# Molecular characteristics of early-onset versus average-onset gastroesophageal adenocarcinoma

Amit Mahipal[1], Emily A. Teslow[2], Yingying Yu[2], Binyam Yilma[2], Stamatina Fragkogianni[2], Melissa C. Stoppler[2], Zhaohui Jin[3]

[1]Department of Oncology, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH, [2]Tempus AI Inc., Chicago, IL, [3]Department of Oncology, Mayo Clinic, Rochester MN

## Background

- Incidence of early-onset gastroesophageal adenocarcinoma (eoGEA, ages <50 years) has been increasing in the United States since the 1990s
- The etiology of which is still unclear, and limited data exists on molecular drivers.
- This study evaluates somatic and germline profiles in eoGEA compared to average-onset GEA (aoGEA, ages≥ 50 years)

## Methods

\+ *Tempus xT assay

**Inclusion criteria**:
- Patients with esophageal, gastroesophageal junction, and gastric adenocarcinoma of all stages
- Tested between 12/2017 and 07/2024

Retrospective review of deidentified patient data for
- Biomarkers
- Somatic and germline alterations

***Tempus xT assay** - A targeted panel that detects single nucleotide variants, insertions and/or deletions, and copy number variants in 598-648 genes, as well as chromosomal rearrangements in 22 genes with high sensitivity and specificity

## Acknowledgements

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## Conclusion

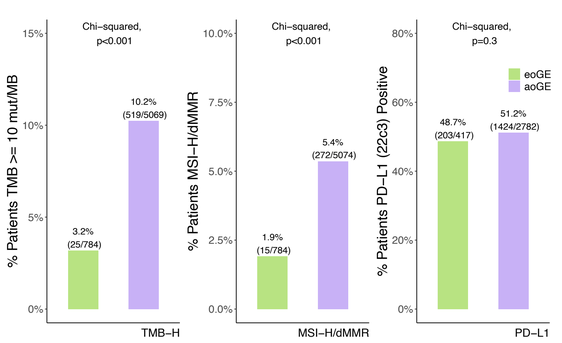
eoGEA has a unique somatic and germline mutation profile compared to aoGEA. Germline mutations were identified in only 1% of eoCRC, and in <1% aoCRC, suggesting predominant somatic and/or epigenetic origin.

## Results

**Table 1.** Cohort Demographics

| Characteristic | eoGE N = 785[1] | aoGE N = 5,078[1] | p-value[2] |
|---|---|---|---|
| Age at Primary Diagnosis | | | <0.001 |
| Median (Q1, Q3) | 43 (38, 47) | 68 (61, 74) | |
| Min, Max | 17, 50 | 50, 89 | |
| Sex | | | <0.001 |
| Male | 509 (65%) | 3,798 (75%) | |
| Female | 276 (35%) | 1,280 (25%) | |
| Race | | | <0.001 |
| White | 280 (69%) | 2,347 (80%) | |
| Black or African American | 49 (12%) | 246 (8.3%) | |
| Other Race | 57 (14%) | 230 (7.8%) | |
| Asian | 21 (5.2%) | 129 (4.4%) | |
| Unknown | 378 | 2,126 | |
| Ethnicity | | | <0.001 |
| Not Hispanic or Latino | 206 (60%) | 1,768 (86%) | |
| Hispanic or Latino | 135 (40%) | 294 (14%) | |
| Unknown | 444 | 3,016 | |
| Disease stage | | | 0.073 |
| IV | 495 (85%) | 2,833 (81%) | |
| III | 62 (11%) | 442 (12%) | |
| II | 17 (2.9%) | 179 (5.1%) | |
| I | 6(1.0%) | 37 (1.0%) | |
| Unknown | 205 | 1,537 | |
| Tumor site | | | <0.001 |
| Stomach | 462 (59%) | 1,830 (36%) | |
| Esophageal | 171 (22%) | 1,982 (39%) | |
| Cardua structure | 152 (19%) | 1,266 (25%) | |

[1] n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test



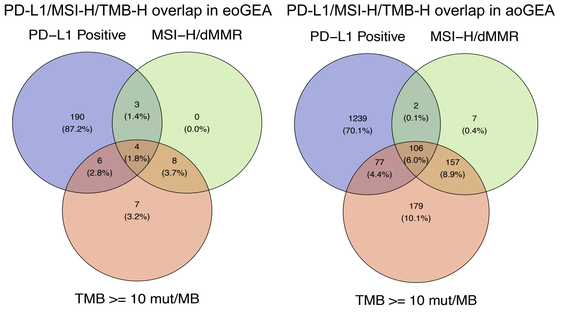




**Figure 1.** Immunological biomarkers and percentage of patients with TMB-H, MSIH/dMMR, and PD-L1 high. TMB-H was defined at greater than 10 mut/Mb. The rates of three markers were assessed for any overlap among aoGE and eoGE.

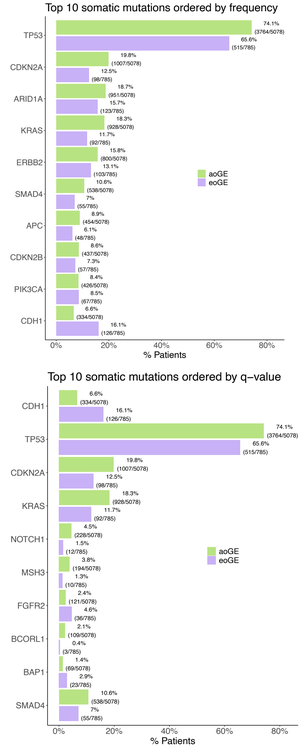



**Figure 2.** Top 10 somatic mutations by frequency (top) and q-value (bottom)

**Table 2.** Top 10 somatic mutations in eoGEA & aoGEA

| Genes | eoGE N = 785[1] | aoGE N = 5,078[1] | p-value[2] | q-value[3] |
|---|---|---|---|---|
| *CDH1* | 126 (16%) | 334 (6.6%) | <0.001 | <0.001 |
| *TP53* | 515 (66%) | 3,764 (74%) | <0.001 | <0.001 |
| *CDKN2A* | 101 (13%) | 1,011 (20%) | <0.001 | <0.001 |
| *KRAS* | 92 (12%) | 931 (18%) | <0.001 | <0.001 |
| *NOTCH1* | 12 (1.5%) | 228 (4.5%) | <0.001 | 0.002 |
| *FGFR2* | 37 (4.7%) | 121 (2.4%) | <0.001 | 0.003 |
| *MSH3* | 10 (1.3%) | 194 (3.8%) | <0.001 | 0.004 |
| *BCORL1* | 3 (0.4%) | 109 (2.1%) | <0.001 | 0.010 |
| *BAP1* | 23 (2.9%) | 69 (1.4%) | <0.001 | 0.012 |
| *SMAD4* | 55 (7.0%) | 538 (11%) | 0.002 | 0.020 |

**Table 3.** Top 10 germline mutations in eoGEA and aoGEA

| Genes | eoGE N = 464[1] | aoGE N = 2,822[1] | p-value[2] | q-value[3] |
|---|---|---|---|---|
| *CDH1* | 10 (2.2%) | 8 (0.3%) | <0.001 | 0.001 |
| *TP53* | 3 (0.6%) | 0 (0%) | 0.003 | 0.039 |
| *BRCA2* | 2 (0.4%) | 38 (1.3%) | 0.10 | 0.6 |
| *BRIP1* | 4 (0.9%) | 10 (0.4%) | 0.12 | 0.6 |
| *SDHD* | 1 (0.2%) | 0 (0%) | 0.14 | 0.6 |
| *VHL* | 1 (0.2%) | 0 (0%) | 0.14 | 0.6 |
| *ATM* | 9 (1.9%) | 32 (1.1%) | 0.15 | 0.6 |
| *APC* | 2 (0.4%) | 4 (0.1%) | 0.2 | 0.7 |
| *CHEK2* | 4 (0.9%) | 17 (0.6%) | 0.5 | >0.9 |
| *MSH2* | 1 (0.2%) | 4 (0.1%) | 0.5 | >0.9 |