Genomic alterations associated with early-onset and average-onset colorectal cancer

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TOPS
Tennessee Oncology Practice Society

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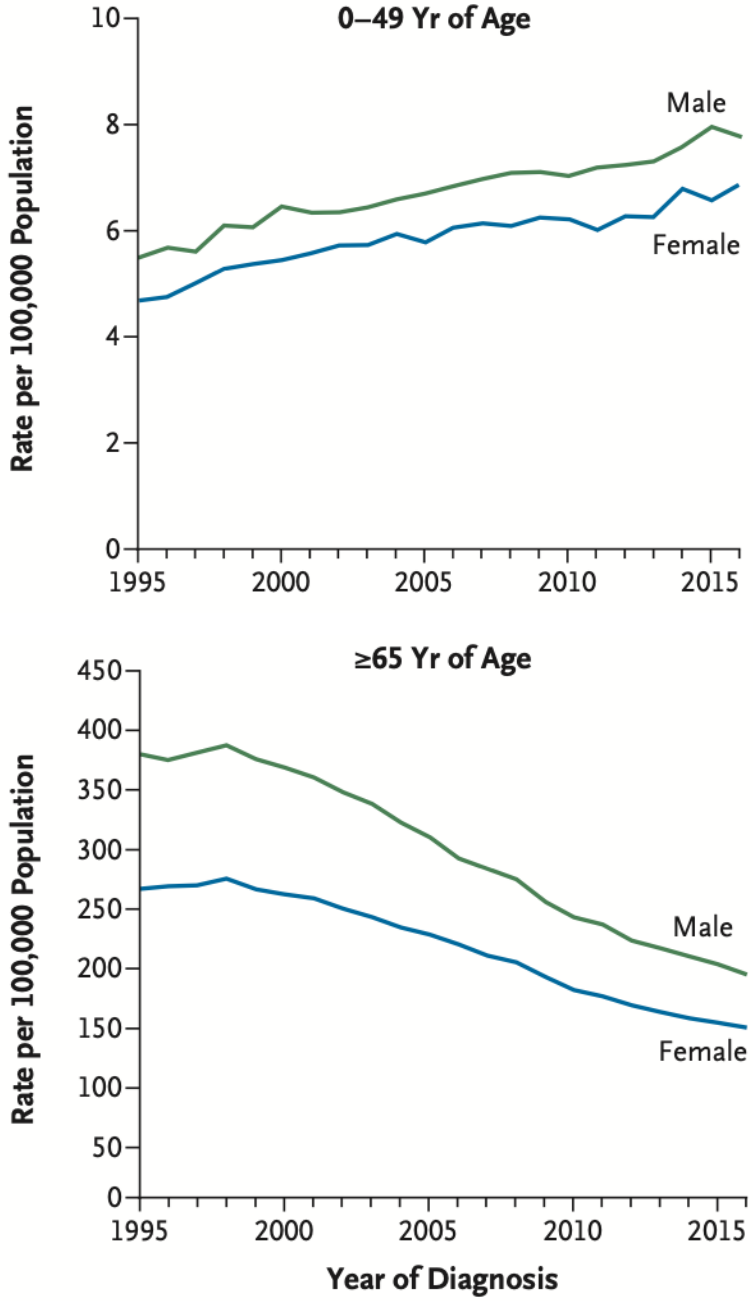
Conflicts of interest

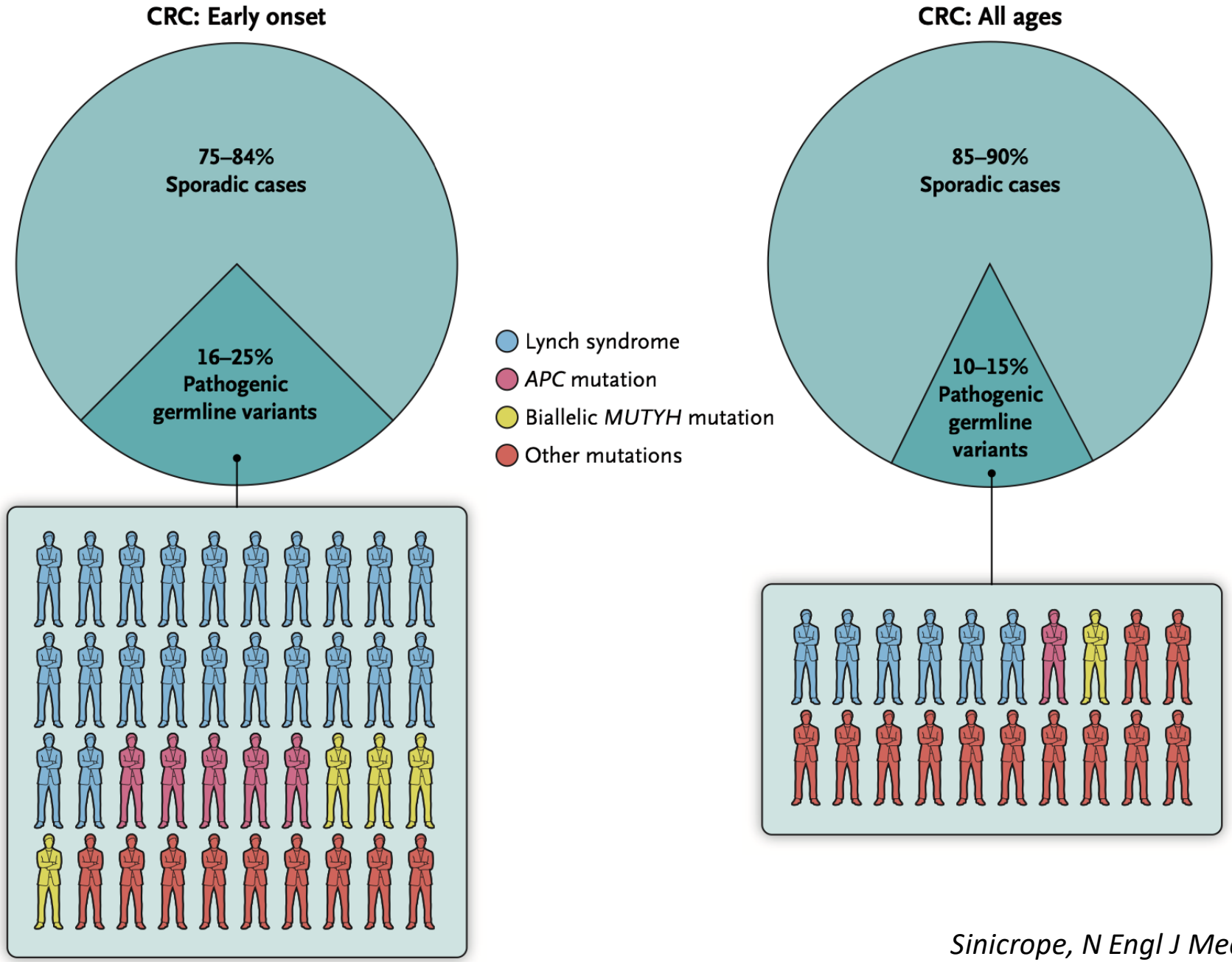
- None

Background

- Early-onset colorectal cancer (EOCRC) = Age < 50
- Average-onset colorectal cancer (AOCRC) = Age > 60
- Incidence has risen 42% over 20 years
- In 10 years, 25% of rectal and 10-12% of colon cases will be early-onset
- Causes not yet verified: Diet, antibiotics, obesity, metabolic syndrome → gut dysbiosis → chronic inflammation



Sinicrope, N Engl J Med 2022; 386:1547-1558



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Methods

13,234 patients with colorectal cancer across the United States

Whole exome sequencing (WES) from baseline tumor biopsy (Signatera, Natera Inc.)

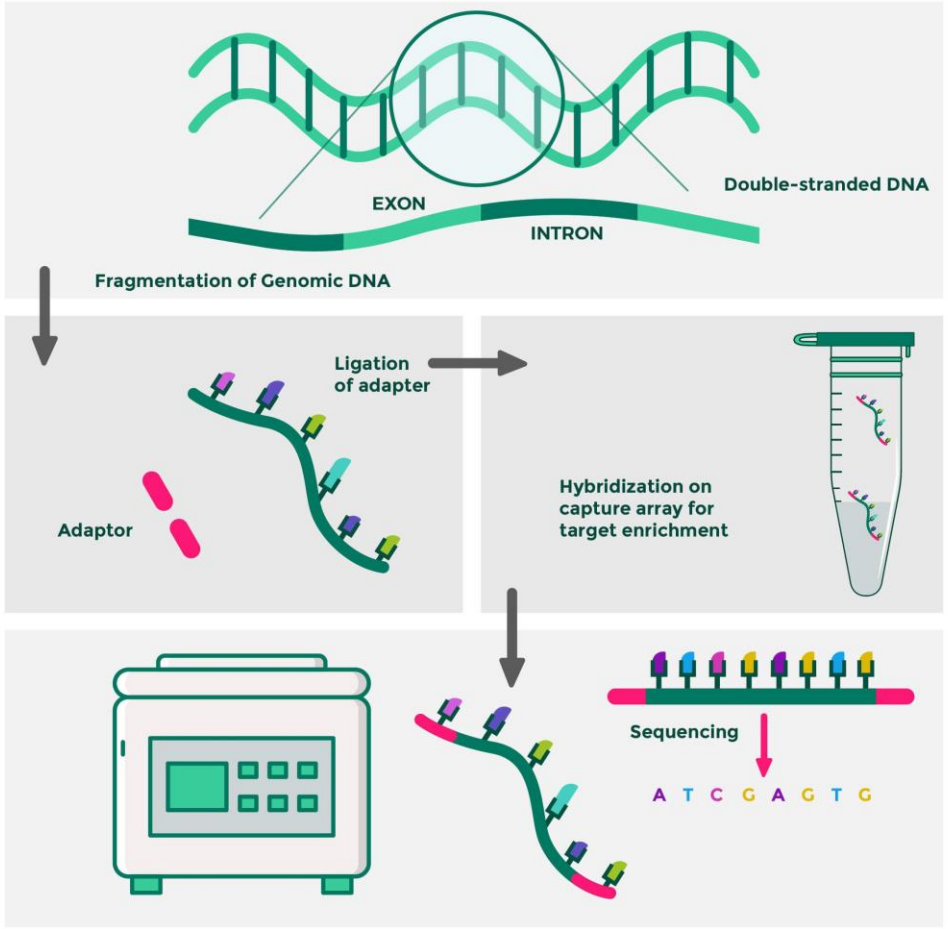
Excluded stage IV

Compare age <50 and age >60 by Fisher's exact testing

Stratify by TMB and MSI status derived from WES

Methods

1. Tumor biopsy –
whole exome sequencing



2. Assess exomes for mutations:

Lander et al., AACR 2023 Abstract #6696

Methods

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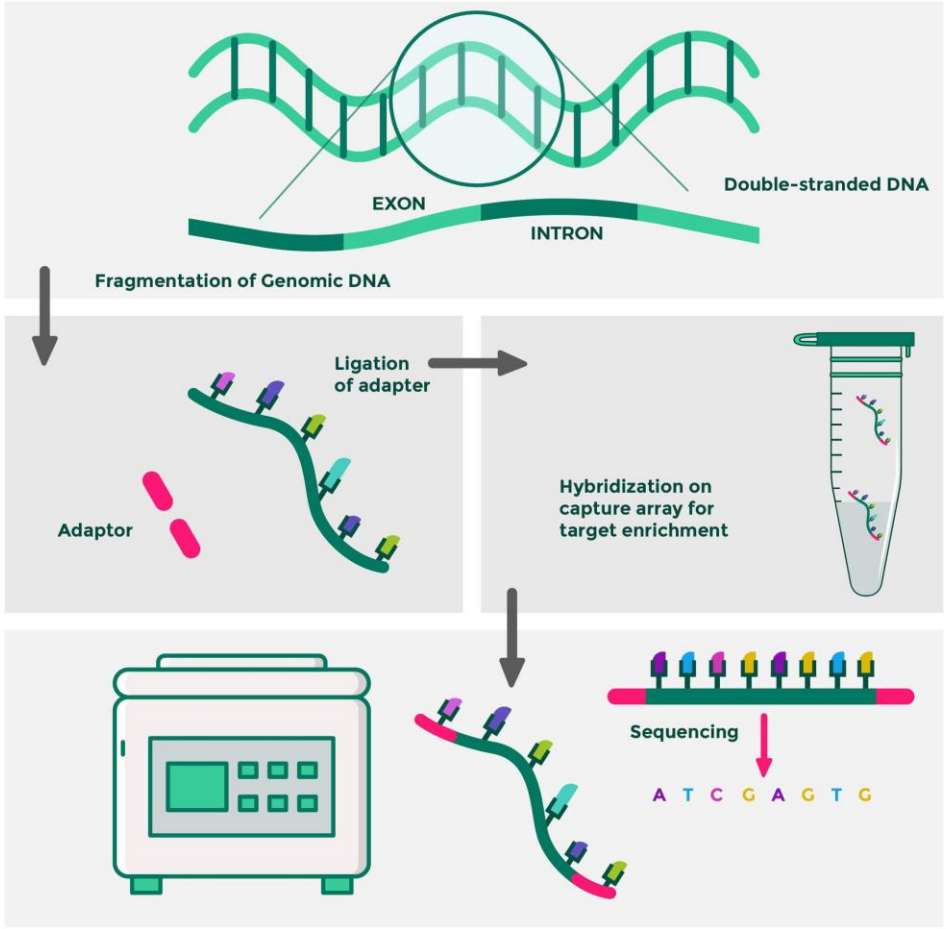
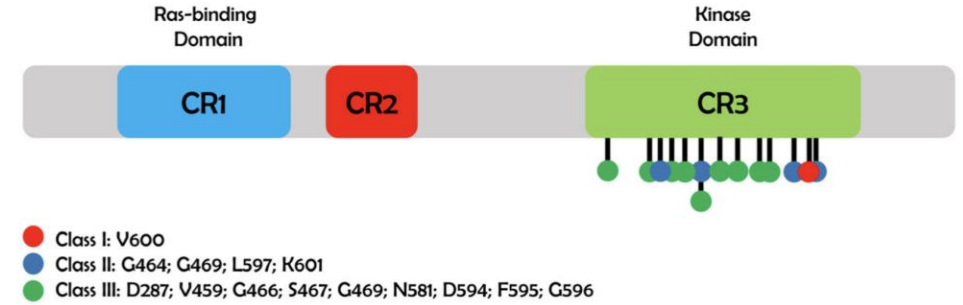
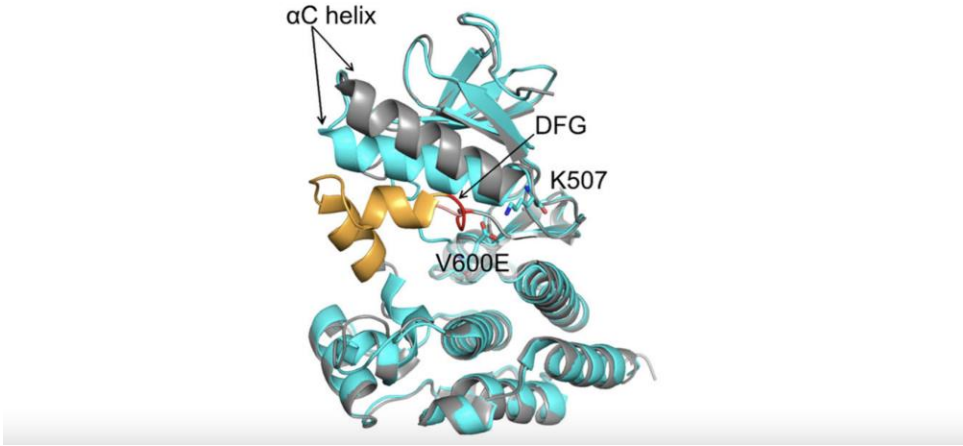


2. Assess exomes for mutations:

A) Pathogenic mutation (e.g. *BRAF V600E*)





Methods

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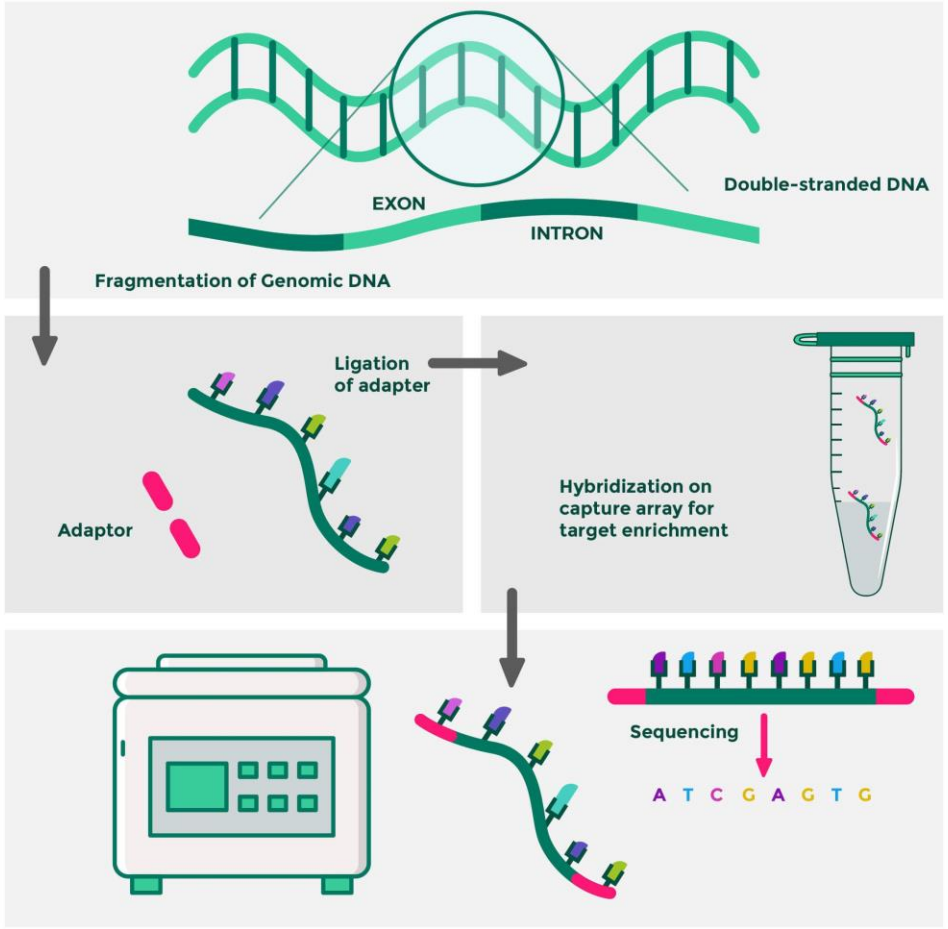
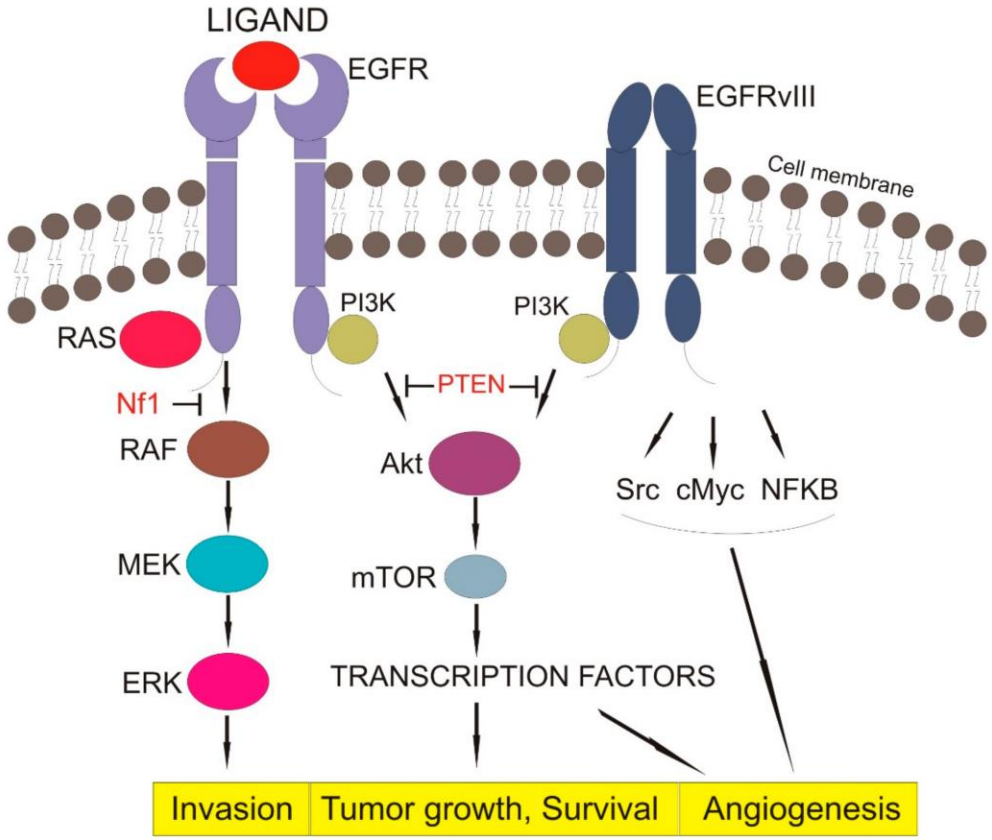
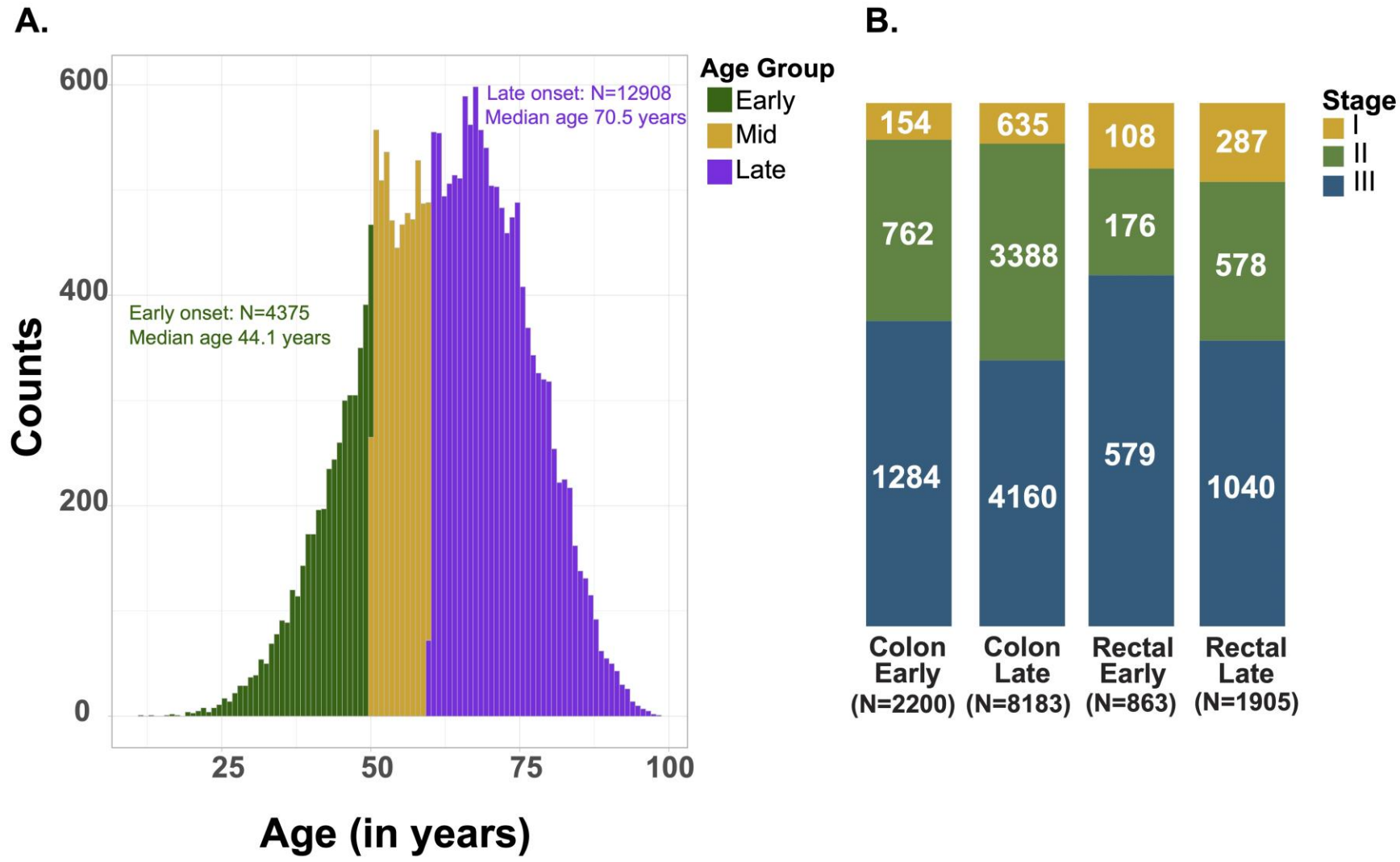


2. Assess exomes for mutations:

B) Oncogenic pathways (e.g. RTK-RAS)



Results – Baseline Characteristics



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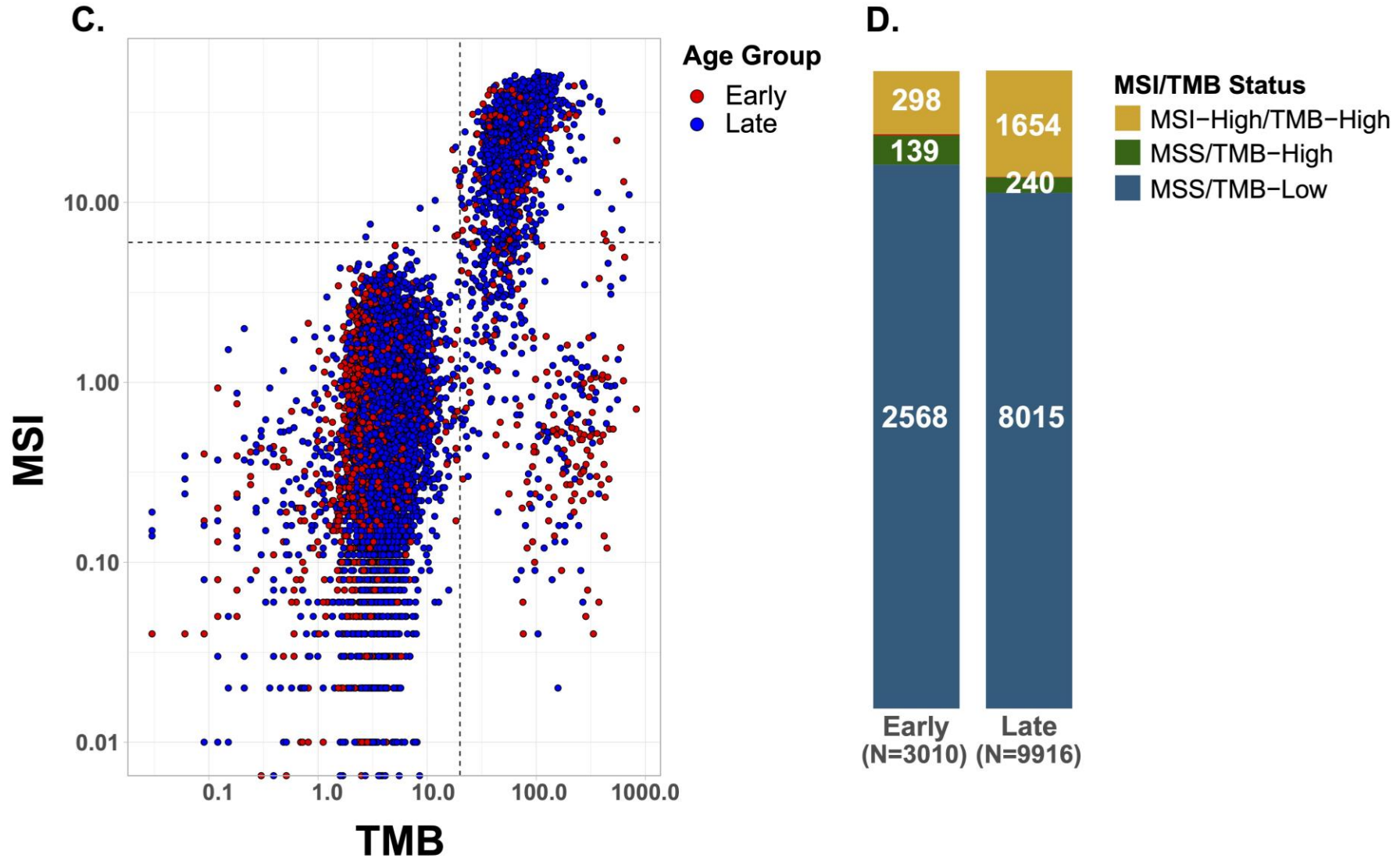
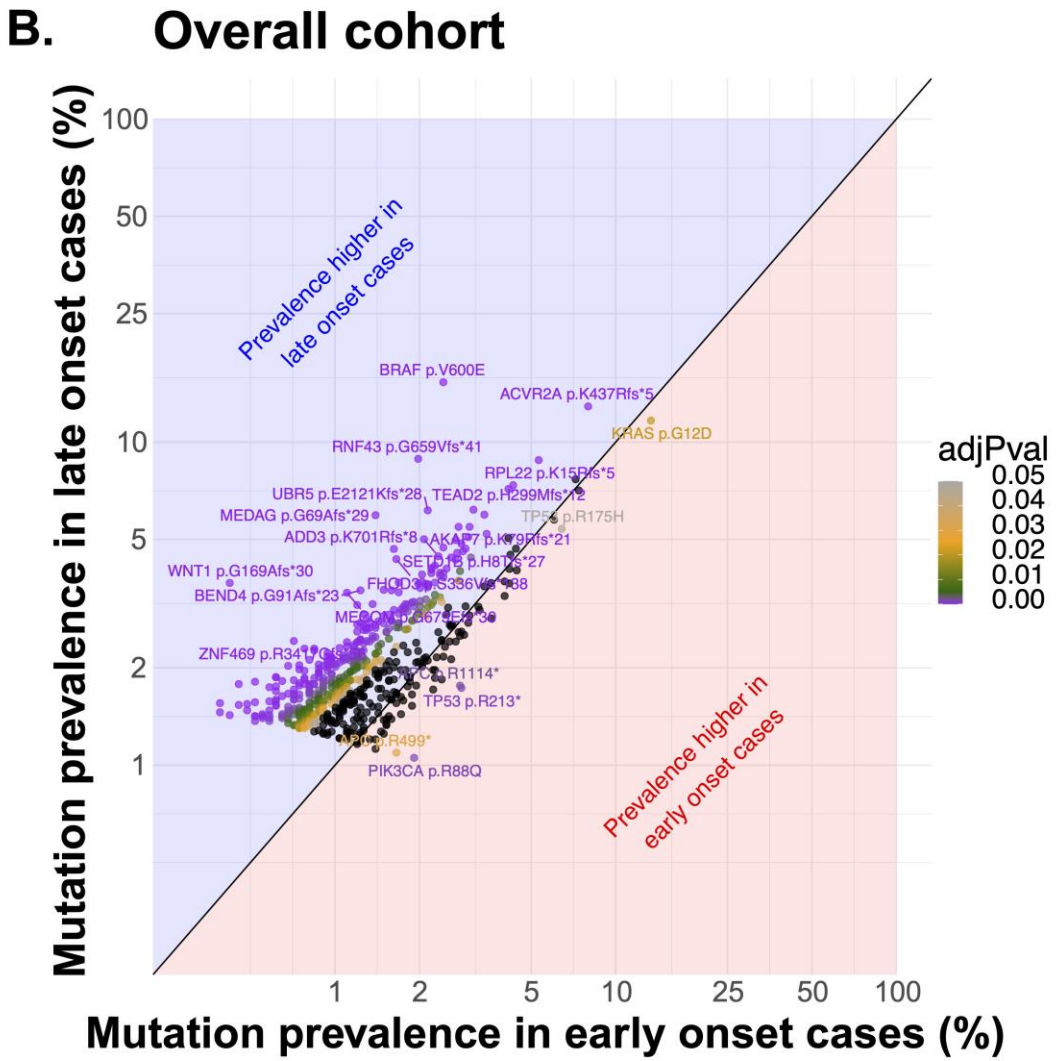
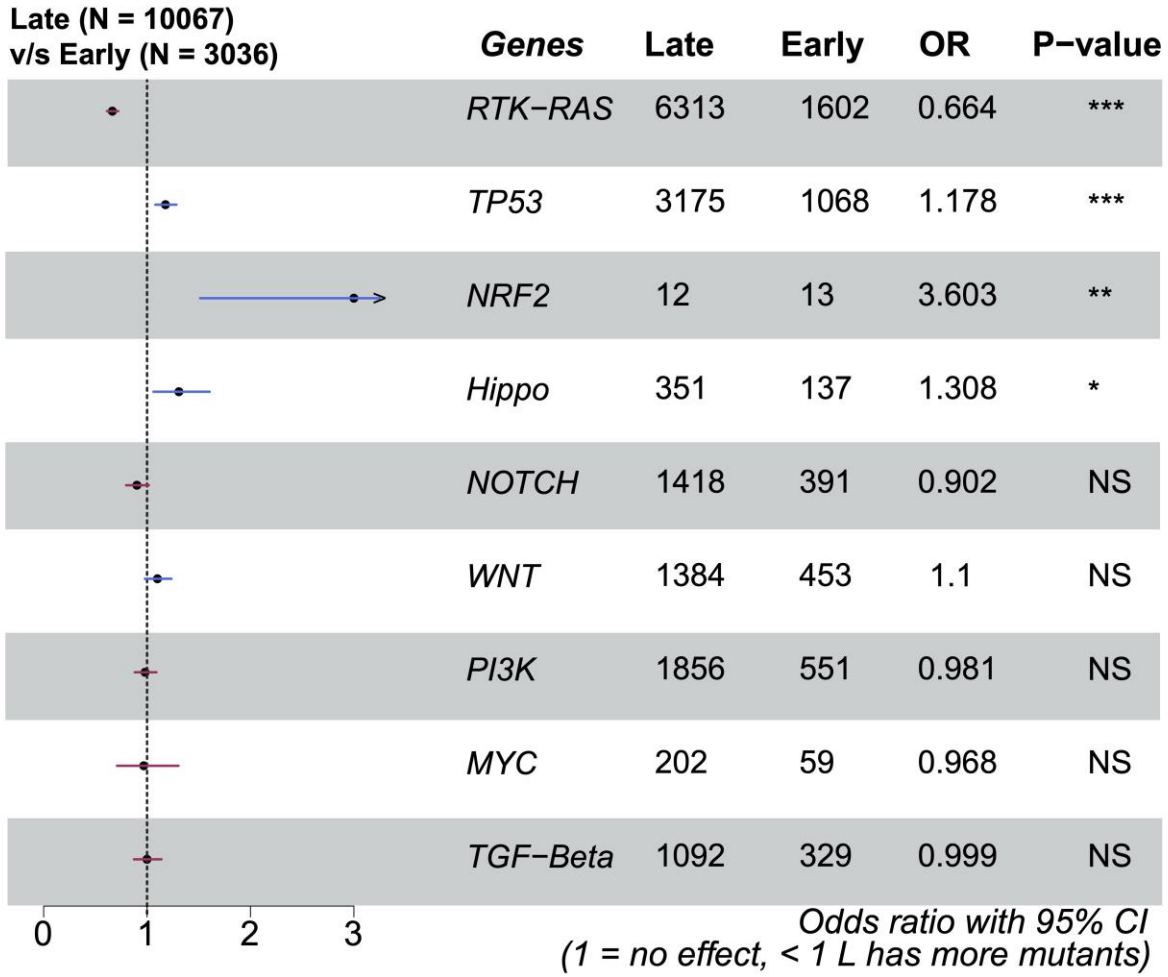


Overall cohort: *BRAF V600E* in 15% of age >60

Gene variant level

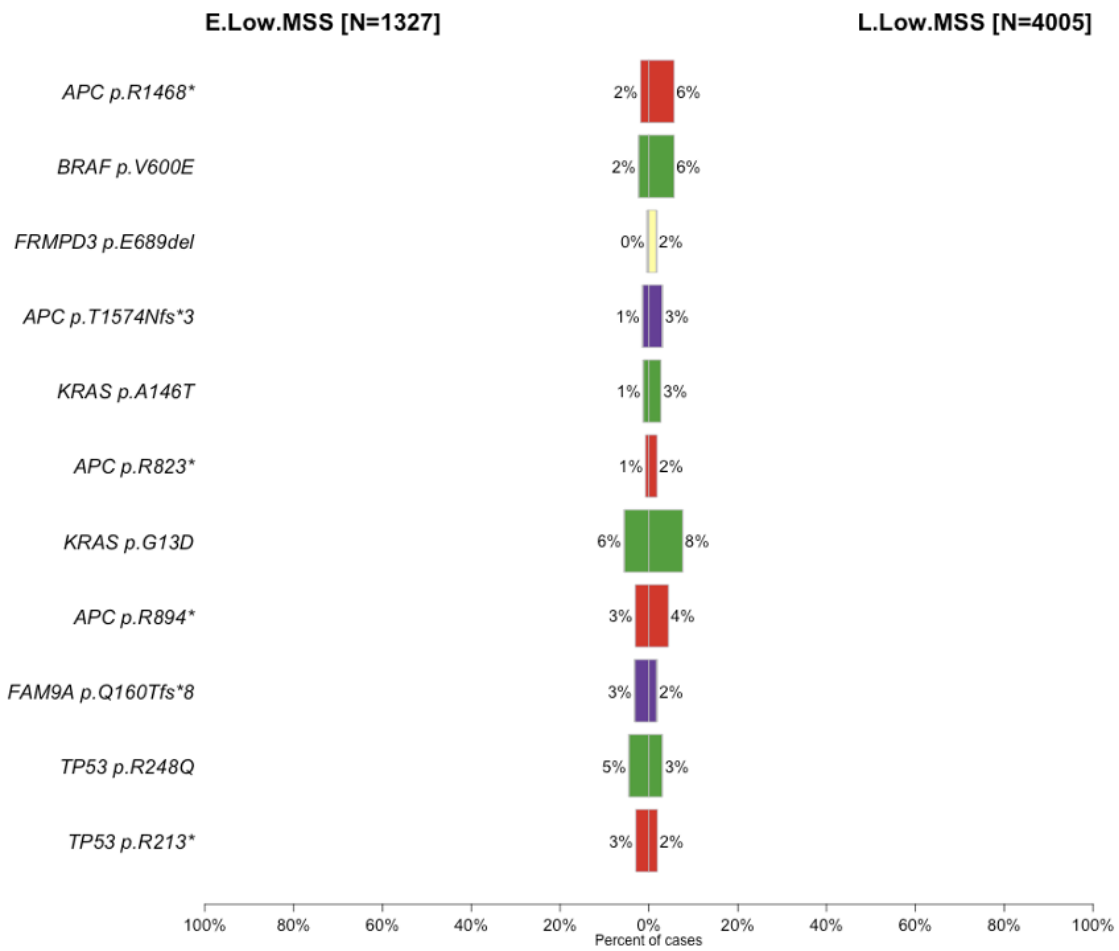


Oncogenic pathways

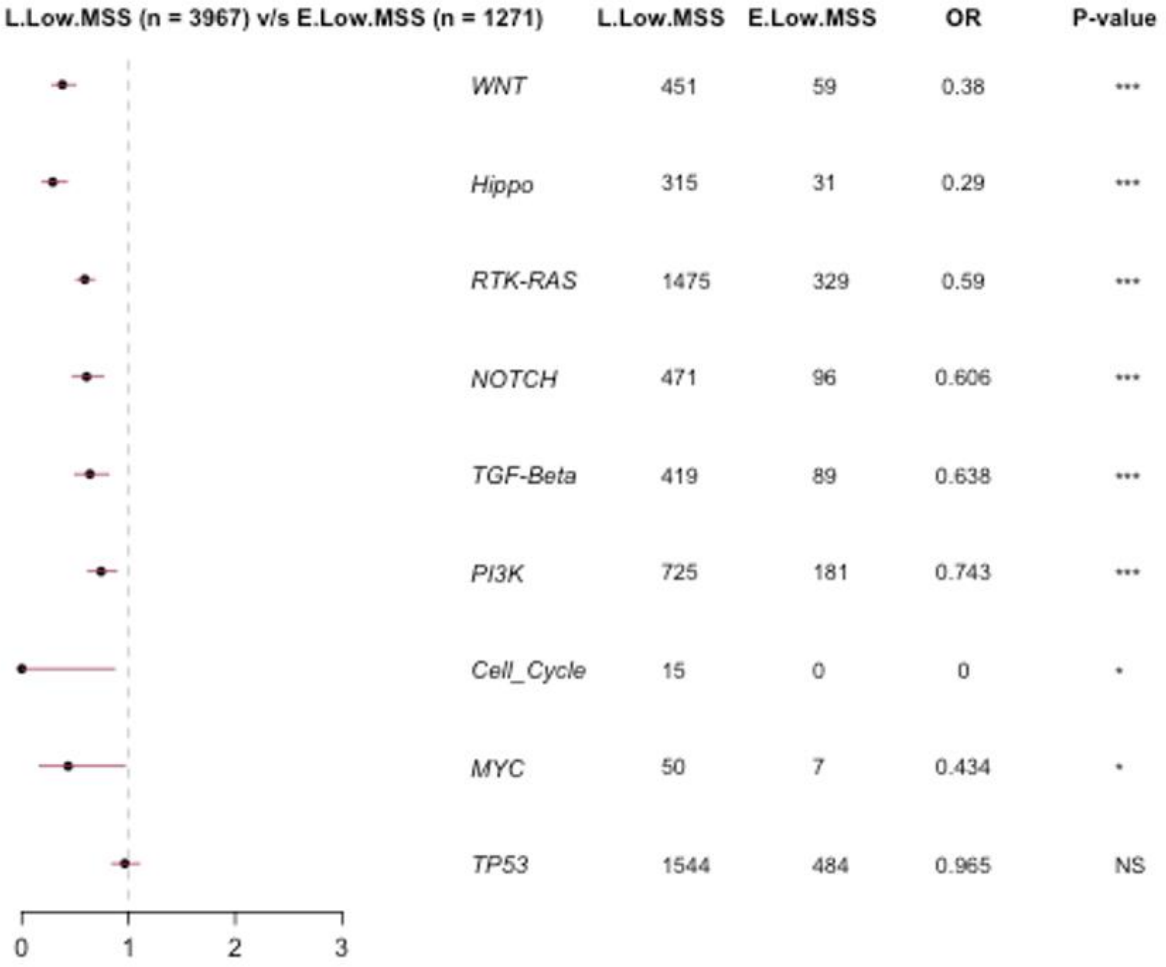


TMB-Low/MSS: EOCRC is ‘colder’ with more *TP53*

Gene variant level

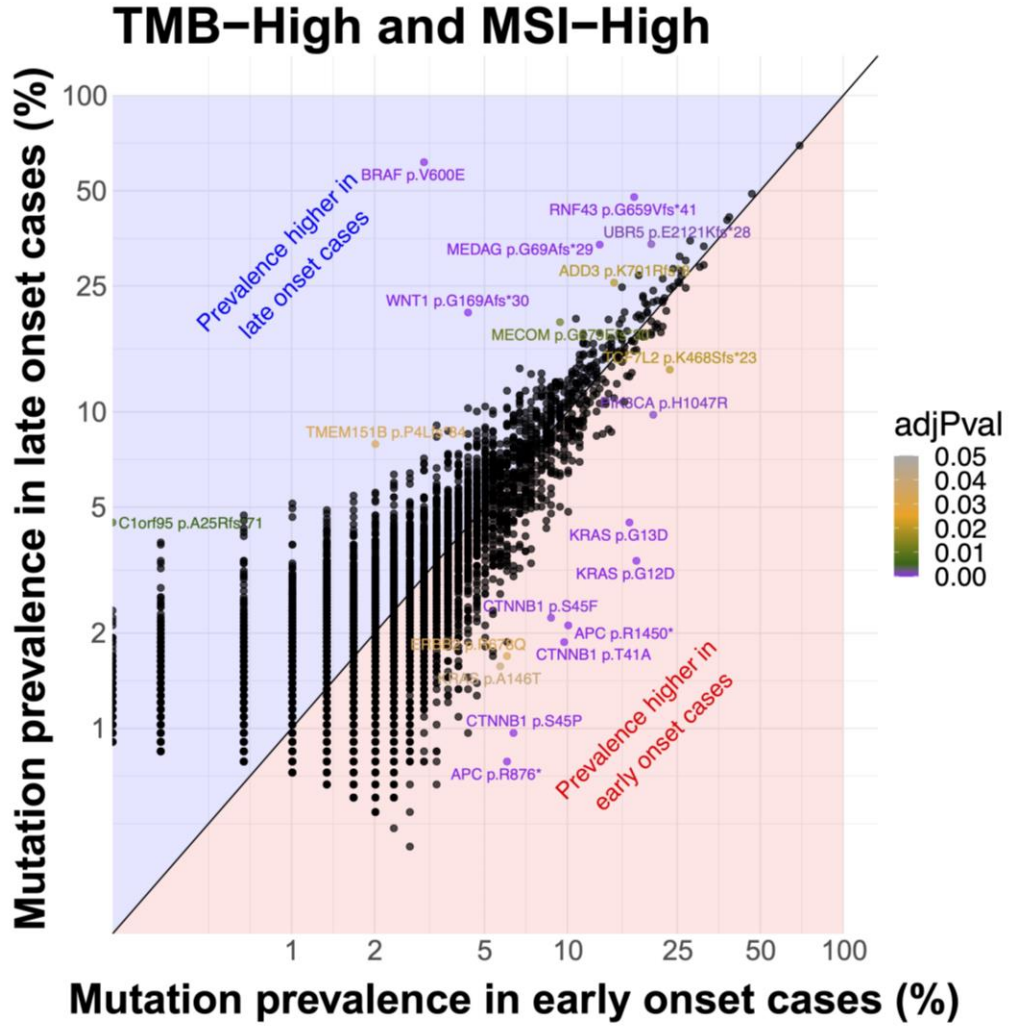


Oncogenic pathways

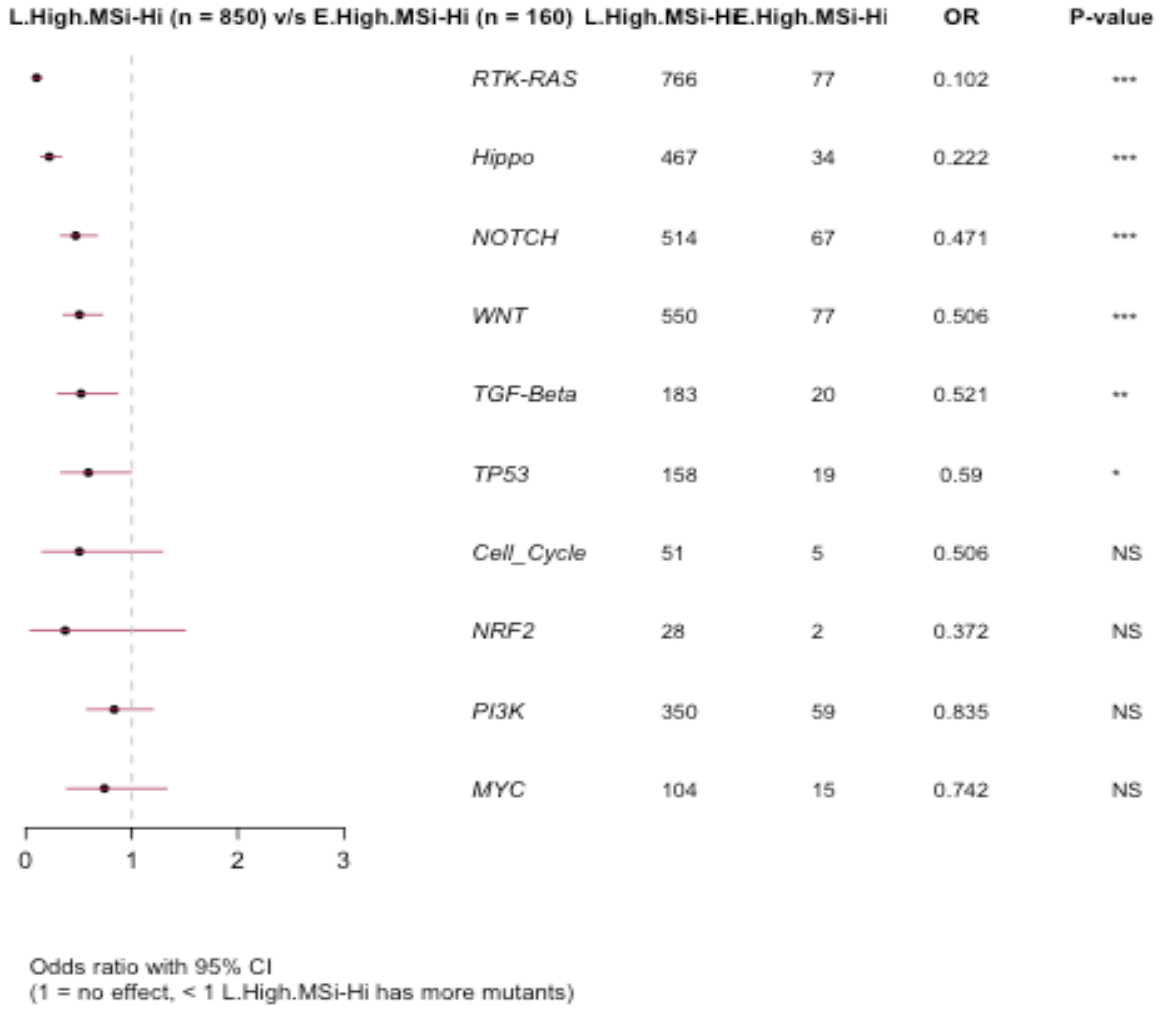


TMB-H/MSI-H: *BRAF V600E* in 60% of AOCRC
PIK3CA H1047R in 22% of EOCRC

Gene variant level

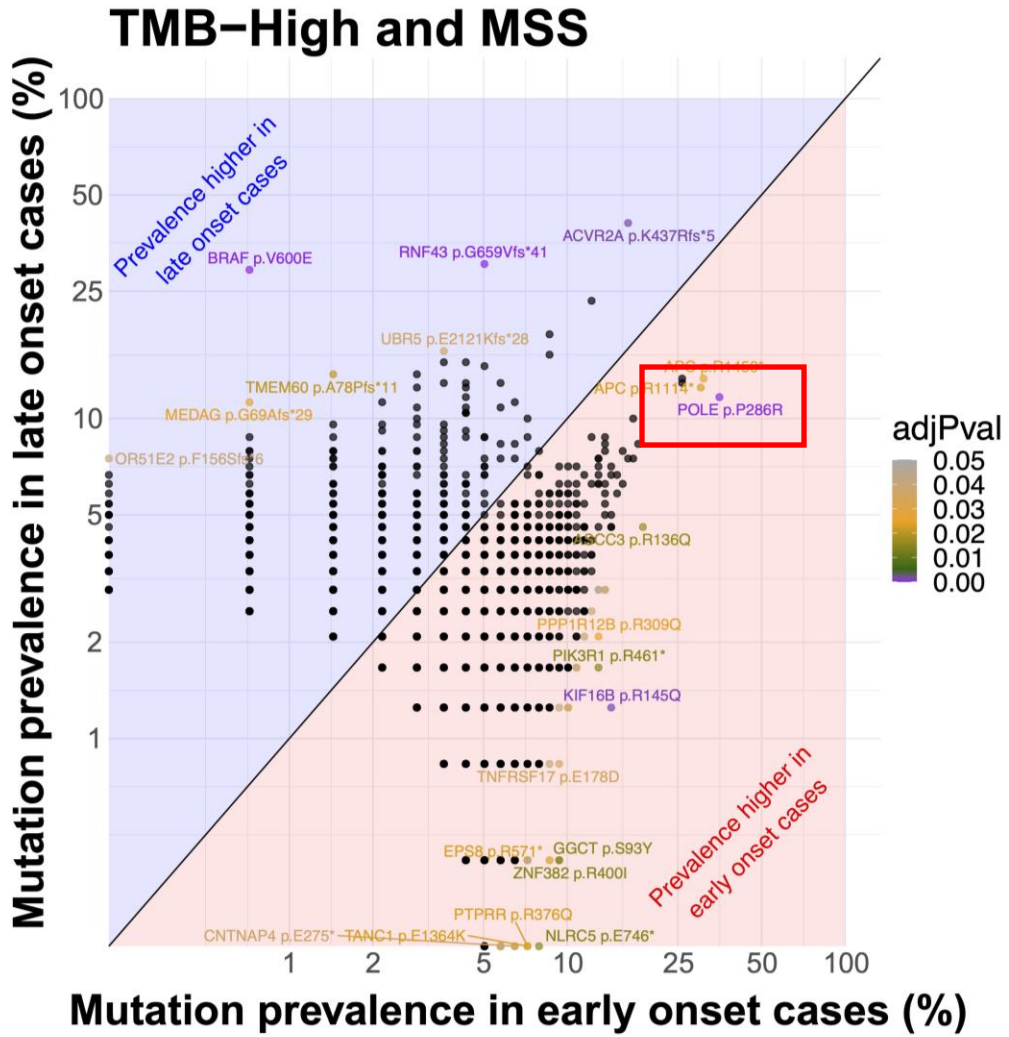


Oncogenic pathways

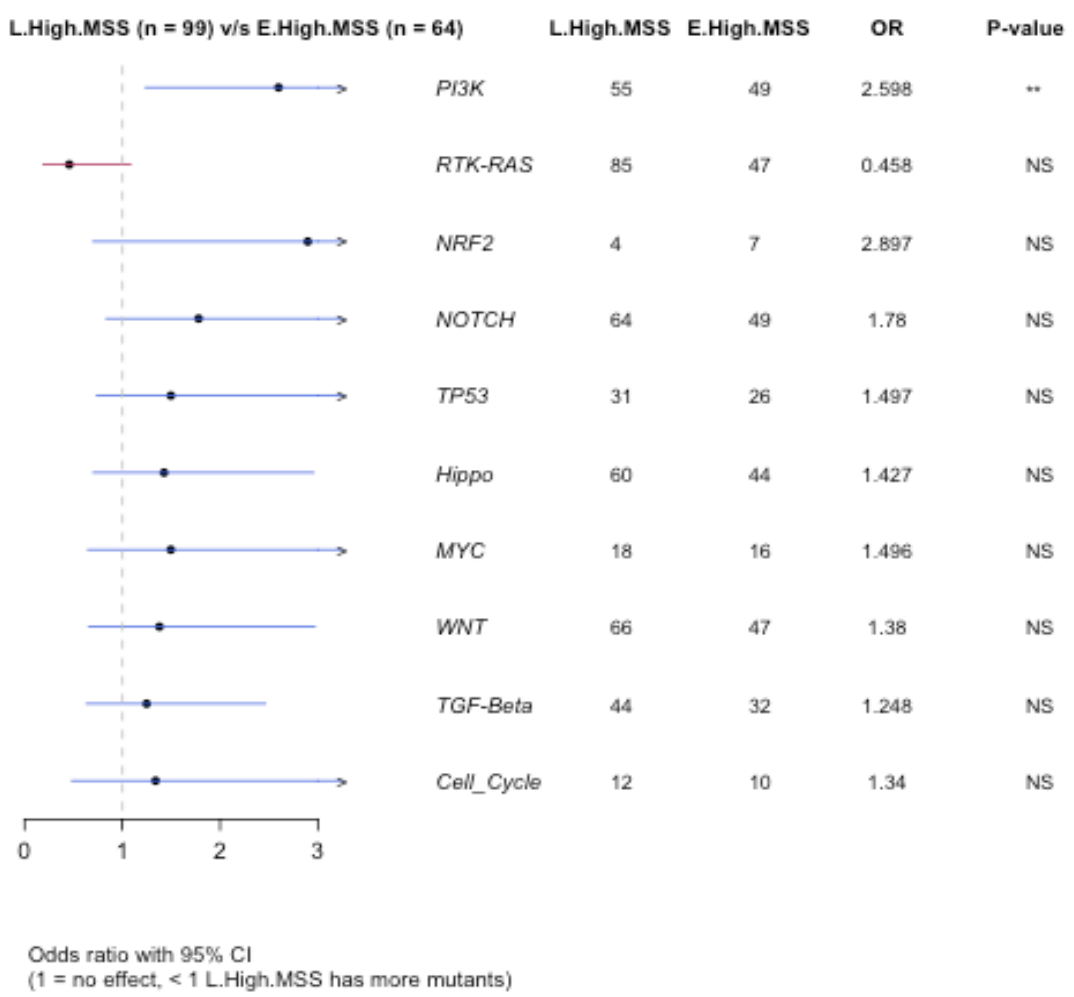


TMB-H/MSS: *POLE* in 38% of EOCRC. Need genetic counseling and consider immunotherapy

Gene variant level



Oncogenic pathways



Key Findings (**all p < 0.01**)

Key difference	Group	EOCRC vs. AOCRC	EOCRC Incidence	AOCRC Incidence
TMB-High	Overall cohort	Less likely	15%	19%
MSI-High	Overall cohort	Less likely	10%	17%
BRAF V600E	Overall cohort	Less likely	3%	15%
Truncated *RNF43*	Overall cohort	Less likely	2%	9%
TP53	TMB-low, MSS	More likely	8%	5%
PIK3CA H1047R	TMB-high, MSI-H	More likely	22%	9%
BRAF V600E	TMB-high, MSI-H	Less likely	4%	60%
Driver in PI3K pathway	TMB-high, MSS	More likely	74%	56%
POLE P286R	TMB-high, MSS	More likely	38%	13%

Lander et al., AACR 2023 Abstract #6696

Limitations/Future directions

- No data on race/ethnicity or tumor sidedness
- Did not sort out germline vs. sporadic

- **Future investigation will include germline data and evaluate age as a continuous variable**
- **Data to be presented at ESMO World GI Congress in July will highlight tumor mutational signatures**

Conclusions

Patients with AOCRC harbored more gene variants and mutations in established pathways of CRC carcinogenesis.

Tumors in EOCRC cases carried unique genomic alterations that varied across the TMB and microsatellite subpopulations.

Future study will sort out germline from somatic mutations, and evaluate clusters of genetic mutations to define groups.

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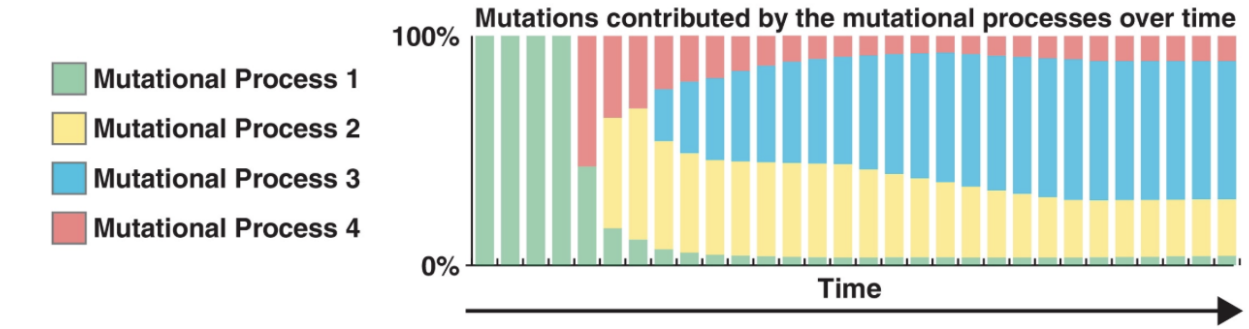
Appendices

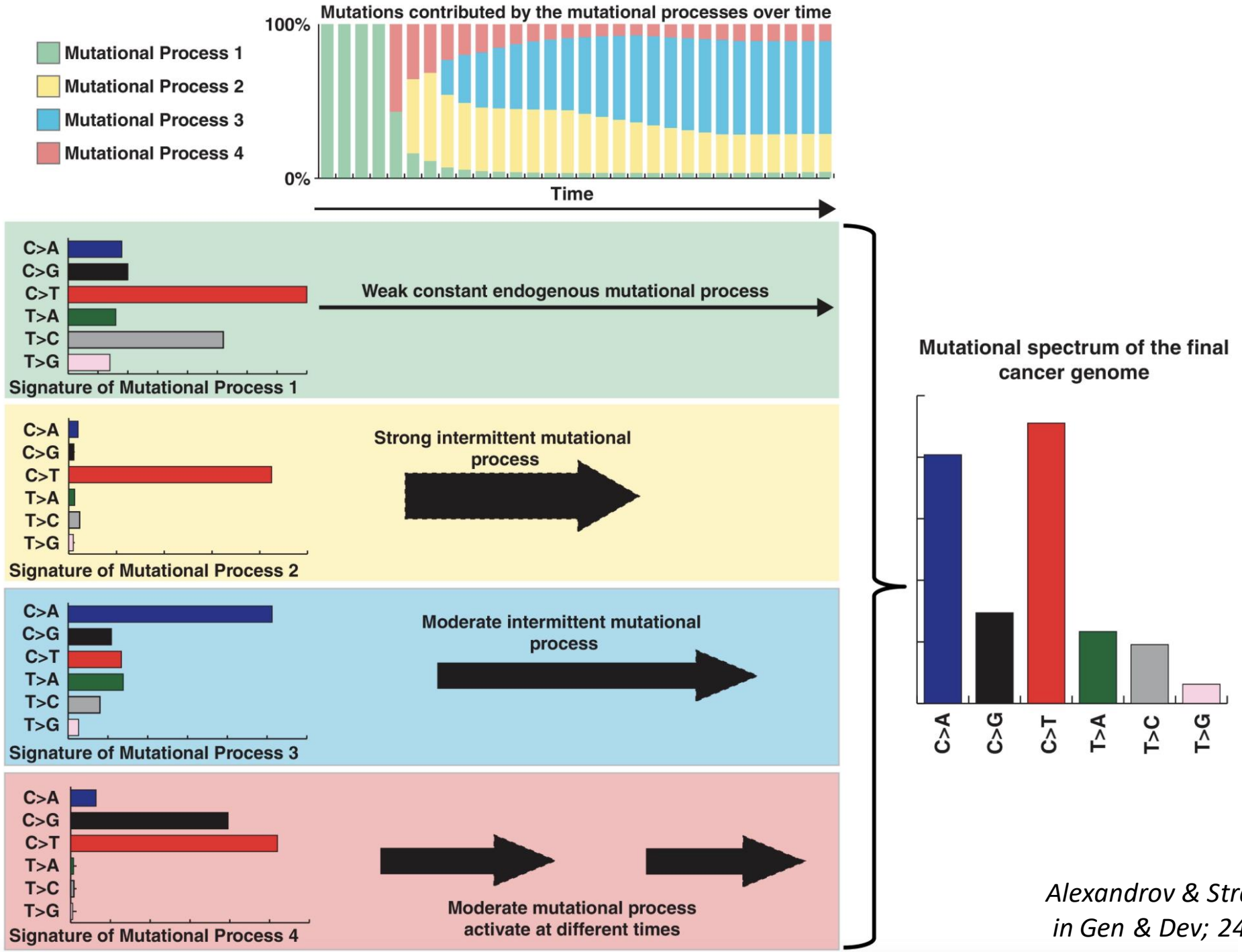
Prior studies investigating EOCRC genomics

Key feature	Lieu et al.[1]	Cercek et al.[2]
Number of institutions	Multi-institution (n = 18,218)	**1** (MSK; n = 1446)
Method of genome analysis	**NGS** (422 genes; FoundationOne)	**NGS** (341-468 genes; MSK-IMPACT)
Key findings	EOCRC: More POLE, TP53, MYC AOCRC: More BRAF, RNF43, others	No genomic differences between age groups
Limitations	Limited TMB data, no tumor sidedness data, different age cutoffs	Single center, smaller sample, limited TMB data

[1]*Lieu CH et al., Clin Cancer Res. 2019 Oct 1;25(19):5852-5858.*
[2]*Cercek A et al., J Natl Cancer Inst. 2021 Nov 29;113(12):1683-1692.*



Alexandrov & Stratton, Curr Opin in Gen & Dev; 24C(100):52-60



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