Comparing the Somatic, Germline, and Immune Landscapes of Upper Tract Urothelial Carcinoma (UTUC) and UC of the Bladder (UCB)

Kit L. Yuen,[1] Margaret Meagher,[1] Jacob Mercer,[2] Binyam Yilma,[2] Melissa Stoppler,[2] Matina Fragkogianni,[2] Nataliya Mar,[3] Arash Rezazadeh,[3] Shilpa Gupta,[4] Petros Grivas,[5] Aditya Bagrodia,[1] Rana R. Mckay,[1] Tyler F. Stewart,[1] and Amirali Salmasi[1]

[1]UC San Diego Health, San Diego, CA // [2]Tempus AI, Inc., Chicago, IL // [3]University of California Irvine, Irvine, CA // [4]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH // [5]University of Washington, Fred Hutchinson Cancer Center, Seattle, WA

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INTRODUCTION

Molecular characterization of anatomically distinct UCs has been limited by the rarity of UTUC; however, recent advances in real-world data curation have enabled larger UTUC cohort generation.

Here, we investigated the somatic, germline, and immunologic landscapes of UTUC compared to UCB.

METHODS

De-identified next-generation sequencing data from UTUC (n=505; 224 ureter and 281 renal pelvis) and UCB (n=2,416; 2,379 bladder and 37 urethra) cases in the Tempus Database were retrospectively analyzed. Tumors were sequenced with the Tempus xT DNA and xR RNA assays.

Pathogenic somatic mutations, immune cell infiltration predicted from gene expression patterns, TMB, PD-L1 from IHC, MSI, and mismatch repair (MMR) were evaluated. Incidental germline alterations were assessed in 46 genes for patients with tumor/normal-matched (T/N) sequencing (UTUC n=285, UCB n=1,359).

Chi-squared, Fisher's exact, and Wilcoxon rank-sum tests were used to assess statistical significance (p<0.05, q<0.05 for false discovery rate correction for multiple testing).

Patient characteristics

Characteristic	Overall, N=2,921[1]	UCB, n=2,416[1]	UTUC, n=505[1]	p-value[2]
Age at Diagnosis				0.003
Median (IQR)	71 (63, 78)	70 (63, 78)	73 (65, 79)	
Gender[3]				<0.001
Male	2,096 (72%)	1,815 (75%)	281 (56%)	
Female	825 (28%)	601 (25%)	224 (44%)	
Race[3]				<0.001
White	1,507 (83%)	1,254 (83%)	253 (80%)	
Black / AA	141 (7.7%)	127 (8.4%)	14 (4.4%)	
Other	103 (5.6%)	84 (5.6%)	19 (6.0%)	
Asian	75 (4.1%)	44 (2.9%)	31 (9.8%)	
Stage[3]				0.002
Stages III-IV	1,346 (87%)	1102 (85%)	244 (93%)	
Stages I-II	202 (12.8%)	186 (14.9%)	16 (6.2%)	
Smoking status				<0.001
Current/former	1,655 (57%)	1,421 (59%)	234 (46%)	
Never	694 (24%)	533 (22%)	161 (32%)	
Unknown	572 (20%)	462 (19%)	110 (22%)	

[1]n (%), [2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test, [3]Percentages calculated from total known. AA, African American.
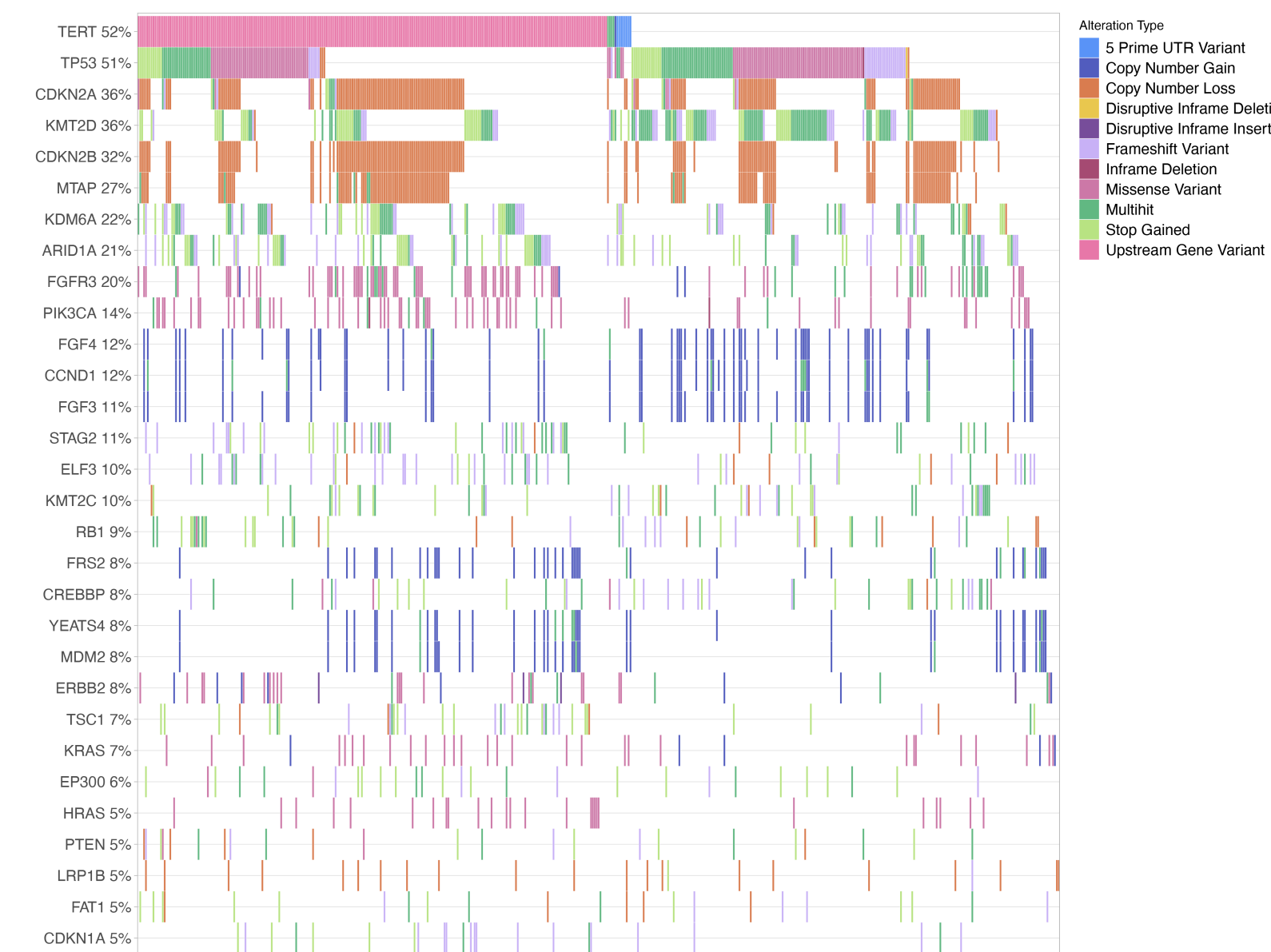
RESULTS

Somatic Landscape
UCB
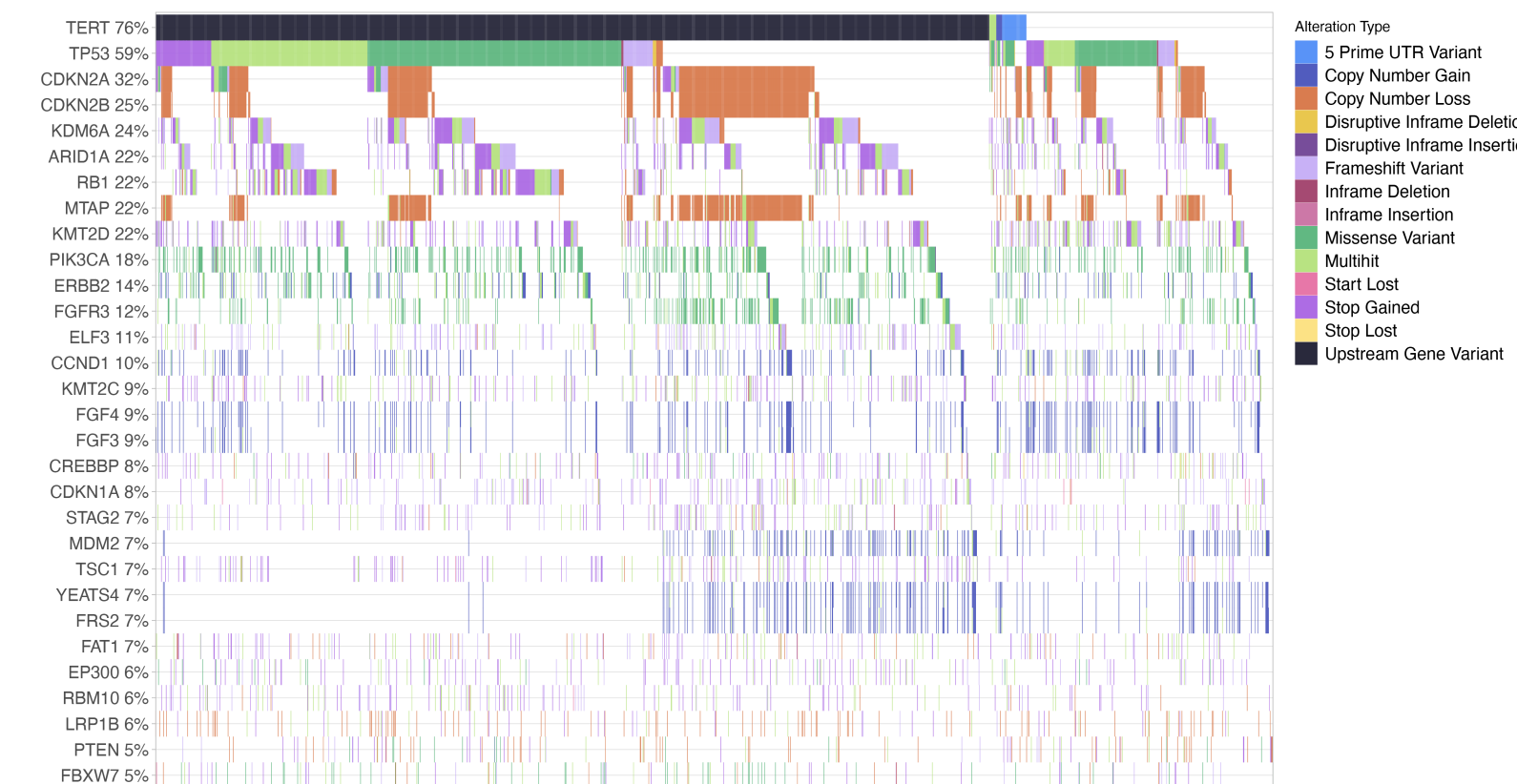
UTUC

Figure 1. Alterations in *TERT*, *TP53*, *RB1*, *ERBB2*, and *CDKN1A* were more frequent in UCB, while *KMT2D*, *FGFR3*, and *CDKN2B*, *KRAS and HRAS* were more frequent in UTUC (q<0.05 for all). Oncoplots do not include alterations that have an unclear effect on function or lack sufficient evidence to determine pathogenicity.

Fusions

Fusion Partner	Overall, N=2,921[1]	UCB, n=2,416[1]	UTUC, n=505[1]	p-value[2]
FGFR3	128 (4.4%)	97 (4.0%)	31 (6.1%)	0.034
FGFR2	13 (0.4%)	9 (0.4%)	4 (0.8%)	0.3
Other	100 (3.4%)	86 (3.6%)	14 (2.8%)	0.5

Table 2. *FGFR3* fusions were more frequent in UTUC compared to UCB (p=0.034).

Germline Mutations

| Gene	UCB, N=1,359[1]	UTUC, n=285[1]	p-value[2]
Any P/LP germline mutation	97 (7.1%)	20 (7.0%)	>0.9
MUTYH	33 (2.4%)	4 (1.4%)	0.3
BRCA2	12 (0.9%)	5 (1.8%)	0.2
BRCA1	8 (0.6%)	3 (1.1%)	0.4
MSH6[4]	3 (0.2%)	3 (1.1%)	0.069
ATM	10 (0.7%)	1 (0.4%)	0.7
BRIP1	7 (0.5%)	1 (0.4%)	>0.9
MLH1[4]	1 (<0.1%)	1 (0.4%)	0.3
MSH2[4]	3 (0.2%)	1 (0.4%)	0.5
MSH3	1 (<0.1%)	1 (0.4%)	0.3
PALB2	4 (0.3%)	1 (0.4%)	>0.9
NBN	4 (0.3%)	0 (0%)	>0.9
APC	3 (0.2%)	0 (0%)	>0.9
CHEK2	3 (0.2%)	0 (0%)	>0.9
CDKN2A	1 (<0.1%)	0 (0%)	>0.9
PMS2[4]	1 (<0.1%)	0 (0%)	>0.9
RAD51C	1 (<0.1%)	0 (0%)	>0.9
RAD51D	1 (<0.1%)	0 (0%)	>0.9
RB1	1 (<0.1%)	0 (0%)	>0.9
RET	1 (<0.1%)	0 (0%)	>0.9
SDHB	1 (<0.1%)	0 (0%)	>0.9
TSC2	1 (<0.1%)	0 (0%)	>0.9

Table 3. Germline variants were found in 7.1% of UCB and 7.0% of UTUC cases, with trends towards higher prevalence of alterations in lynch-associated genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) in UTUC (0.6% vs 1.8%, p=0.059).

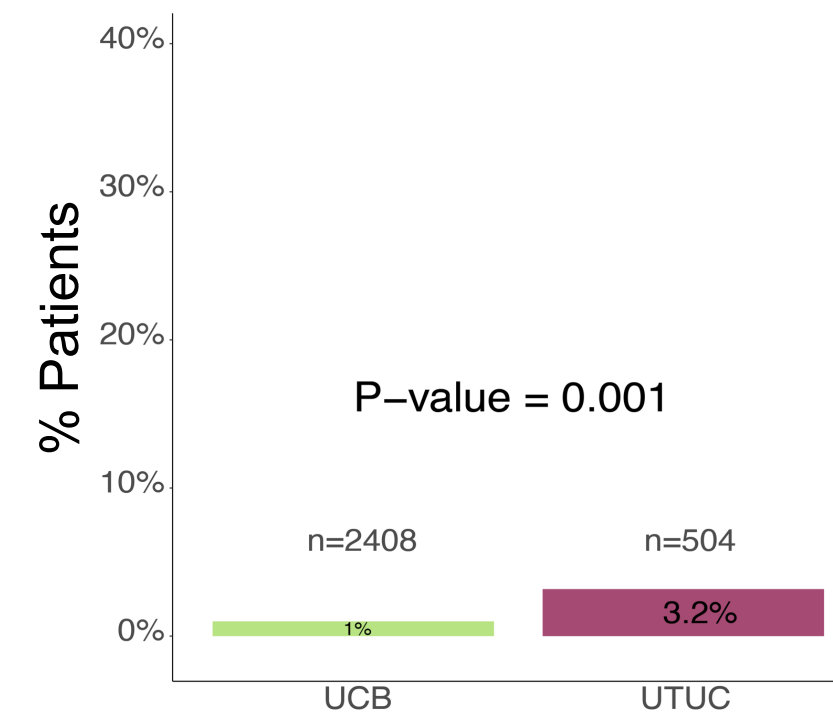### Comprehensive Molecular Biomarkers

High TMB(≥10 mut/Mb)
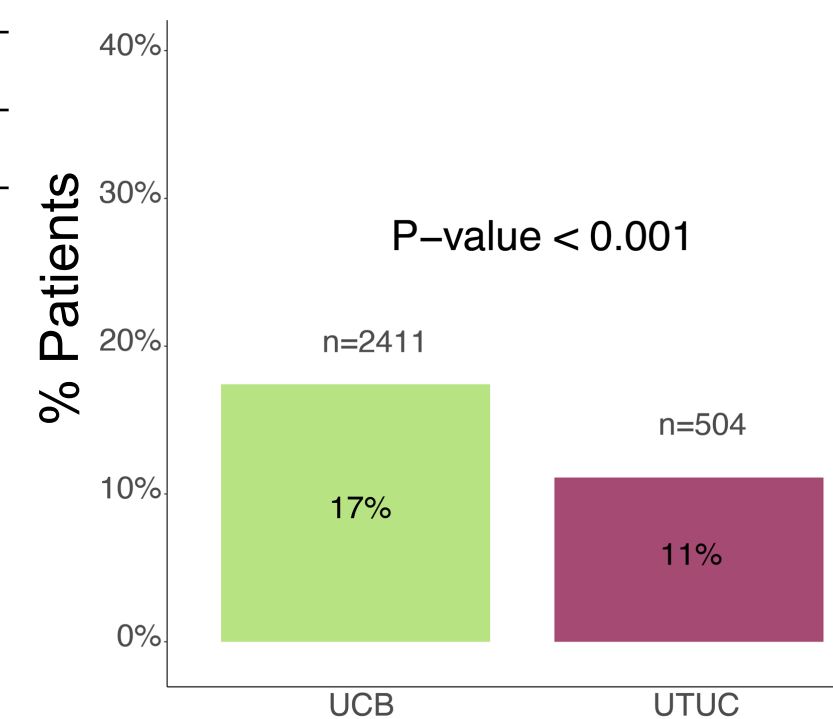
PD-L1 Positivity (IHC)
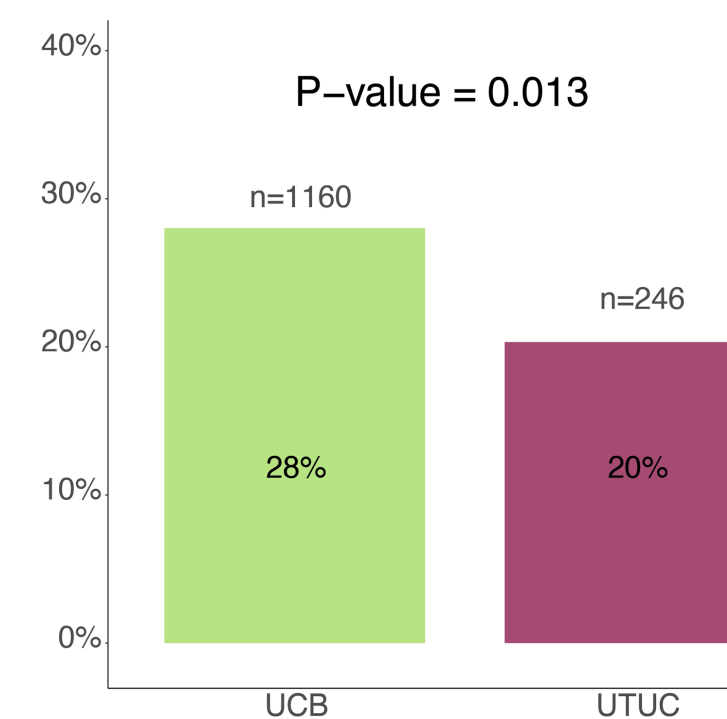
Microsatellite Instability
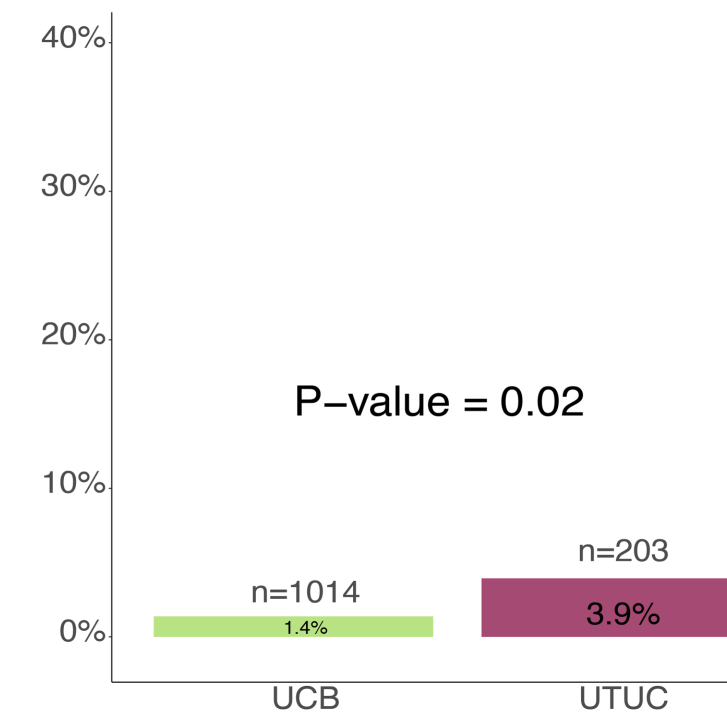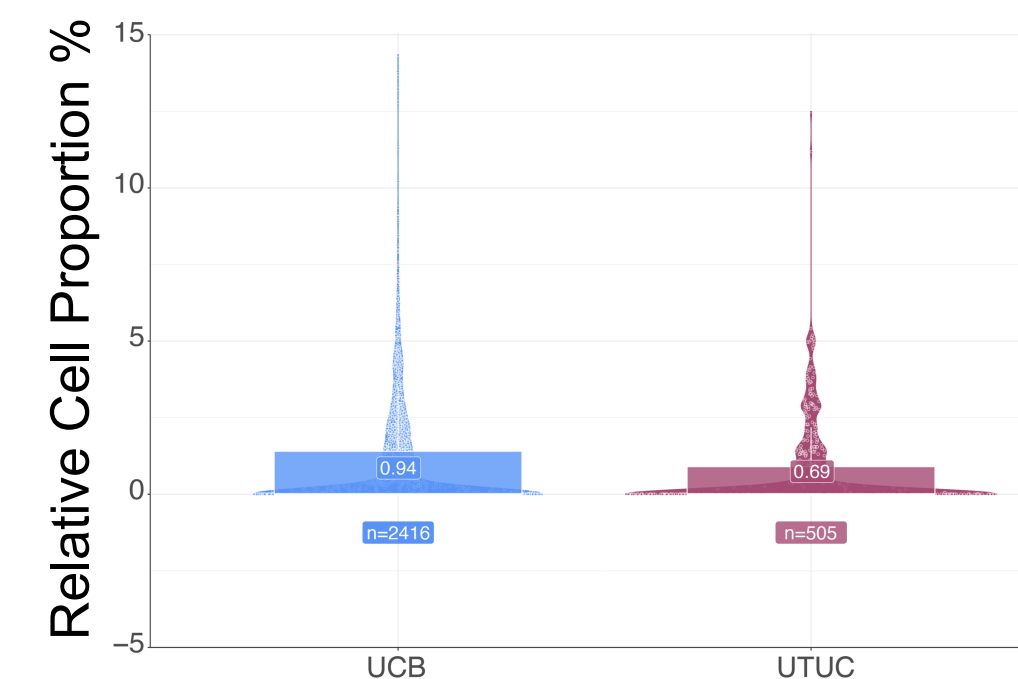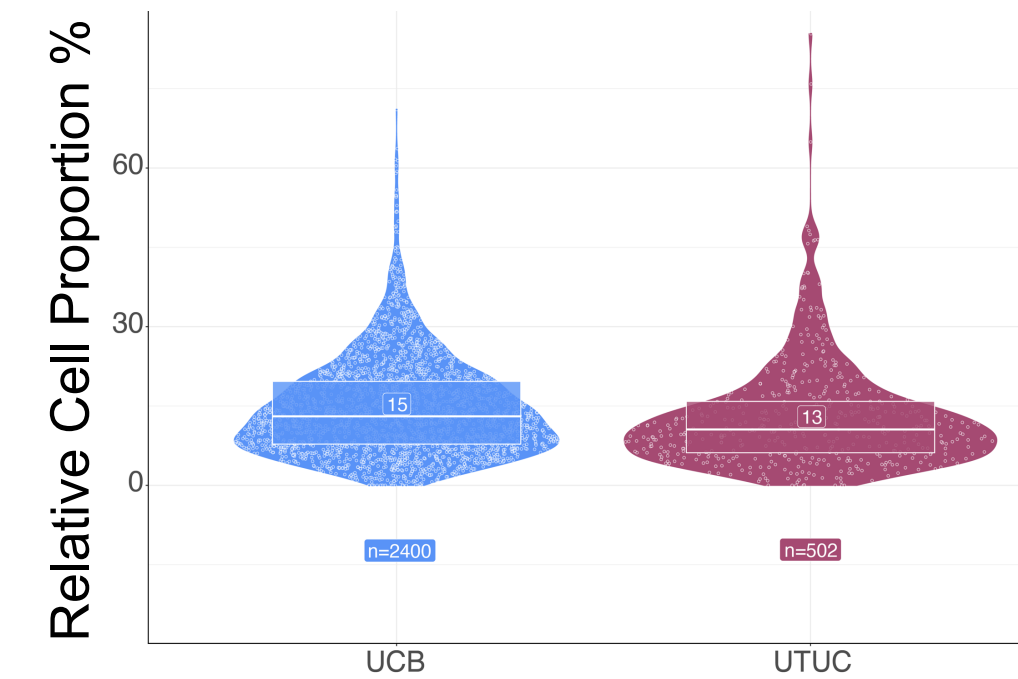

Deficient Mismatch Repair (IHC)

Figure 2. The prevalence of TMB ≥ 10 mut/Mb was higher in UCB vs UTUC (17% vs 11%, p<0.001). UCB had increased PD-L1 positivity (p=0.013), whereas UTUC had more MSI-high (UTUC = 3.2% vs UCB = 1%, p=0.001) and deficient MMR (p=0.020) cases.

Immune Infiltration
Regulatory T Cells
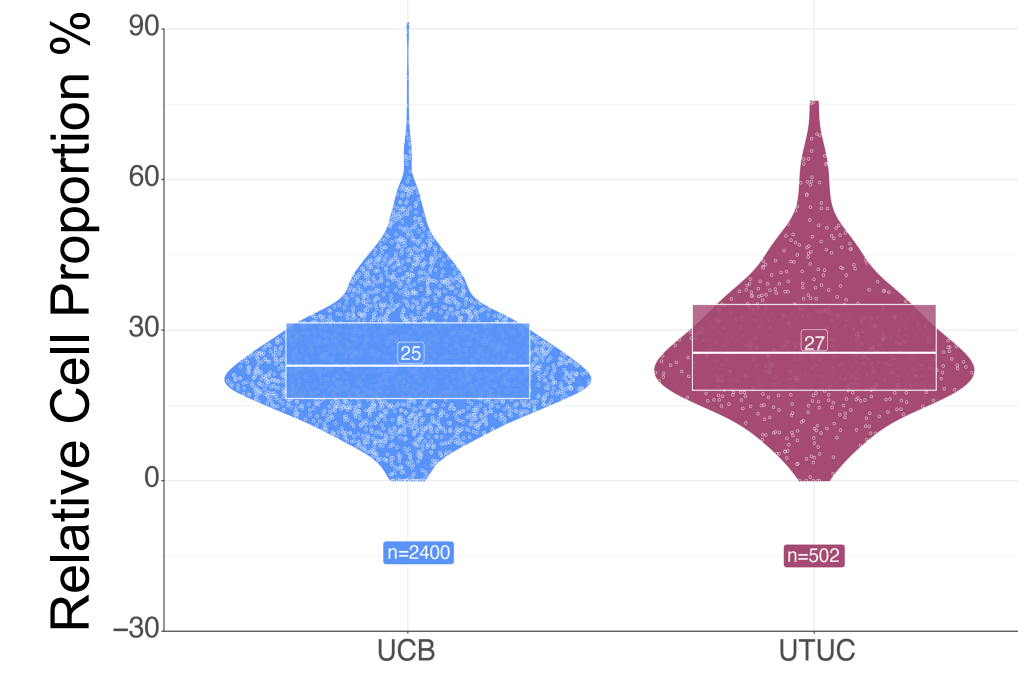

NK Cells

CD4 T Cells

Figure 3. There were similar proportions of total immune infiltrates in UCB and UTUC. However, UTUC harbored a higher percentage of CD4+ T cells (p<0.001), while UCB had a higher proportion of regulatory T and NK cells (p<0.001).

SUMMARY

- Via comprehensive molecular characterization of UC, we observed distinct DNA alteration and tumor microenvironment patterns in UTUC and UCB.

- The germline results underline how T/N testing can identify patients with UTUC and/or UCB who can benefit from dedicated germline testing.

Correspondence: asalmasi@health.ucsd.edu