Abstract 3536

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# Genomic landscapes of early-onset versus average-onset colorectal cancer populations

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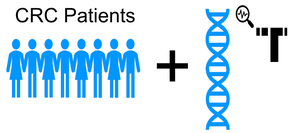
## INTRODUCTION

- Early-onset colorectal cancer (eoCRC, initial CRC diagnosis at age <50 years) has been increasing in the past two decades.
- This study evaluates somatic and germline profiles in eoCRC compared to average-onset CRC (aoCRC, initial CRC diagnosis at age ≥ 50 years).

## METHODS




Inclusion Criteria:
- CRC tumors of all stages
- Tumors with sidedness known
- Tested from 2017 - 2022

Retrospective review of deidentified patient data:
- Immune 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.

## ACKNOWLEDGMENTS

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## SUMMARY

- eoCRC has a **unique mutational profile. Germline mutations were identified in 6.9% of eoCRC, and in 5% aoCRC**, indicating a potential role for universal germline testing in CRC.

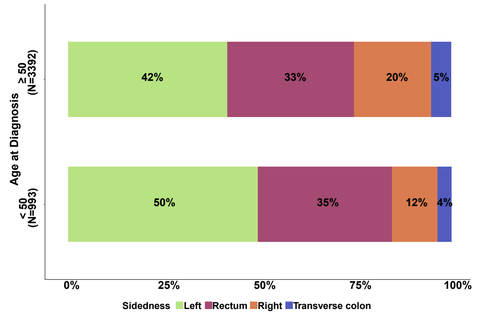
## RESULTS

**Table 1.** Cohort Demographics

| Characteristic | < 50, N = 2,379[1] | ≥ 50, N = 8,627[1] | p-value[2] |
|---|---|---|---|
| **Age at Diagnosis** | | | |
| Median (IQR) | 43 (38, 47) | 64 (57, 72) | |
| **Gender** | | | <0.001 |
| Male | 1,275 (54%) | 4,967 (58%) | |
| **Race** | | | <0.001 |
| White | 931 (72%) | 3,992 (77%) | |
| Black | 187 (14%) | 666 (13%) | |
| Other | 109 (8.4%) | 316 (6.1%) | |
| Asian | 67 (5.2%) | 203 (3.9%) | |
| Unknown | 1,085 | 3,450 | |
| **Stage*** | | | 0.030 |
| Stage 4 | 1,389 (81%) | 5,278 (80%) | |
| Stage 3 | 245 (14%) | 917 (14%) | |
| Stage 2 | 63 (3.7%) | 361 (5.5%) | |
| Stage 1 | 14 (0.8%) | 51 (0.8%) | |
| Unknown | 668 | 2,020 | |

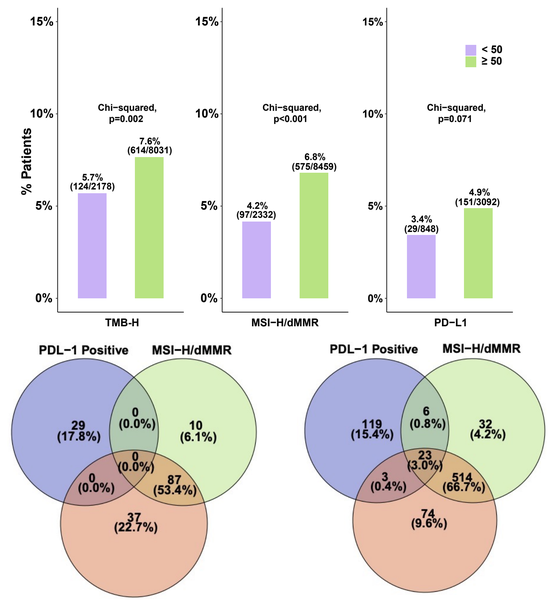
*Within 60 days of sample collection; [1]n (%); [2]Wilcoxon rank sum test; Pearson's Chi-squared test

**Figure 1.** Sidedness of CRC According to Age at Diagnosis




Left-sided primaries were more common in eoCRC. (85% left/rectum in eoCRC vs. 75% left/rectum in aoCRC (p<0.001)) Figure restricted to patients with colorectal tissue sequenced.

**Figure 2.** Immunological Markers




**(a)** Percentage of patients with TMB-H, MSI-H/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 aoCRC and eoCRC. It was found that the rates of microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) were lower in **(b)** eoCRC compared to **(c)** aoCRC (4.2% vs. 6.8%, p<0.001).

**Table 2.** Germline Mutations

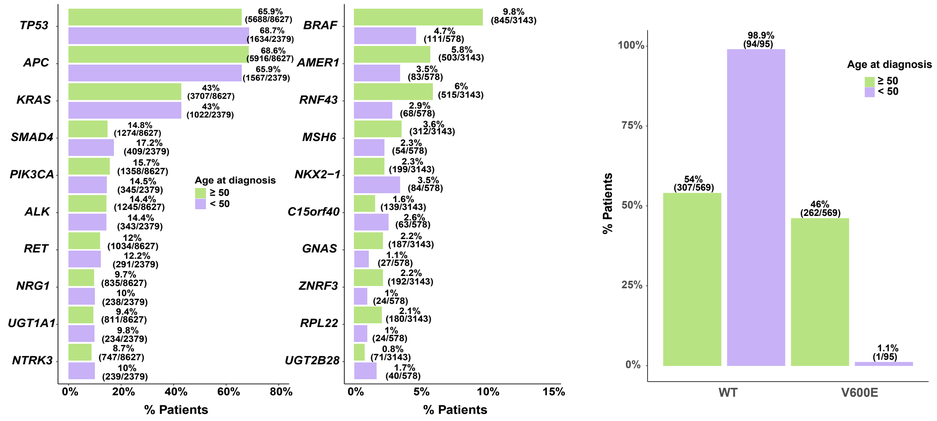
| Characteristic | <50, N = 1,413[1] | ≥ 50, N = 4,898[1] | p-value[2] | q-value[3] |
|---|---|---|---|---|
| *TP53* | 5 (0.4%) | 2 (<0.1%) | 0.008 | 0.2 |
| *APC* | 9 (0.6%) | 11 (0.2%) | 0.027 | 0.4 |
| *ATM* | 11 (0.8%) | 19 (0.4%) | 0.060 | 0.4 |
| *RAD51C* | 4 (0.3%) | 3 (<0.1%) | 0.049 | 0.4 |
| *MUTYH* | 18 (1.3%) | 84 (1.7%) | 0.2 | 0.6 |
| *MSH2* | 5 (0.4%) | 8 (0.2%) | 0.2 | 0.6 |
| *BRIP1* | 4 (0.3%) | 5 (0.1%) | 0.12 | 0.6 |
| *MSH3* | 4 (0.3%) | 6 (0.1%) | 0.2 | 0.6 |
| *RAD51D* | 3 (0.2%) | 4 (<0.1%) | 0.2 | 0.6 |
| *FH* | 2 (0.1%) | 2 (<0.1%) | 0.2 | 0.6 |

| Characteristic | N = 1,413[1] |
|---|---|
| *MUTYH* | 18 (1.3%) |
| *ATM* | 11 (0.8%) |
| *APC* | 9 (0.6%) |
| *CHEK2* | 7 (0.5%) |
| *BRCA2* | 6 (0.4%) |
| *MSH2* | 5 (0.4%) |
| *TP53* | 5 (0.4%) |
| *BRIP1* | 4 (0.3%) |
| *MLH1* | 4 (0.3%) |
| *MSH3* | 4 (0.3%) |

| Characteristic | N = 4,898[1] |
|---|---|
| *MUTYH* | 84 (1.7%) |
| *CHEK2* | 21 (0.4%) |
| *ATM* | 19 (0.4%) |
| *BRCA2* | 14 (0.3%) |
| *MSH6* | 13 (0.3%) |
| *MLH1* | 12 (0.2%) |
| *PMS2* | 12 (0.2%) |
| *APC* | 11 (0.2%) |
| *BRCA1* | 9 (0.2%) |
| *MSH2* | 8 (0.2%) |

**(top)** Top germline mutations among all patients. **(left)** Age at diagnosis: < 50 **(right)** Age at diagnosis: > 50

**Figure 3.** Mutational Profile by Age at Diagnosis




**(a)**Top 10 somatic mutations. **(b)** Top 10 somatic mutations by q-value. **(c)** Types of *BRAF* alterations among patients with MSI−H and/or MMR−D status and had TMB ≥ 10. There were no patients with *BRAF* CN amp and other mutation types among the eoCRC cohort.