vs score of 19.67 in non-white, p-value: 0.0025), and (F) TRA receptor. Unpaired t-tests were used to compare categorical data. p-value significance represented by * < 0.05, ** < 0.01, *** < 0.001



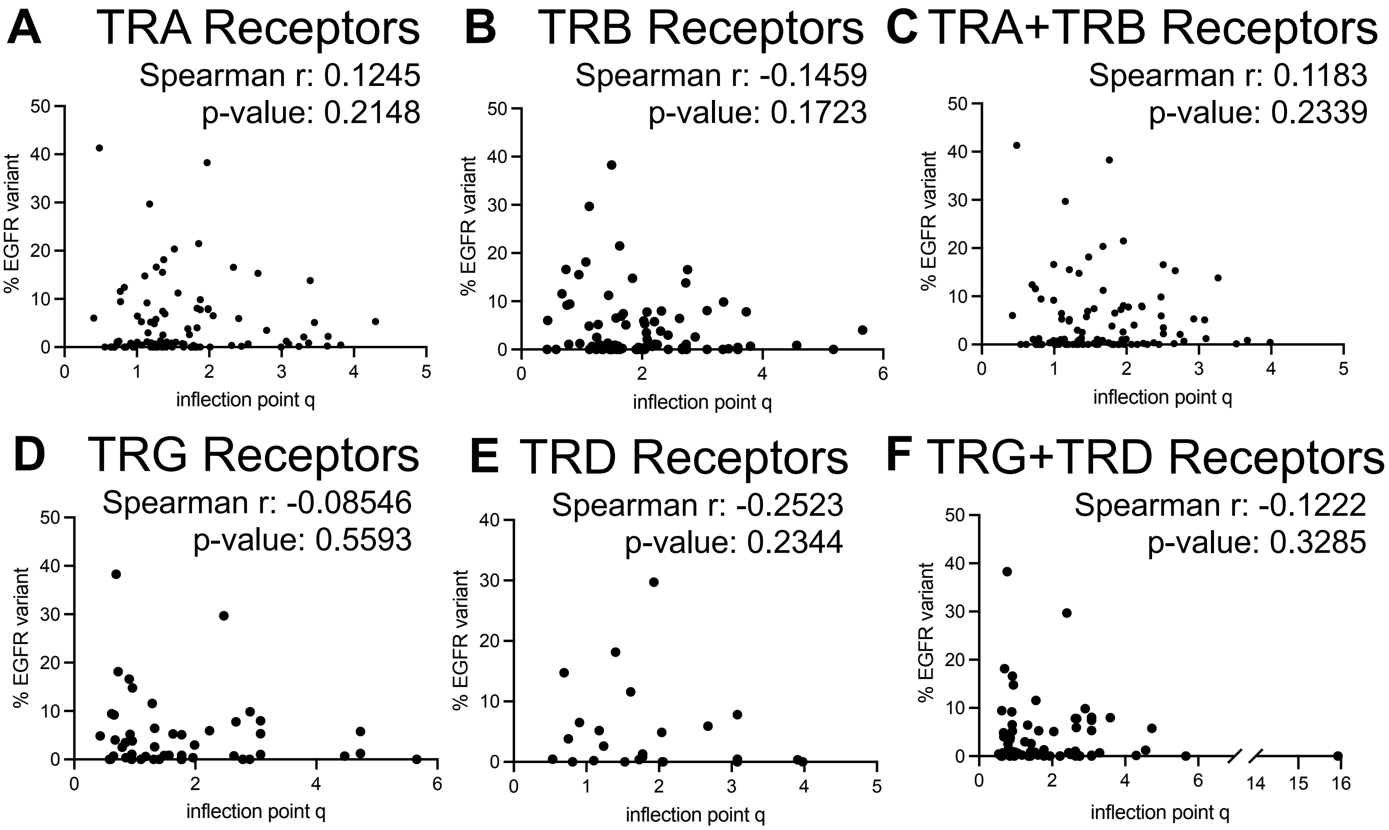
Supplemental Figure S18: Inflection point q diversity can also capture gender-based difference in T-cell receptor CDR3 recoveries in the Moffitt TCC cohort. (A) T-cell receptor gamma (TRG) inflection point q (IP q) was elevated in female patients compared to males (mean IP q in male patients was 1.442, mean IP q in female patients was 2.503; p-value: 0.0033). (B) T-cell receptor delta (TRD) inflection point q was elevated in female patients compared to males (mean IP q in male patients was 1.454, mean IP q in female patients was 2.883; p-value: 0.0003). Unpaired t-tests were used to compare categorical data. p-value significance represented by * < 0.05, ** < 0.01, *** < 0.001



Supplemental Figure S19: Gender-based diversity differences trends exist in T-cell receptor evenness groupings in both the Moffitt TCC Cohort and the CPTAC-3 Cohort. (A) T-cell receptor gamma (TRG) high q diversity was elevated in Moffitt TCC female patients compared to males (mean score in male patients was 1.963, mean score in female patients was 2.663; p-value: 0.1330). (B) T-cell receptor delta (TRD) high q diversity was elevated in Moffitt TCC female patients compared to males (mean score in male patients was 1.791, mean score in female patients was 2.699; p-value: 0.0500). (C) Combination TRG and TRD high q diversity was also elevated in Moffitt TCC female patients (mean score in male patients was 2.195, mean score in female patients was 2.977; p-value: 0.1130). These findings in the Moffitt TCC Cohort were supported in the CPTAC-3 Cohort. (D) TRD high q diversity was elevated in CPTAC-3 female patients compared to males (mean score in male patients was 2.183, mean score in female patients was 2.769; p-value: 0.0914). (E) Combination TRG and TRD high q diversity was also elevated in CPTAC-3 female patients (mean score in male patients was 19.61, mean score in female patients was 64.90; p-value: < 0.0001; excluding the outstanding female score of 242 reduces the mean female score to 35.35 with a p-value of 0.0042 significant difference compared to the male scores). Unpaired t-tests were used to compare categorical data. p-value significance represented by * < 0.05, ** < 0.01, *** < 0.001



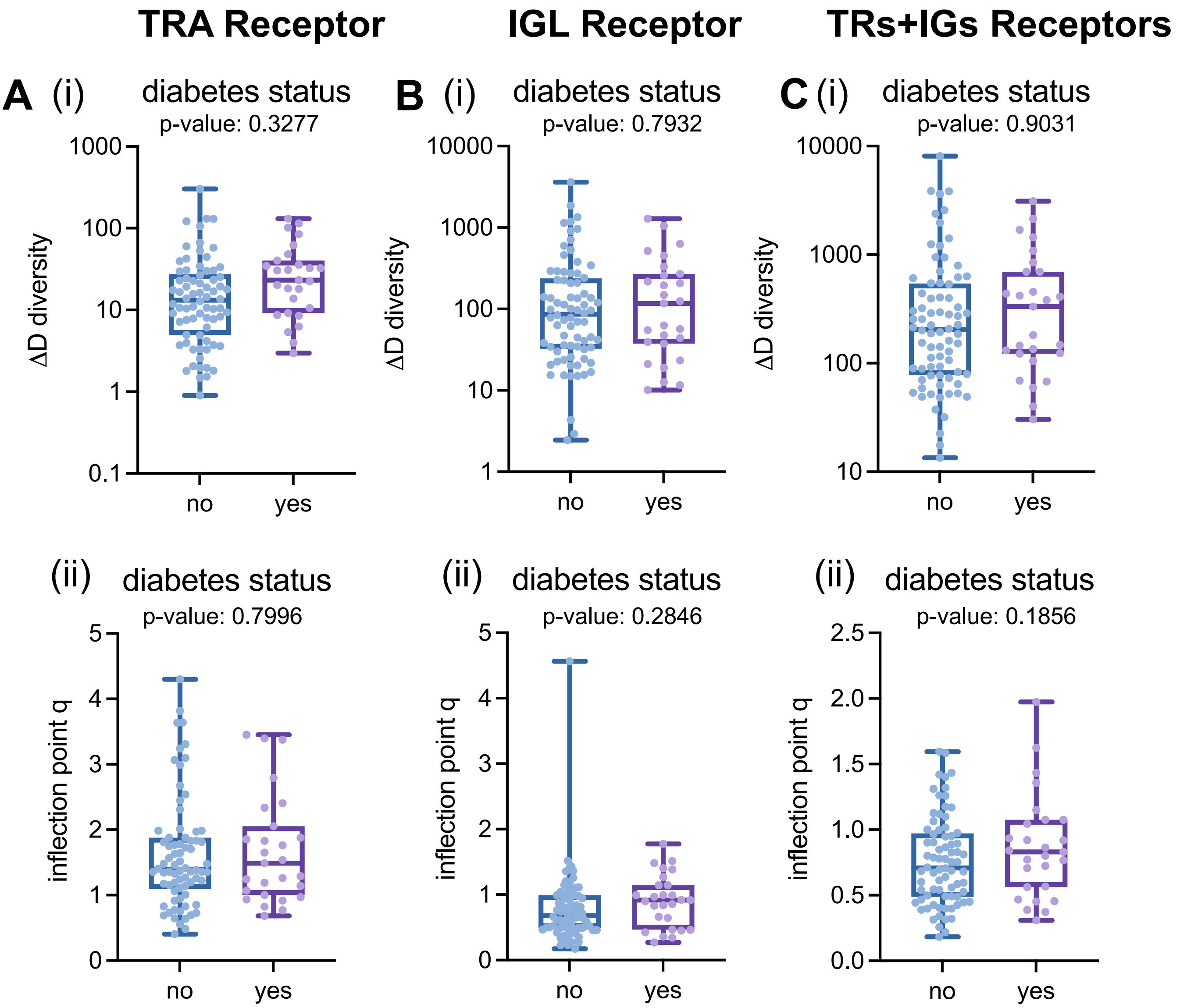
Supplemental Figure S20: B-cell receptor inflection point q diversity may be a surrogate for the proportion of a renal cell carcinoma tumor with an EGFR variant. (A) IGH receptor inflection point q measures versus % EGFR variant reflected a significant weak correlation (Spearman r: 0.2256; p-value: 0.0233). (B) IGK receptor inflection point q measures versus % EGFR variant reflected a significant weak correlation (Spearman r: 0.2619; p-value: 0.0078). (C) IGL receptor inflection point q measures versus % EGFR variant reflected a significant weak correlation (Spearman r: 0.3430; p-value: 0.0004). (D) Full combination of B-cell receptor inflection point q measures versus % EGFR variant reflected a significant weak correlation (Spearman r: 0.3445; p-value: 0.0004). p-value significance represented by * < 0.05, ** < 0.01, *** < 0.001



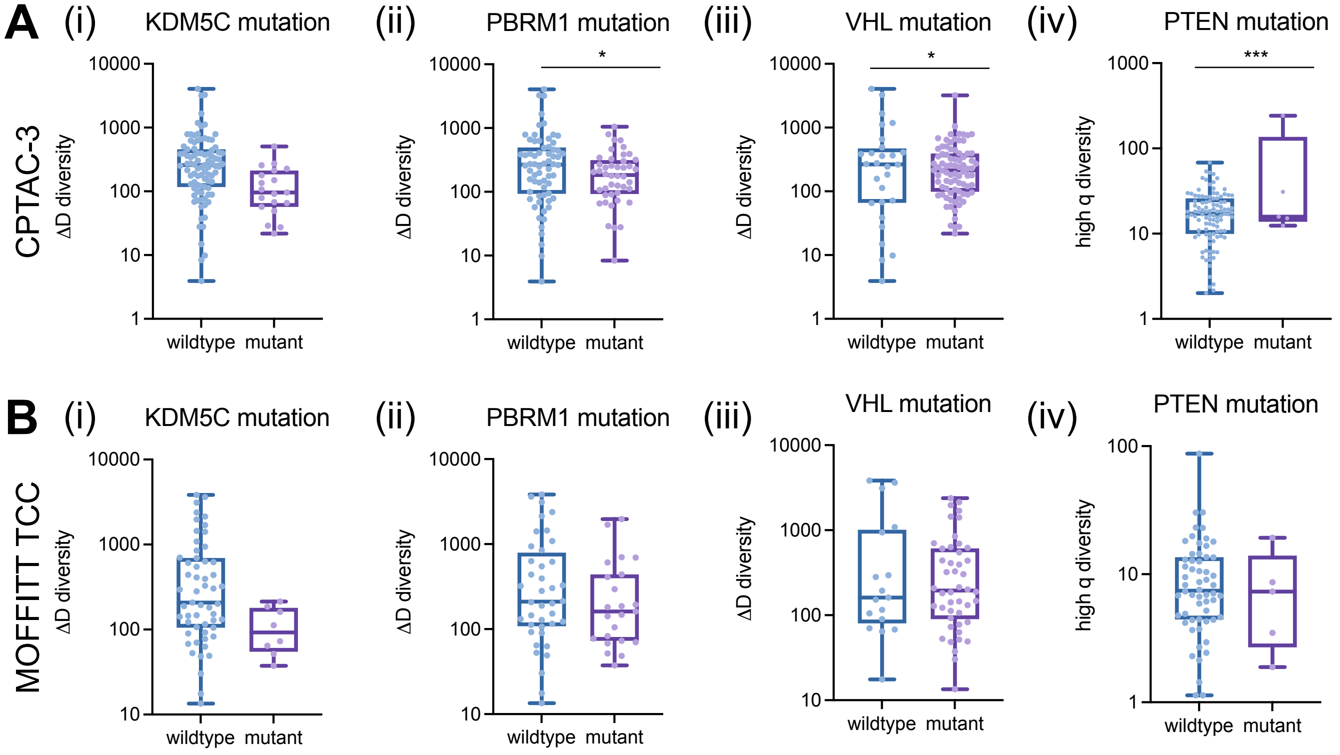
G

Receptor Combination	Spearman Correlation, r (confidence interval)	p-value
TRA	0.1245 (-0.07854, 0.3176)	0.2148
TRB	-0.1459 (-0.3493, 0.07048)	0.1723
TRG	-0.08546 (-0.3655, 0.2087)	0.5593
TRD	-0.2523 (-0.6032, 0.1805)	0.2344
TRA + TRB	0.1183 (-0.08271, 0.3101)	0.2339
TRG + TRD	-0.1222 (-0.3601, 0.1307)	0.3285
IGH	0.2246 (0.02566, 0.4064)	0.0233 *
IGK	0.2619 (0.06526, 0.4390)	0.0078 **
IGL	0.3430 (0.1544, 0.5074)	0.0004 ***
IGH + IGK + IGL	0.3445 (0.1561, 0.5087)	0.0004 ***
TRs + IGs	0.3360 (0.1467, 0.5015)	0.0005 ***

Supplemental Figure S21: T-cell receptor inflection point q diversity does not significantly correlate with % EGFR variant in the Moffitt TCC Cohort. No significant correlations were evaluated for inflection point q measures versus % EGFR variant in recovered (A) TRA receptors, (B) TRB receptors, (C) combined TRA and TRB receptors, (D) TRG receptors, (E) TRD receptors, or (F) combined TRG and TRD receptors. (G) Summary table of correlation statistics for all receptor combinations. p-value significance represented by * < 0.05, ** < 0.01, *** < 0.001



Supplemental Figure S22: No associations with diabetes status and CDR3 diversity metrics in the Moffitt TCC Cohort. No significant associations were evaluated for ΔD diversity and inflection point q measures versus diabetes status in recovered (A) TRA recoveries, (B) IGL recoveries, (C) total (TRs+IGs) recoveries. (A) TRA receptors had (i) ΔD diversity had a mean score of 35.19 in individual with diabetes and mean score of 26.11 in those who did not have diabetes (p-value: 0.3277) and (ii) inflection point q had a mean score of 1.671 in individuals with diabetes and mean score of 1.623 in those who did not have diabetes (p-value: 0.7996). (B) IGL receptor had (i) ΔD diversity had a mean score of 231.2 in individual with diabetes and mean score of 259.2 in those who did not have diabetes (p-value: 0.7932) and (ii) inflection point q had a mean score of 0.9042 in individuals with diabetes and mean score of 0.7808 in those who did not have diabetes (p-value: 0.2846). (C) Total T-cell and B-cell receptors had (i) ΔD diversity had a mean score of 574.2 in individual with diabetes and mean score of 504.4 in those who did not have diabetes (p-value: 0.9031) and (ii) inflection point q had a mean score of 0.8662 in individuals with diabetes and mean score of 0.7601 in those who did not have diabetes (p-value: 0.1856). Unpaired t-tests were used for these analysis with p-value significance represented by * < 0.05, ** < 0.01, *** < 0.001



Supplemental Figure S23: Total (TRs+IGs) recovery and diversity metric associations over the mutational landscape in clear cell renal cell carcinoma. (A) Total (TRs+IGs) recoveries had reduced richness in CPTAC-3 patients with (i) KDM5C mutations (mean score of wildtype was 431.1 and mutant was 138.0; p-value: 0.0515), (ii) PBRM1 mutations (mean score of wildtype was 473.7 and mutant was 240.7; p-value: 0.0448), and (iii) VHL mutations (mean score of wildtype was 575.9 and mutant was 313.8; p-value: 0.0446) and increased evenness in patients with (iv) PTEN mutations (mean score of wildtype was 19.14 and mutant was 63.30; p-value: <0.0001). (B) Total recoveries had reduced richness in Moffitt TCC patients with (i) KDM5C mutations (mean score of wildtype was 627.6 and mutant was 112.4; p-value: 0.1128), (ii) PBRM1 mutations (mean score of wildtype was 674.6 and mutant was 366.6; p-value: 0.1716), and (iii) VHL mutations (mean score of wildtype was 835.1 and mutant was 461.3; p-value: 0.1253) and increased evenness in patients with (iv) PTEN mutations (mean score of wildtype was 10.92 and mutant was 8.121; p-value: 0.6183). Unpaired t-tests were used to compare two group data and ANOVA was used to compare grade, three group data. p-value significance represented by * < 0.05, ** < 0.01, *** < 0.001