Conclusions Several human esophageal adenocarcinoma models were successfully established, primarily from endoscopic biopsy of treatment-naïve patients as neoadjuvant therapy proved to be a significant barrier. These models will be useful to explore GUCY2C-directed CAR-T cell therapies and other novel therapies targeting intestine-like esophageal cancer, prior to testing in early-phase clinical trials.

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Ethics Approval The study was approved by the Thomas Jefferson University Institutional Review Board (#18D.495) and Institutional Animal Care and use Committee (#01529).

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740 BIOMARKERS DIVERGING BETWEEN TUMOR MUTATION BURDEN AND MICROSATELLITE INSTABILITY

Background DNA repair is a critical process to maintain DNA integrity. It is conducted by distinct pathways of genes, many of whose alterations are thought to result in genomic instability and hypermutability, ultimately contributing to tumorigenesis. Tumor Mutation Burden (TMB) and Microsatellite Instability (MSI) are considered as efficacy biomarkers for immunotherapy.1,2 However, there has been little characterization of the association between DNA repair genes and TMB/MSI in cancer. This study aims to further understand DNA repair genes and evaluate the contribution of their alteration to TMB and MSI.

Methods We systematically analyzed 282 DNA repair genes involved in 20 DNA repair pathways. These genes were evaluated for mutations based on 274 sequenced colorectal tumor samples from the TCGA database. The functional impacts of these mutations were analyzed, and only damaging mutations were used for the subsequent analysis. The most frequently mutated genes were identified. The association between the damaging mutations and TMB/MSI status was calculated for each gene, and the significant genes were subject to further pathway enrichment analysis. We also compared the gene expression between TMB high and low as well as between MSI-H and MSI-L/MSS for each gene based on their RNAseq data. The potential associations with TMB/MSI high phenotypes were evaluated.

Results 94 genes were identified to be significantly mutated in TMB high, including all of the 26 genes that were significant in MSI-H. The genes are enriched in multiple pathways, including Fanconi anemia, Base excision repair, and Mismatch repair. At the expression level, 28 genes are significantly upregulated in TMB high and MSI-H compared to TMB low and MSI-L/MSS, respectively. The expression changes of these genes were validated using expression data from TCGA.

Conclusions Several human esophageal adenocarcinoma models were successfully established, primarily from endoscopic biopsy of treatment-naïve patients as neoadjuvant therapy proved to be a significant barrier. These models will be useful to explore GUCY2C-directed CAR-T cell therapies and other novel therapies targeting intestine-like esophageal cancer, prior to testing in early-phase clinical trials.

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including POLE, were identified that are significantly mutated in TMB-high samples compared to MSI-H samples (table 1). Loss of function of these genes may result in an ultra-mutated phenotype. Contradicting the notion that POLE mutation in a subset of cancer patients with intact MMR, were identified that are significantly mutated in TMB-high samples as compared to MSI-H samples (table 1). Loss of function of these genes may result in an ultra-mutated phenotype. Contradicting the notion that POLE mutation in a subset of cancer patients with intact MMR, 4–6 we found about half of POLE-mutant samples (8/16) were MSI high, five of which had MMR mutations (figure 2).

Conclusions The study investigated the association of DNA repair genes with TMB and MSI. We compared genes significantly altered in TMB high and MSI-H samples and identified genes pointing to a potential mechanism that induces ultra-mutation in a subset of cancer patients with intact MMR, which can serve as potential biomarkers for immunotherapy efficacy linked with high TMB.

### REFERENCES


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### Abstract 740 Table 1

<table>
<thead>
<tr>
<th>Gene</th>
<th>P Value</th>
<th>Number of Samples</th>
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<tr>
<td>POLE</td>
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<tr>
<td>ATR</td>
<td>0.0090</td>
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<tr>
<td>EZH2</td>
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<td>ATM</td>
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<tr>
<td>HSP90B1</td>
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<tr>
<td>BRIP1</td>
<td>0.0406</td>
<td>8</td>
</tr>
<tr>
<td>ERCC3</td>
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</tr>
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<td>POLI</td>
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</tr>
<tr>
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</tr>
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</table>

### Abstract 740 Figure 2

MLH1 expressed significantly lower in MSI-H samples

Background The skull base is the location of a wide variety of malignant tumors. Among them is sinonasal undifferentiated carcinoma (SNUC), a highly aggressive sinonasal neoplasm that was recently reclassified into subgroups of high-grade carcinomas with unique genomic events (e.g., SMARC-deficient carcinoma, nuclear protein in testis NUT carcinoma). Other high-grade carcinomas in this location are neuroendocrine carcinomas, sinonasal adenocarcinomas, and teratocarcinosarcomas. Given the rarity of these tumors, little transcriptomic data is available. The aim of this study was to characterize the immune-oncology gene expression profile in SNUC and other high-grade sinonasal carcinomas.

Methods Next-generation sequencing was performed in 30 high-grade sinonasal carcinoma samples using the HTG Edge-Seq Immuno-Oncology Panel. Ingenuity pathway analysis was performed to understand the immunobiology, signaling, and functional perturbations during tumor development.

Results The samples were divided into 3 groups: 21 SNUCs and SMARC-deficient sinonasal carcinomas; 5 high-grade neuroendocrine carcinomas (HGNECs), with small cell and large cell variants; and 4 high-grade sinonasal carcinomas (HGSNCs) of mixed histology (1 NUT carcinoma, 1 teratocarcinosarcoma, and 2 sinonasal adenocarcinomas). PRAME and ASCL1 emerged as upregulated transcripts with strong protein validation for SNUC and HGNECs; other upregulated candidates EZH2 and BRCA1 offer consideration for alternative targeted therapy, and downregulation of major histocompatibility complex molecules and chemokines represent another hurdle in the development of effective immunotherapy.

Conclusions This immune-oncology gene expression analysis of 3 groups of high-grade sinonasal carcinoma with emphasis on SNUC identified a number of differentially expressed transcripts reflecting effects on tumorigenesis. Identification of immune pathways should be further investigated for possible integration of immunotherapy into a multidisciplinary approach to these cancers and personalized treatment.

Ethics Approval MD Anderson Cancer Center Institutional Review Board approval was obtained prior to the start of the study.

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