Racial differences in TMB measures between paired tumor/normal and tumor-only sequencing across endometrial, bladder, and non-small cell lung cancers

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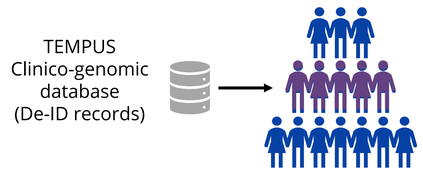
INTRODUCTION

- Tumor mutational burden (TMB), defined as the number of somatic mutations per megabase, is routinely used as a predictive biomarker for immunotherapy response in metastatic cancer patients.
- Sequencing of paired tumor and normal specimens allows for correction of TMB estimates with patient-specific germline variants.
- For tumor only assays, TMB estimates are corrected using germline variant annotations derived from population-scale germline variant surveys.
- These surveys often underrepresent individuals of non-European descent, leading to potential inaccuracies in TMB estimates in these populations.

METHODS

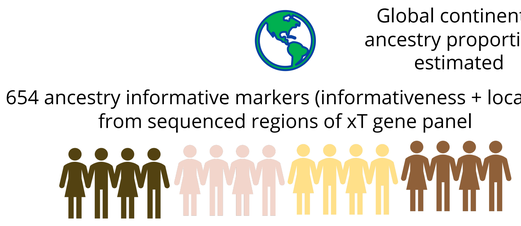
Cohort selection



Patient Characteristics:
- Cancer types: non-small cell lung (NSCLC, n=4,583) endometrial (n=3,084), or urothelial (n=2,806)
- Sequenced with Tempus xT NGS platform[1]

TMB values (mut/Mb), race/ethnicity labels and other metadata were obtained. Comparisons between tumor-only sequencing (TOS) vs. paired tumor/normal sequencing (PS) were performed.

Ancestry inference and race imputation



We have previously shown that a heuristic method combining global ancestry proportions can impute race and ethnicity categories. This allowed us to include more patients in our analysis.

Statistical analysis

- The Kruskall-Wallis test was used to compare TMB distributions within sequencing modality groups.
- The Mann-Whitney test was used for pairwise comparisons between TOS and PS values for a given race/ethnicity and sequencing modality.
- TMB differences in paired sequencing (PS) and tumor-only sequencing (TOS) were evaluated for each imputed race/ethnicity category and cancer type.

SIGNIFICANCE

- Differences across PS and TOS were **significant in each cancer type** (p<0.0001).
- When all cancer types were combined, the mean inflation of TMB median values was 1.6 for White whereas non-White patients was 3 (p<0001).
- PS **reduces estimated TMB** compared to TOS across all racial groups.

RESULTS

- TMB median values were studied for cohorts of patients with NSCLC, urinary tract, and endometrial cancers.
- A statistically significant inflation of TMB median values is observed for all race/ethnicity categories studied
- The inflation in TMB values tends to be maximum in Black patients, and occasionally in Asian patients.
- Among 4,583 NSCLC patients (13% Black (B), 6% Asian (A), 6% Hispanic/Latino (H/L), 75% White (W), 2,505 had PS, and 2,078 had TOS performed.
- Median TMB for B, A, H/L and W patients was 1.9, 4.2, 3.2, and 3.8 (within group p<0.0001), respectively in patients with PS, and 5, 7.6, 5, and 5.4 (within group p<0.0001), in patients with TOS.
- Comparisons across PS and TOS were highly significant (p<0.0001). The absolute difference in median TMB was 3, 3.4, 1.8, and 1.6, respectively.

Figure 1. TMB for each racial group across NSCLC

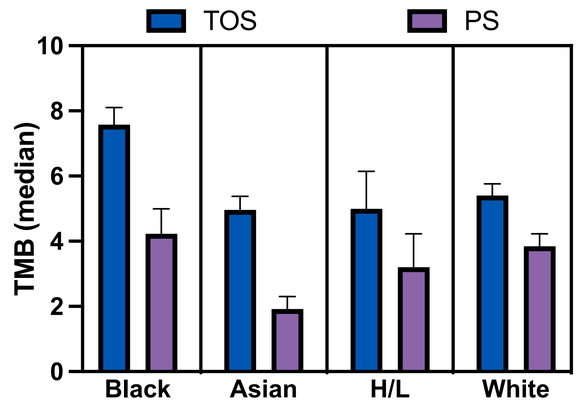
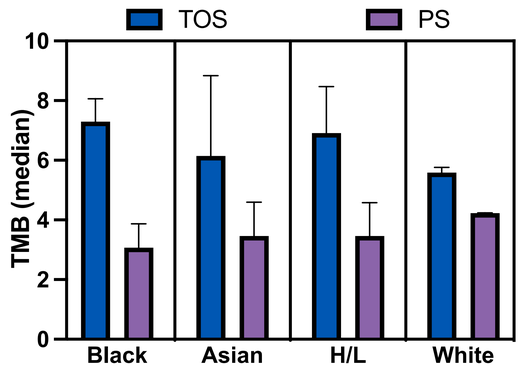
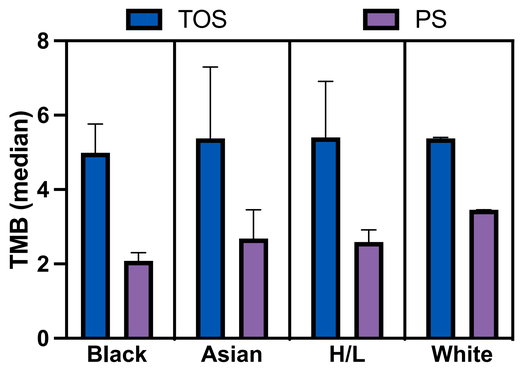


Figure 2. TMB for each racial group across urinary tract cancer



- Among 2,806 urothelial cancer patients (5% Black (B), 2% Asian (A), 4% Hispanic/Latino (H/L), 89% White (W), 1,666 had PS, and 1,140 had TOS performed.
- Median TMB for B, A, H/L, and W patients was 3.5, 3, 3.5 and 4.2 (within group p<0.0001), respectively in patients with PS, and 6.1, 7.3, 6.9 and 5.6 (within group p<0.0001), in patients with TOS.
- Comparisons across PS and TOS were highly significant (p<0.0001, except in H/L which was p<001). The absolute difference in median TMB was 2.7, 4.2, 3.5 and 1.4, respectively.

Figure 3. TMB for each racial group across endometrial cancer



- Among 3,084 endometrial cancer patients (9% Black (B), 3% Asian (A), 5% Hispanic/Latino (H/L), 84% White (W), 1,955 had PS, and 1,129 had TOS performed.
- Median TMB for B, A, H/L and W patients was 2.9, 2, 2.6 and 3.5 (within group p<0.0001), respectively in patients with PS, and 5.4, 5, 5.4 and 3.5 (within group p<0.001), in patients with TOS.
- Comparisons across PS and TOS were highly significant (p<0.0001). The absolute difference in median TMB was 2.5, 2.9, 2.8 and 1.9, respectively.

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