The Enigma of Early Onset Colorectal Cancer (EOCRC): Digestive Cancers Europe (DiCE) Masterclass 2024

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VANDERBILT-INGRAM CANCER CENTER

DISCLOSURES

Consultant:

- Abbvie
- Amgen
- General Electric
- Merck
- Natera
- Taiho

Institutional Grants

- Agenus
- Gritstone
- Hutchmed
- Janssen
- Merck
- Pfizer
- Sumitomo

Objectives:

1. Acknowledge the rising incidence of early onset colorectal cancer (EOCRC)
2. Identify the signs and symptoms of EOCRC
3. Understand the unmet needs of an EOCRC patient

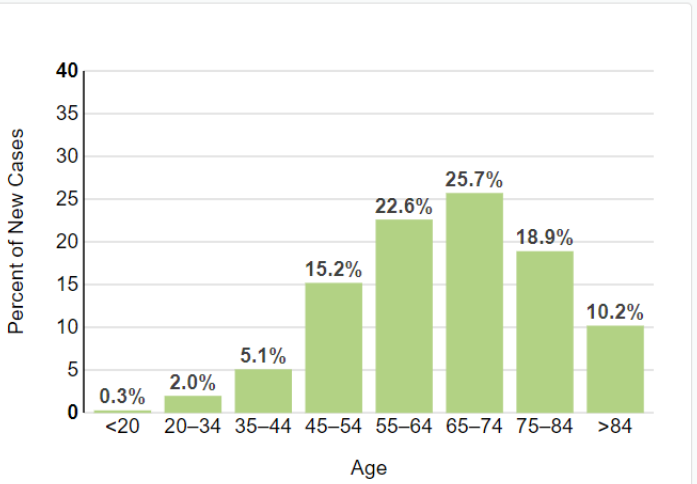
Incidence and Mortality of Colorectal CA in the US and Globally (GloboCan)

At a Glance

Estimated New Cases in 2024	152,810
% of All New Cancer Cases	7.6%

Estimated Deaths in 2024	53,010
% of All Cancer Deaths	8.7%

Percent of New Cases by Age Group: Colorectal Cancer



Colorectal cancer is most frequently diagnosed among people aged 65–74.

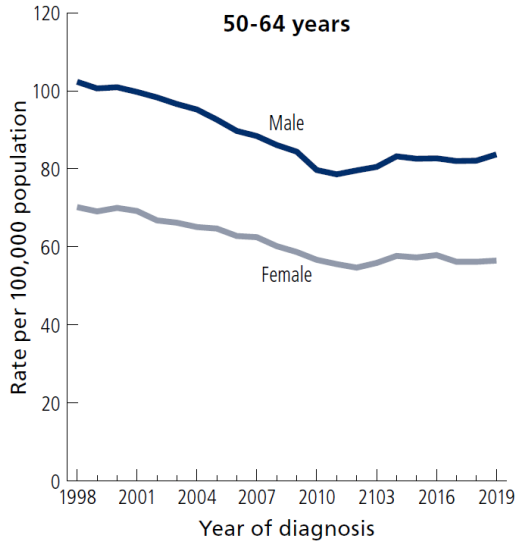
Median Age At Diagnosis
66

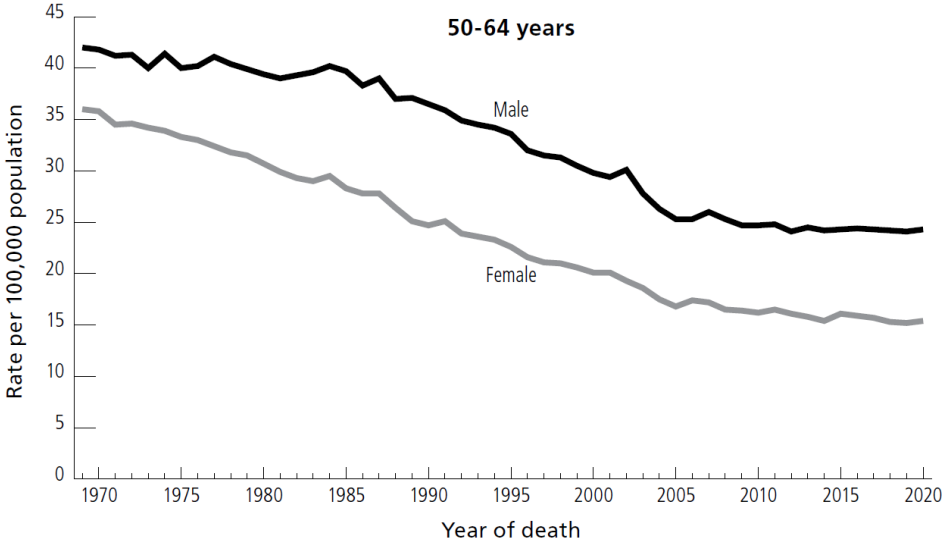
Estimated number of new cases from 2020 to 2040.

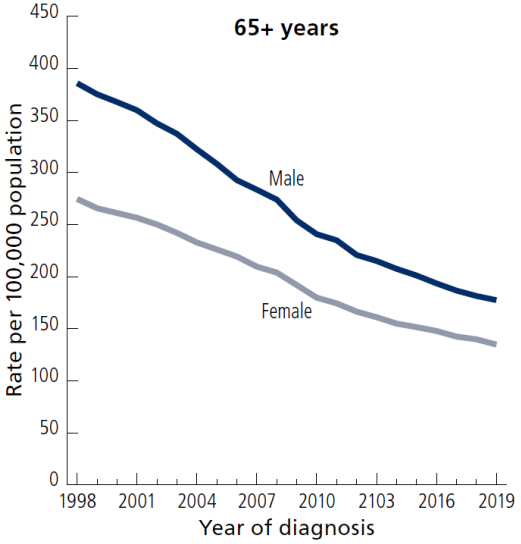
Cancer sites	2020		2040
Colon	1,148,515	↑ 67%	1,916,781
Rectum	732,210	↑ 58%	1,160,296

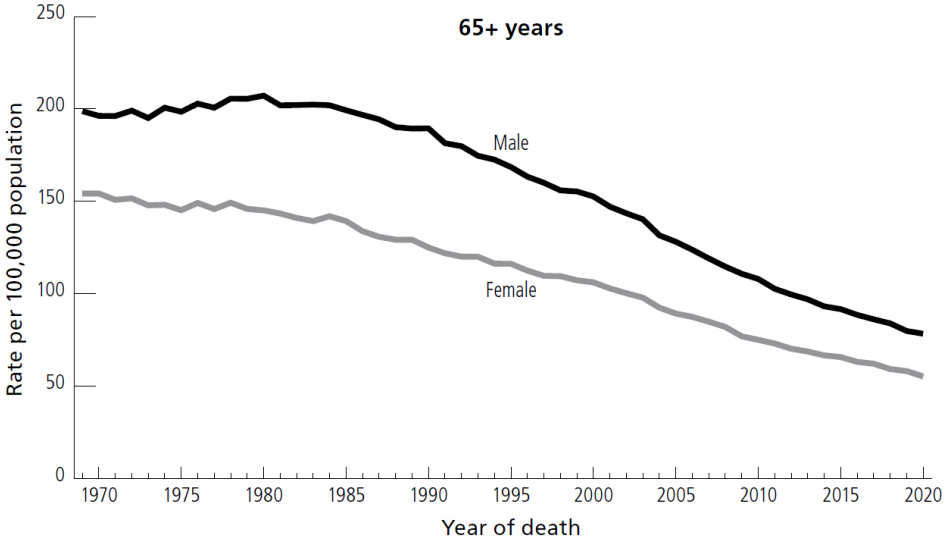
www.seer.cancer.gov; Morgan et al: Gut, 2023

Overall, the incidence of CRC is decreasing



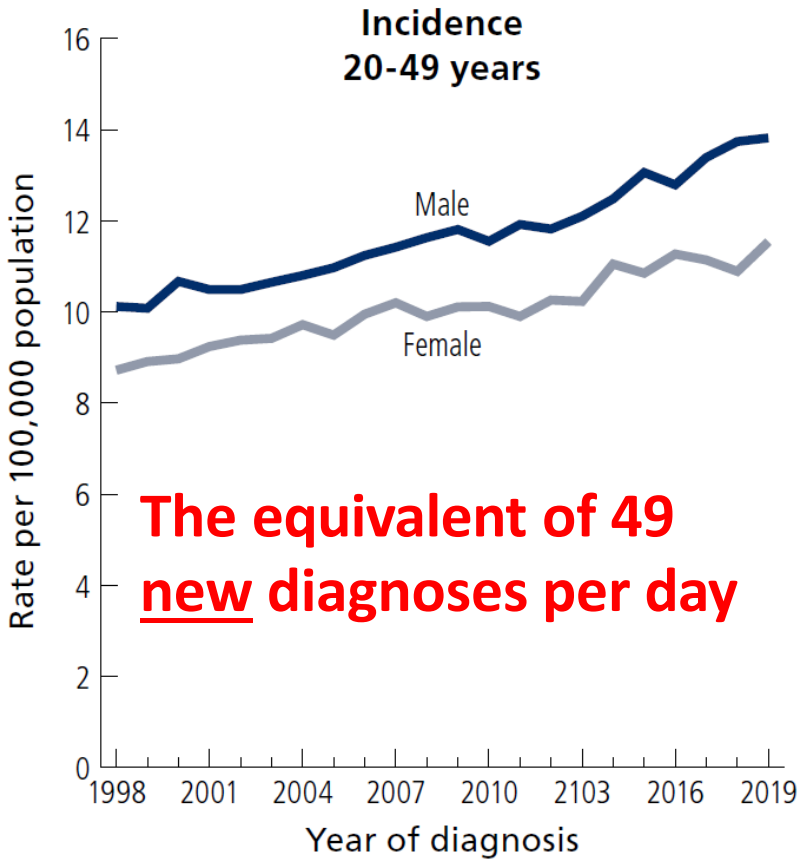




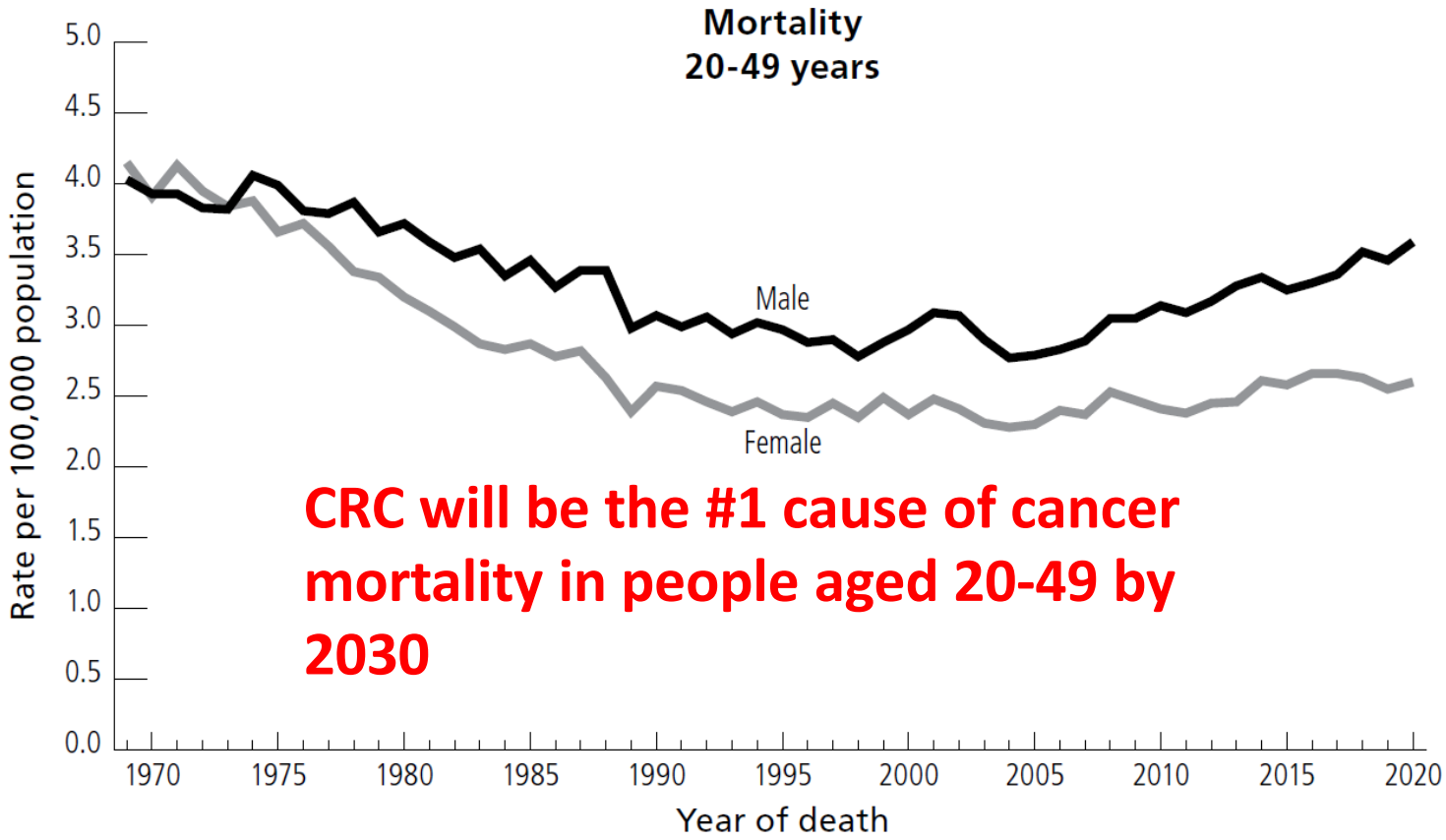


Colorectal Cancer Facts and Figures 2023-2025

Increasing in EOCRC Patients



The equivalent of 49 <u>new</u> diagnoses per day

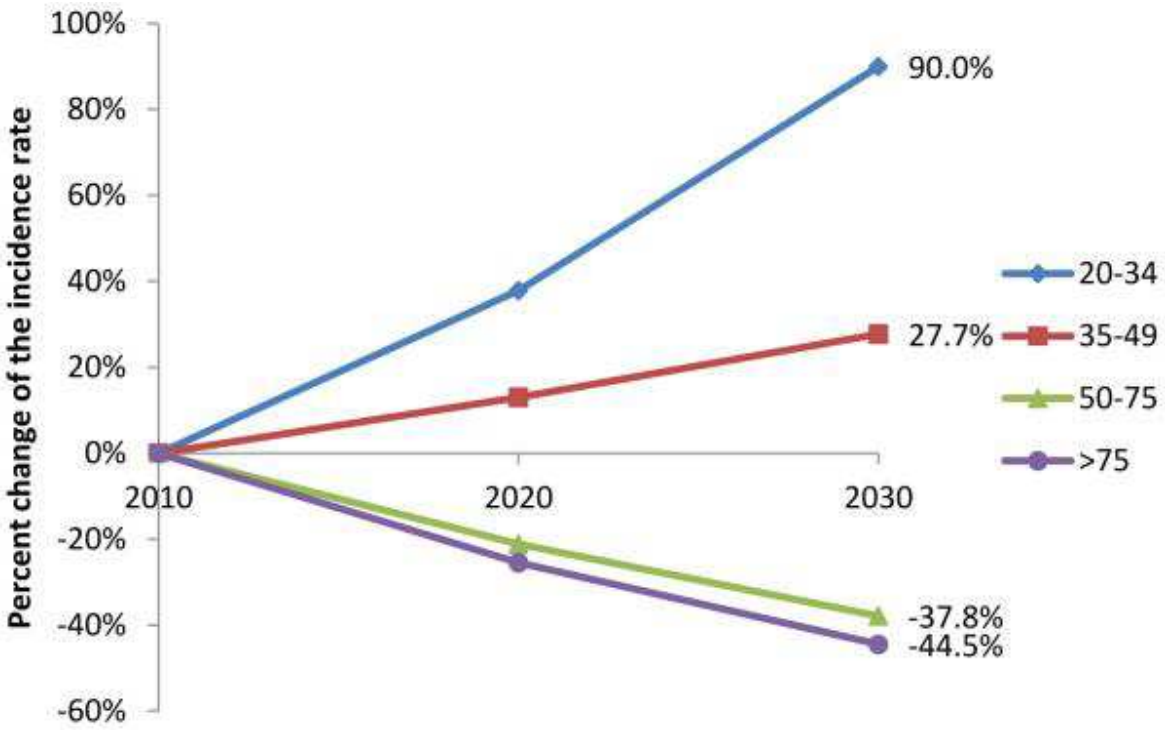


CRC will be the #1 cause of cancer mortality in people aged 20-49 by 2030

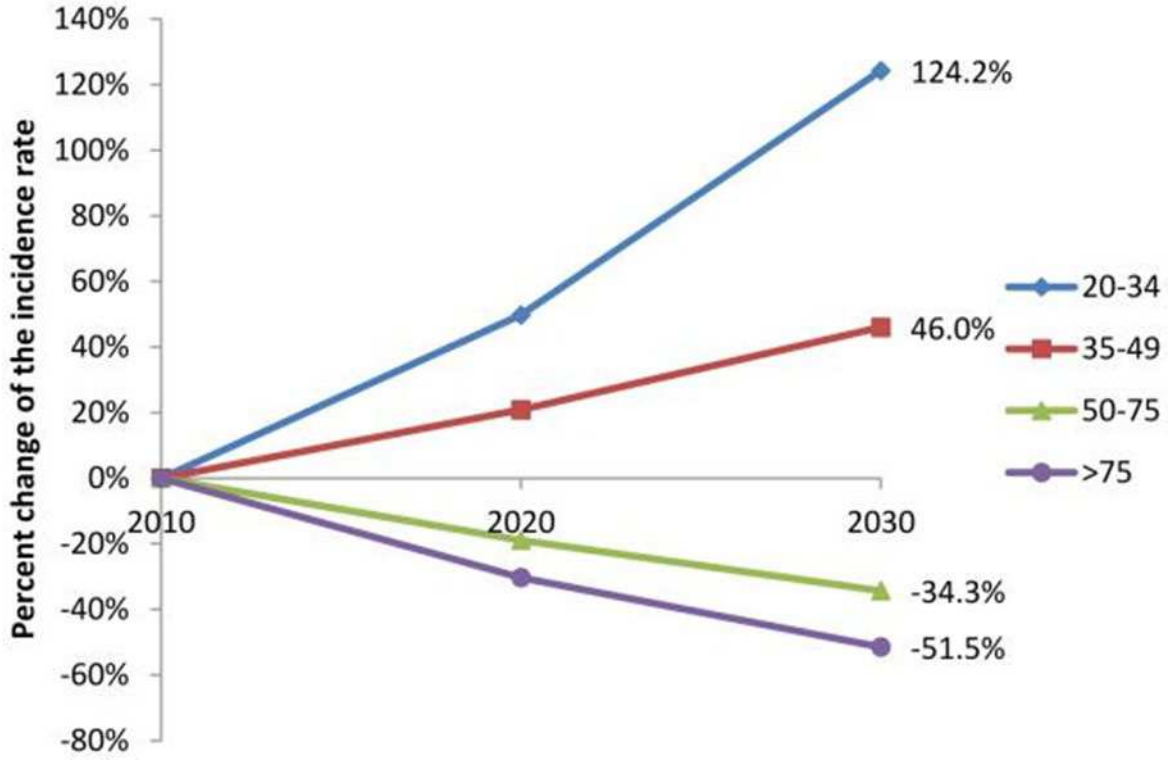
Colorectal Cancer Facts and Figures 2023-2025

Trends in EOCRC Incidence from 2010 to 2030

Colon Cancer

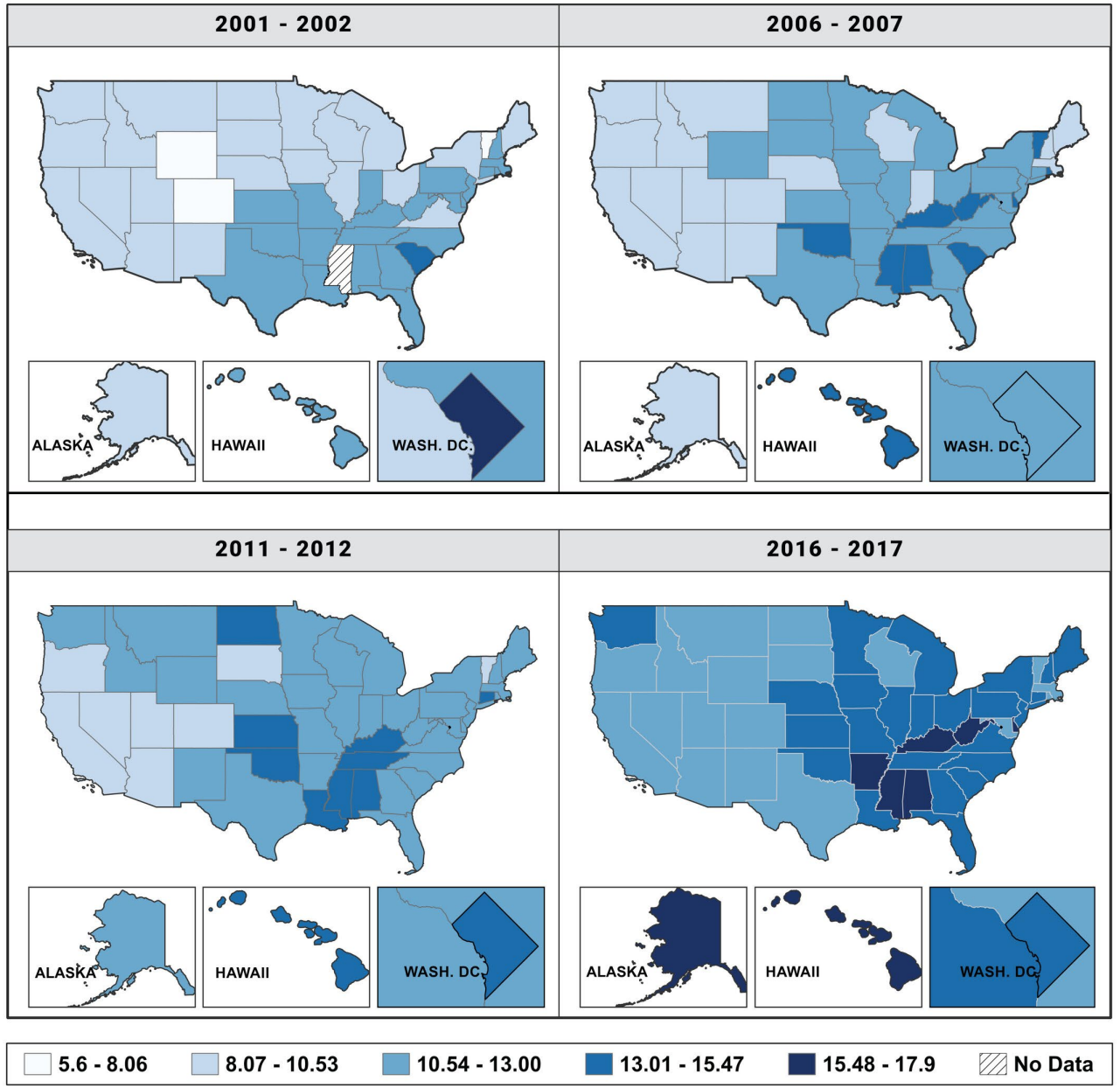


Rectal Cancer



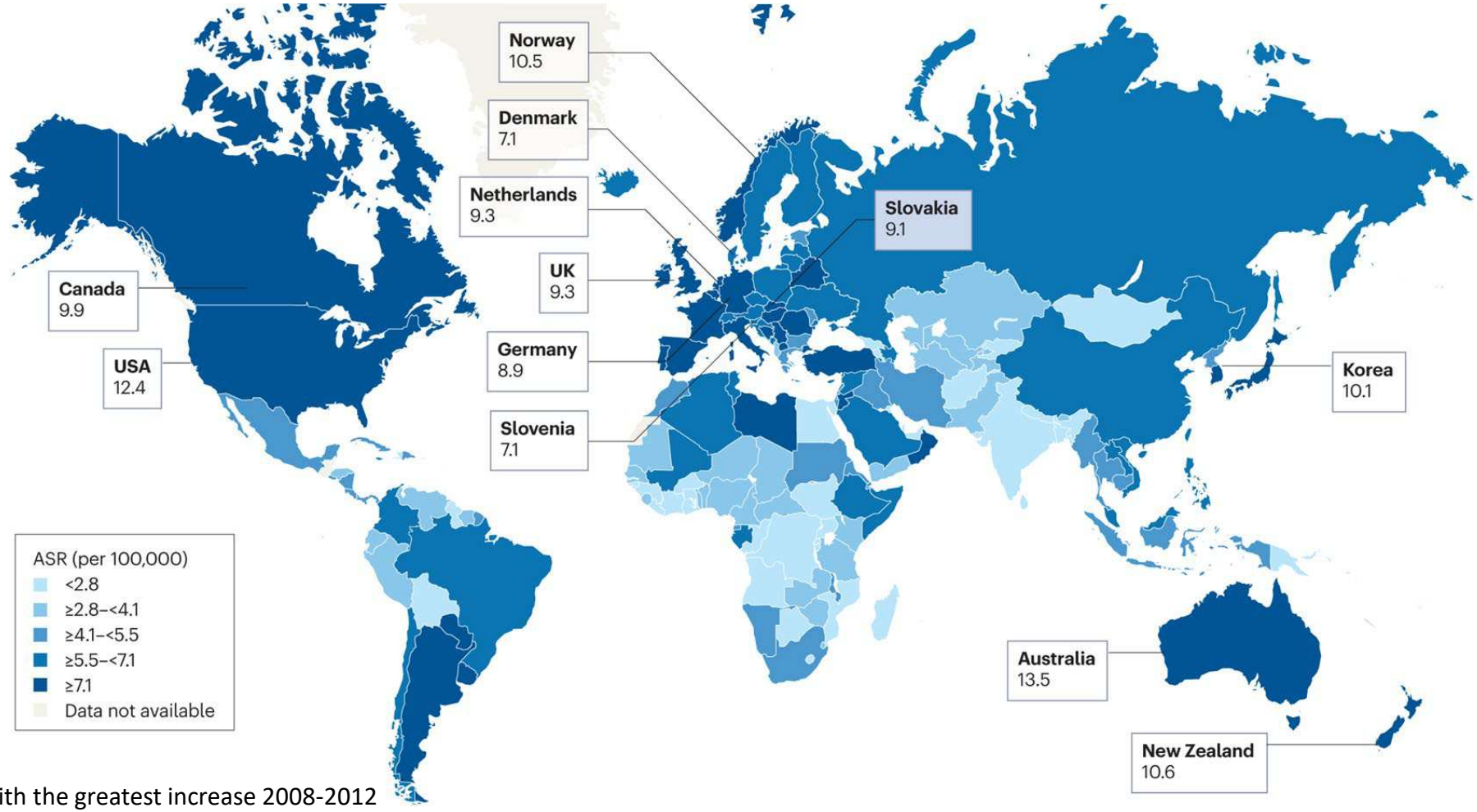
Bailey et al: Jama Surgery, 2015

Geographic Trends: Age-adjusted EOCRC incidence rates



Shah et al. *Cancer* 2021.

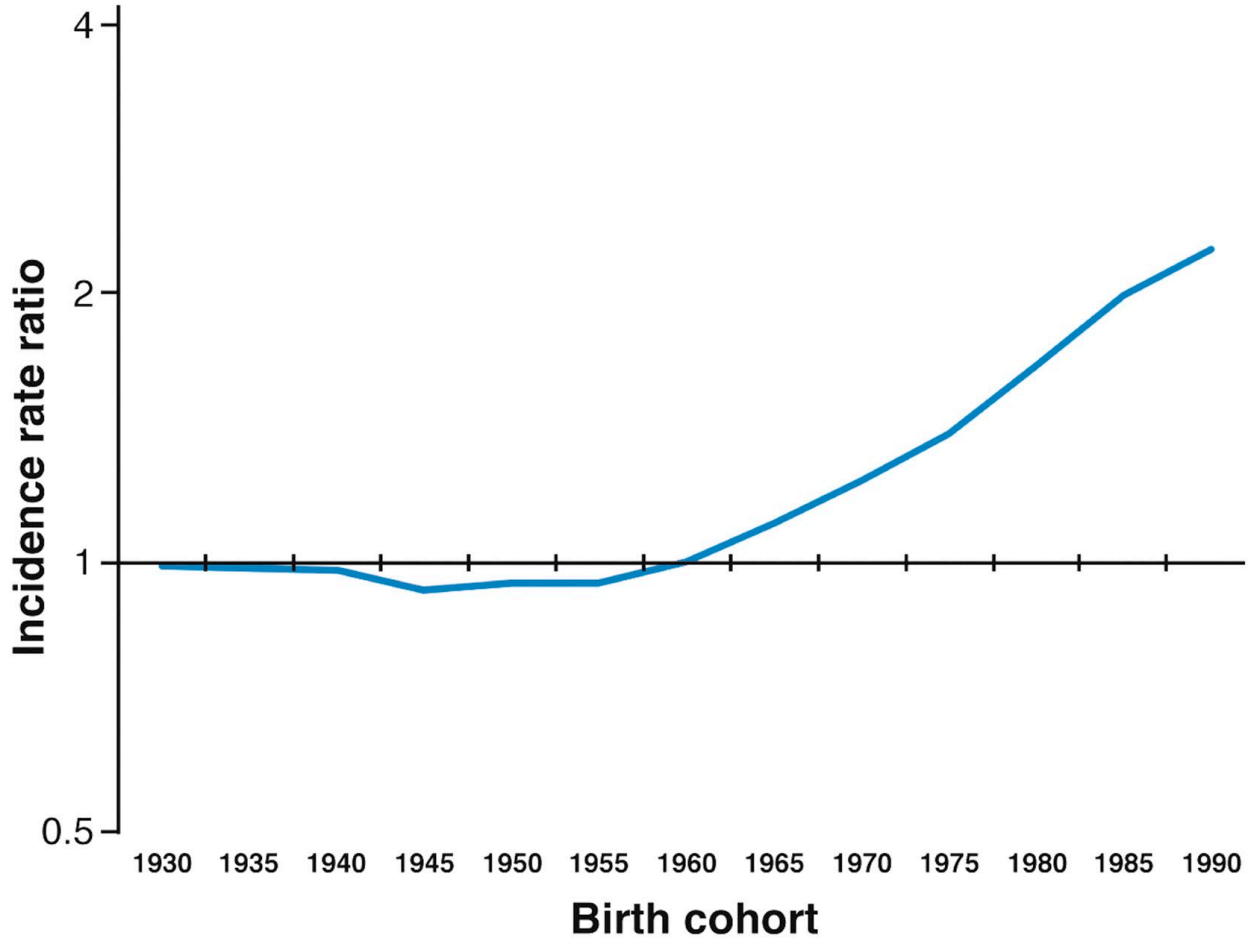
Global Concern: Age standardized incidence rate (ASR) of EOCRC (YO-CRC; age 20–49 years) in both sexes worldwide for the year 2020



*Highlighted are those with the greatest increase 2008-2012

Spaander et al. Nat Rev Dis Prim, 2023

Overall CRC Incidence by Birth Cohort

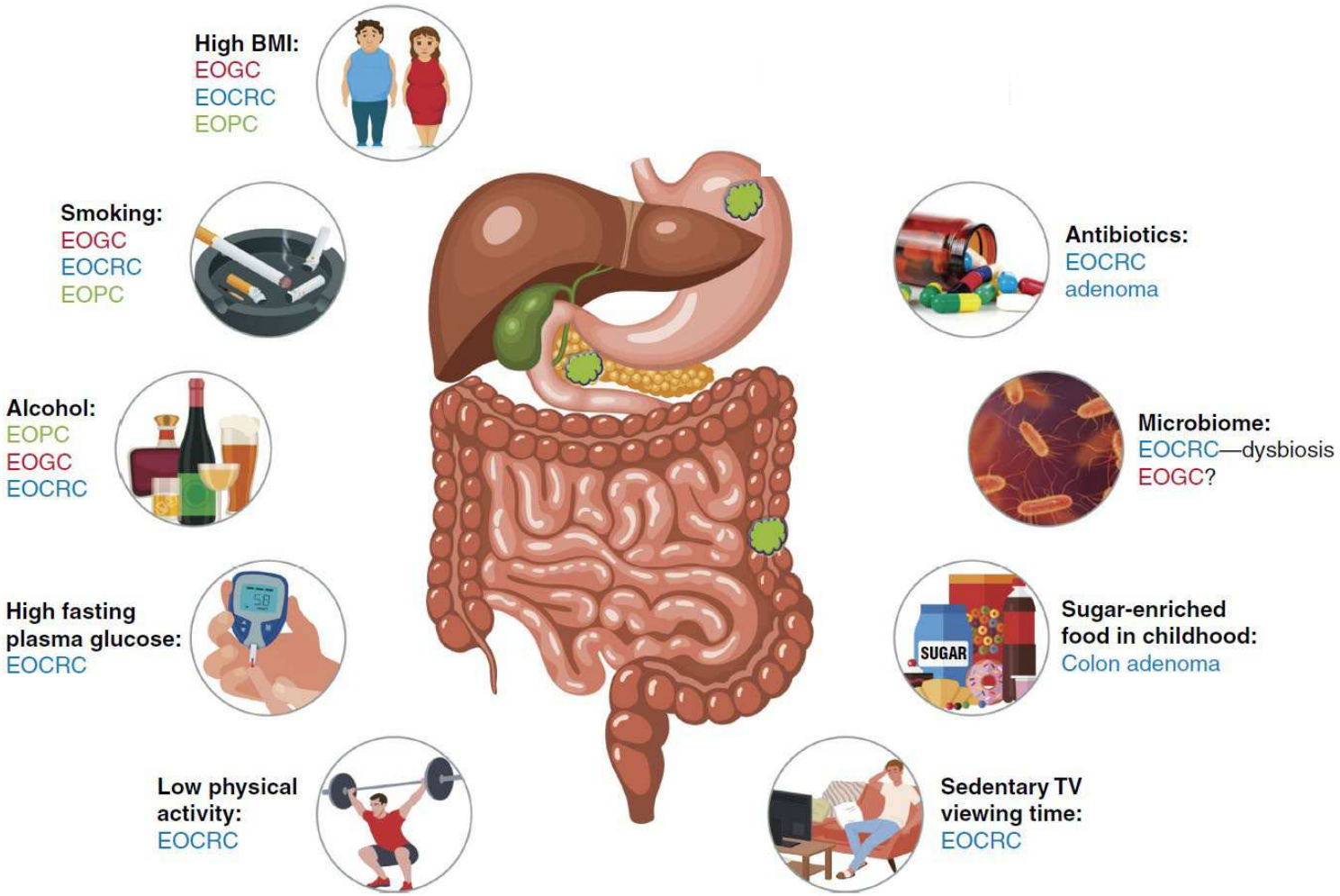


Those born ~ **1990:**

- **Two-fold higher risk** of colon cancer (incidence rate ratio (IRR) **2.40**, 95% CI 1.11–5.19)
- **Four-fold** higher risk of rectal cancer (IRR **4.32**, 95% CI 2.19–8.51)

Stoffel et al: Gastroenterology 2020; Siegel et al. J. Natl Cancer Inst. 2017

Multifactorial Etiology for EOCRC?



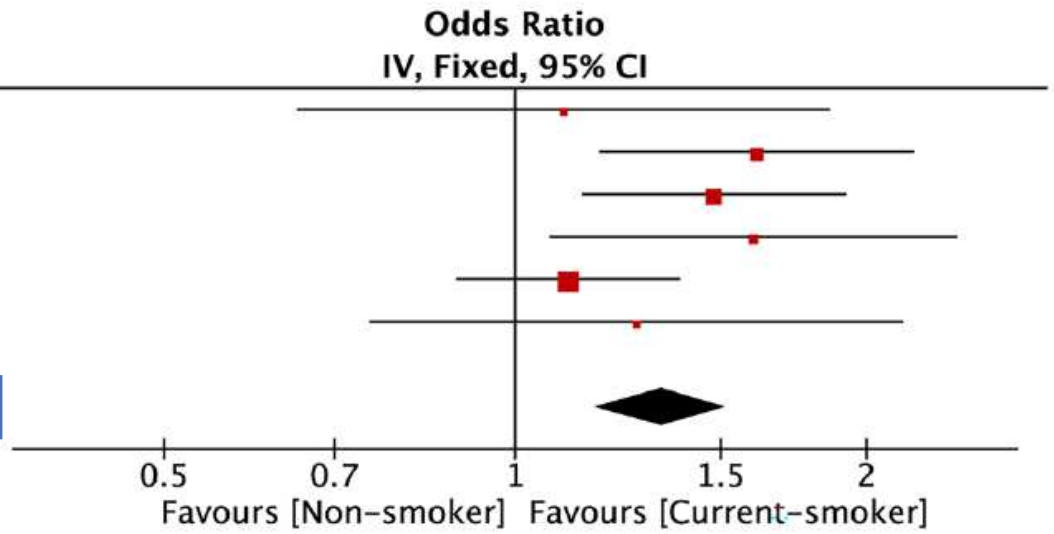
Ben-Ahron et al: Cancer Disc, 2023

Smoking as a risk factor for EOCRC: Systemic Meta-Analysis

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Agazzi, et al 2021	0.0953	0.2684	6.1%	1.10 [0.65, 1.86]
Koo, et al 2016	0.4762	0.1585	17.6%	1.61 [1.18, 2.20]
Kwak, et al 2015	0.392	0.1332	24.9%	1.48 [1.14, 1.92]
Lee, et al 2016	0.47	0.2053	10.5%	1.60 [1.07, 2.39]
Low, et al 2020	0.1044	0.1127	34.8%	1.11 [0.89, 1.38]
Shen, et al 2021	0.239	0.2687	6.1%	1.27 [0.75, 2.15]
Total (95% CI)			**100.0%**	**1.33 [1.17, 1.52]**

Heterogeneity: $Chi^2 = 6.01$, $df = 5$ ($P = 0.31$); $I^2 = 17\%$

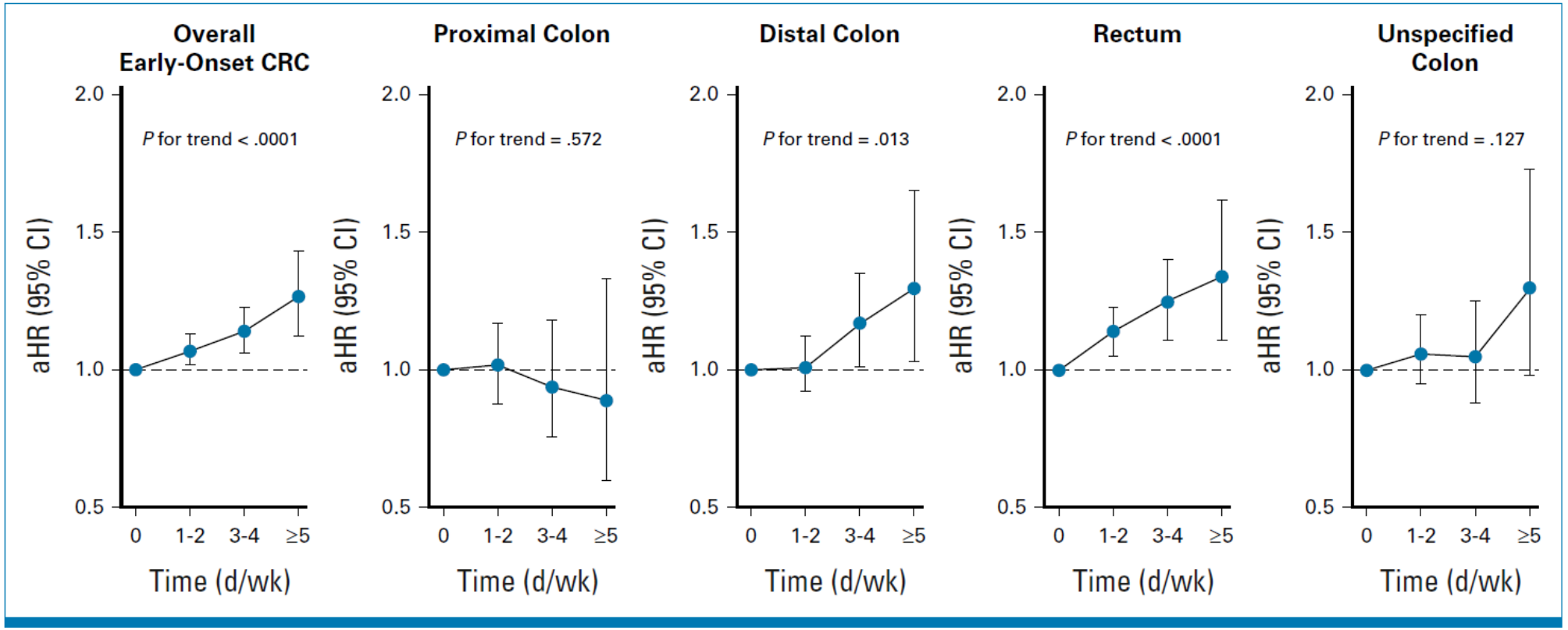
Test for overall effect: $Z = 4.32$ ($P < 0.0001$)



Li et al: International Journal of Colorectal Disease, 2023

Sex and Tumor-Site Association With Alcohol Intake With the Risk of EOCRC (Korea: 2009-2019)

- N=5.67M
- Median F/U = 9.1 yrs
- EOCRC: N = 8314
- Dose-response for mod-heavy vs. light
- But when stratified by sex, only applied to males
- 7%, 14%, and 27% increased risk for 1-2, 3-4, and ≥5 d/wk



*nondrinker, light (reference), moderate, and heavy drinker were defined as 0, <10, 10 to <30, and ≥30 g/d for men and 0, <10, 10 to <20, and ≥20 g/d for women (1 shot = 42 g)

Jin et al: JCO, 2023

Association of Female Obesity with EOCRC

Variable	No. of Cases	No. of Person-Years	Age-Adjusted RR (95% CI)	Multivariable-Adjusted RR (95% CI)[a]
All Participants				
Current BMI				
18.5-22.9	29	455 250	1 [Reference]	1 [Reference]
23.0-24.9	20	217 271	1.27 (0.71-2.24)	1.33 (0.75-2.36)
25.0-29.9	30	296 763	1.32 (0.79-2.22)	1.37 (0.81-2.30)
≥30	35	230 169	1.86 (1.13-3.06)	1.93 (1.15-3.25)
Each 5-unit increase	NA	NA	1.18 (1.04-1.35)	1.20 (1.05-1.38)
P for trend[b]	NA	NA	.01	.01
Participants Without Family History of Colorectal Cancer				
Current BMI				
18.5-22.9	25	429 876	1 [Reference]	1 [Reference]
23.0-24.9	17	205 824	1.22 (0.66-2.27)	1.27 (0.68-2.36)
25.0-29.9	27	280 184	1.36 (0.79-2.36)	1.40 (0.81-2.44)
≥30	30	216 759	1.82 (1.06-3.11)	1.88 (1.07-3.30)
Each 5-unit increase	NA	NA	1.17 (1.01-1.35)	1.18 (1.02-1.38)
P for trend[b]	NA	NA	.03	.03

- The Nurses' Health Study II: 25 to 42 y/o (1989-2011).
- 85,256 women NED at enrollment were included
- 114 cases of EAOCRC
- Median follow-up was 13.9 years

Liu et al: Jama Onc, 2018

Changes in Weight in Men from Childhood to Adulthood Associated with Colorectal Cancer

Weight status			*n*	Cases (*n*)	HR	95% CI	*p*
Age 7 years	Age 13 years	Early adulthood					
NW	NW	NW	54,273	614	1.00	Reference	
NW/OW	NW/OW	NW	1909	17	0.83	(0.51; 1.34	0.45
NW/OW	NW/OW	OW	4312	56	1.34	(1.02; 1.76)	0.04
OW	OW	OW	704	17	2.62	(1.62; 4.25)	<0.001

- Weight and height were measured at 7 or 13 years and in early adulthood (17–26 years) in 64,675 boys in the Copenhagen School Health Records Register and the Danish Conscription Database.
- Cases of colon cancer (n = 751) were identified in the Danish Cancer Registry.

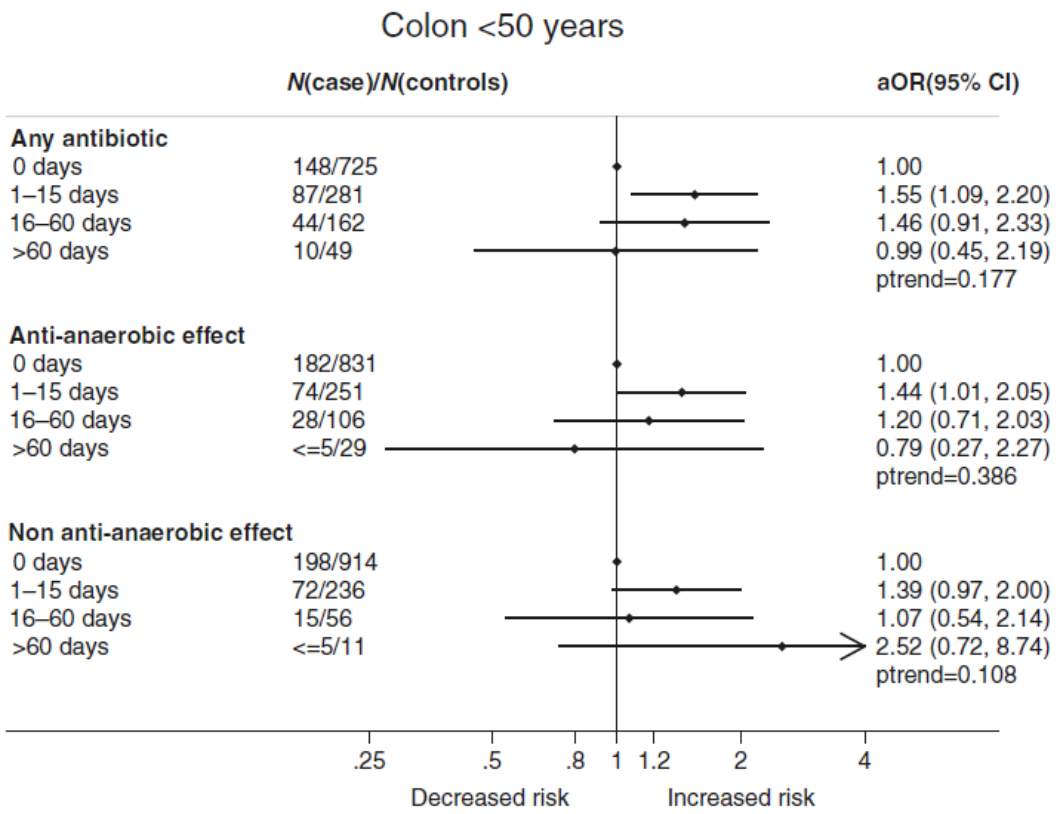
Jensen et al: Int J of Obesity, 2018

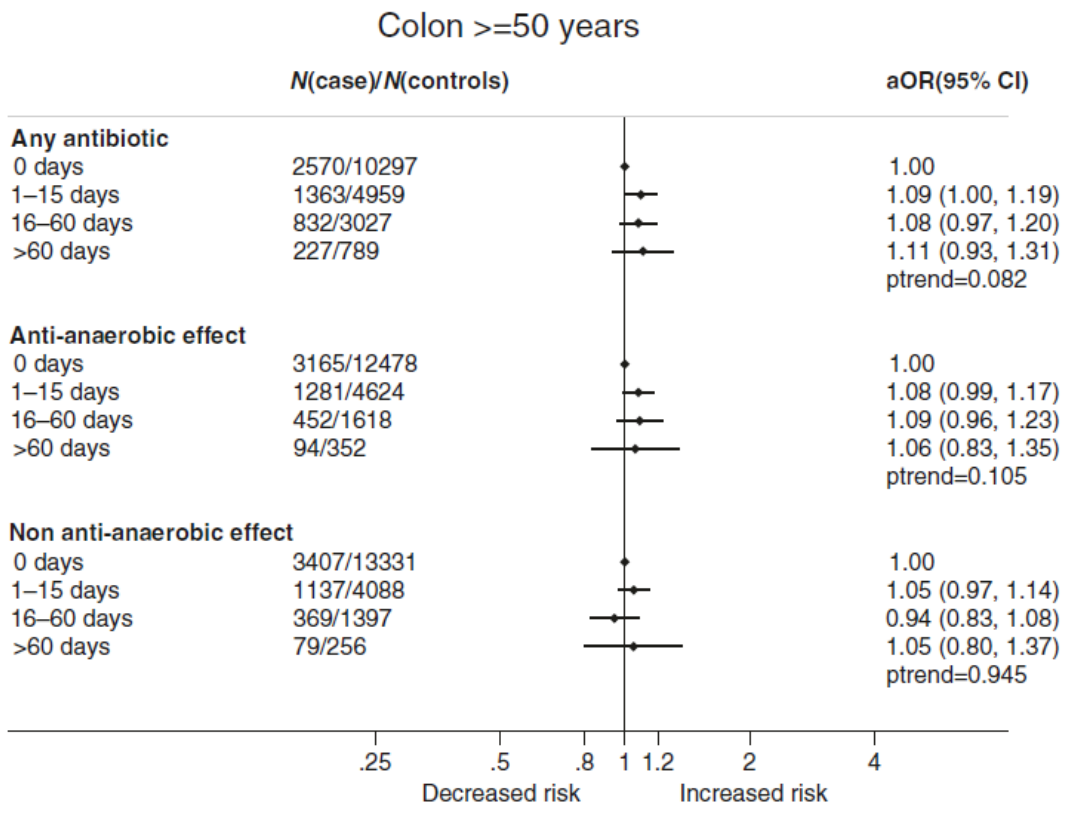
Metabolic Syndrome: Risk of EOCRC

	Participants with conditions, No. (%)			
	Cases	Controls	Multivariable-adjusted OR (95% CI)*	Multivariable-adjusted OR (95% CI)†
Age 18–49				
MetS	280 (6.0)	1763 (4.3)	1.39 (1.22 to 1.60)	1.25 (1.09 to 1.43)
Number of comorbid conditions‡				
0	2847 (60.9)	26 729 (65.5)	1 (reference)	1 (reference)
1	1048 (22.4)	8525 (20.9)	1.15 (1.06 to 1.24)	1.09 (1.00 to 1.17)
2	519 (11.1)	3957 (9.7)	1.22 (1.10 to 1.35)	1.12 (1.01 to 1.24)
≥3	259 (5.5)	1621 (4.0)	1.48 (1.29 to 1.70)	1.31 (1.13 to 1.51)
Per condition			1.12 (1.08 to 1.16)	1.07 (1.03 to 1.11)
P_{trend}			<0.001	<0.001
Age 50–64				
MetS	2195 (14.7)	16 602 (12.6)	1.20 (1.14 to 1.26)	1.21 (1.15 to 1.27)
Number of comorbid conditions‡				
0	5520 (37.0)	49 434 (37.4)	1 (reference)	1 (reference)
1	3987 (26.7)	36 165 (27.4)	0.99 (0.95 to 1.03)	1.03 (0.99 to 1.08)
2	3282 (21.9)	30 304 (22.9)	0.97 (0.92 to 1.01)	1.01 (0.96 to 1.06)
≥3	2139 (14.3)	16 217 (12.3)	1.18 (1.12 to 1.24)	1.22 (1.15 to 1.29)
Per condition			1.03 (1.02 to 1.05)	1.05 (1.03 to 1.07)
P_{trend}			<0.001	<0.001

Chen et al: Gut, 2020

Case Control Study of Antibiotics: EOCRC



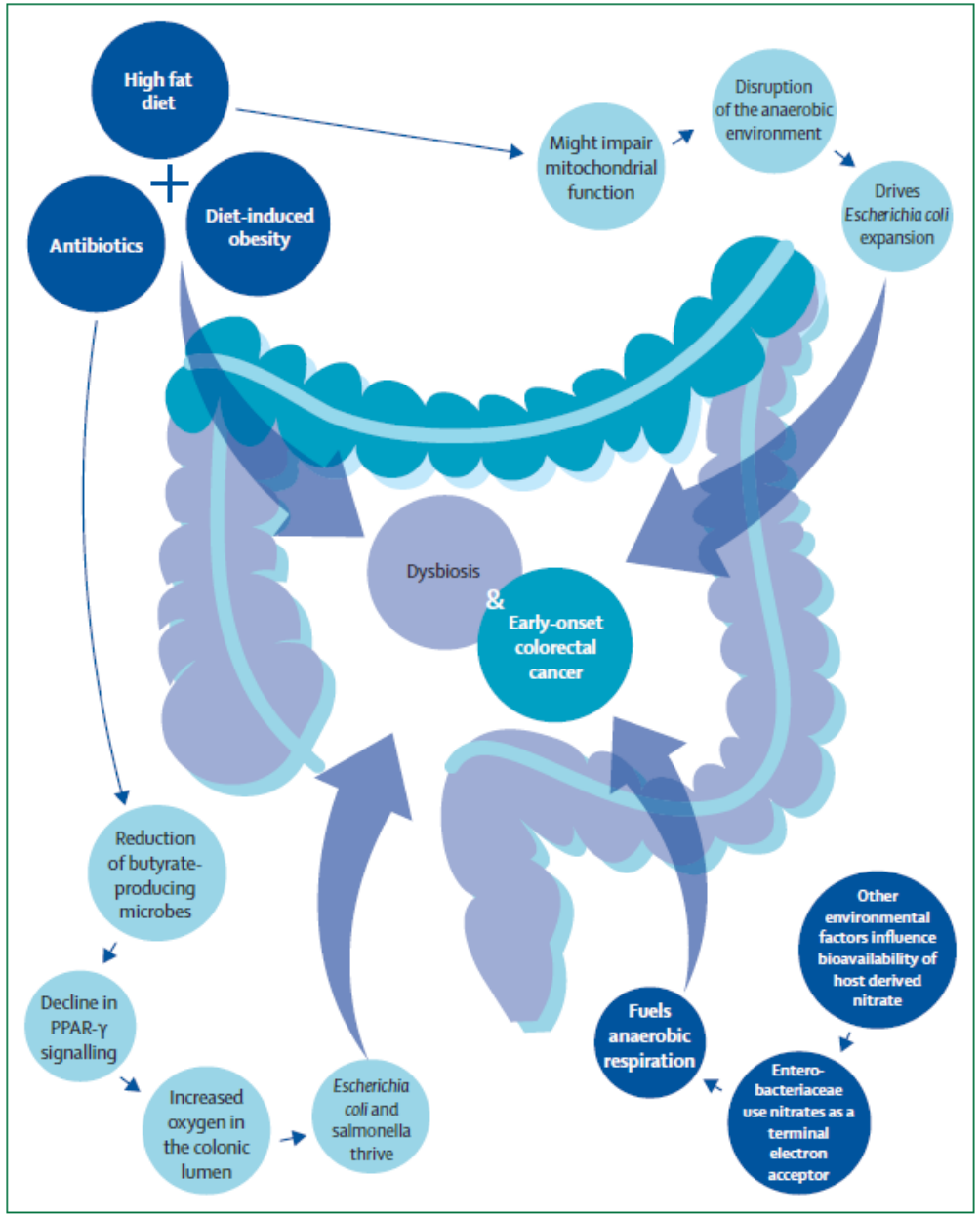


- **Scotland (1993-2011); PCP practices (N=393)**
- **EOCRC (N=445) vs. AOCRC (N=7903) vs. Controls (N=30,418)**
- **Associated with colon cancer in EOCRC [ORR: 1.49 (95% CI 1.07, 2.07), p = 0·018] and AOCRC [ORR: 1.09 (1.01, 1.18), p = 0·029)].**
- **<u>Not</u> associated with rectal cancer**

*AOCRC = average-age onset CRC

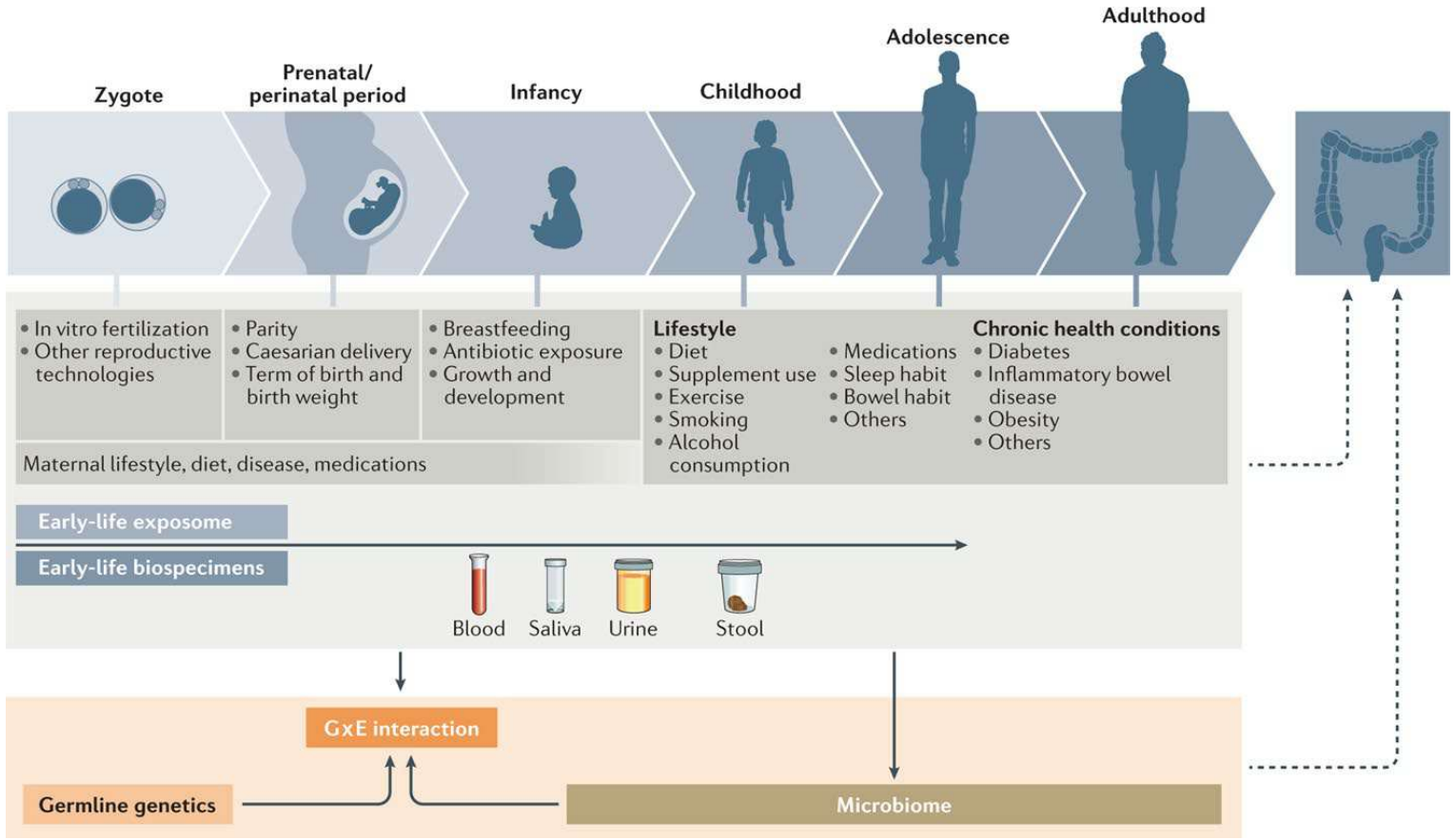
McDowell et al: BJC, 2022

Diet and Antibiotics May Impact Dysbiosis



Eng et al: Lancet Onc, 2022

Lifetime Exposure: Exposome



Akimoto et al. *Nat Rev Clin Oncol* 2020.

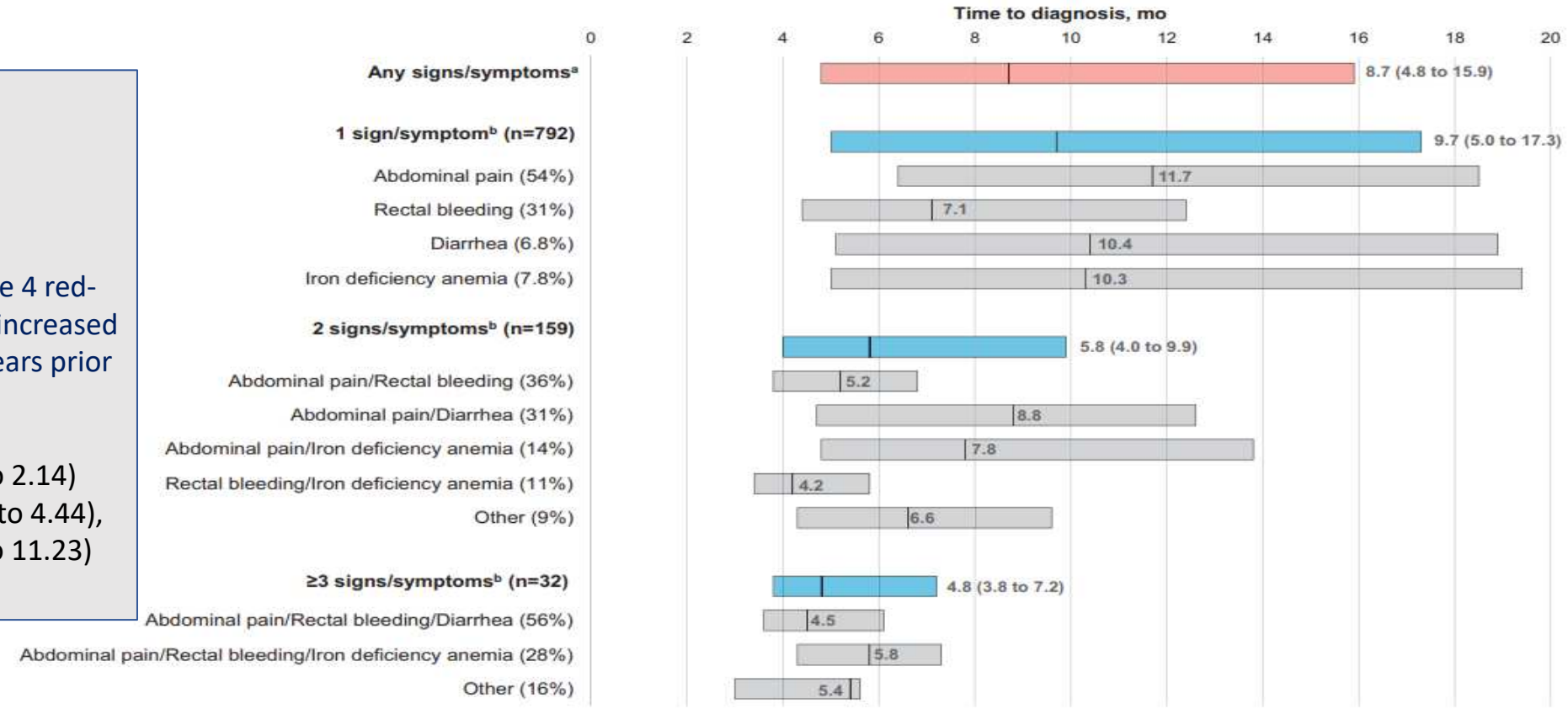
Symptoms of EOCRC and Timing of Diagnosis

Matched Case Control Study: Signs and Symptoms of Colorectal Cancer

- N=5075 (EOCRC)
- US commercial insurance database
  - N=113M
  - 2006-2015
  - ≥ 2 yrs of enrollment

*A total of 983 cases have had ≥ 1 or more 4 red-flag signs and symptoms associated with increased risk of EOCRC between 3 months and 2 years prior to diagnosis

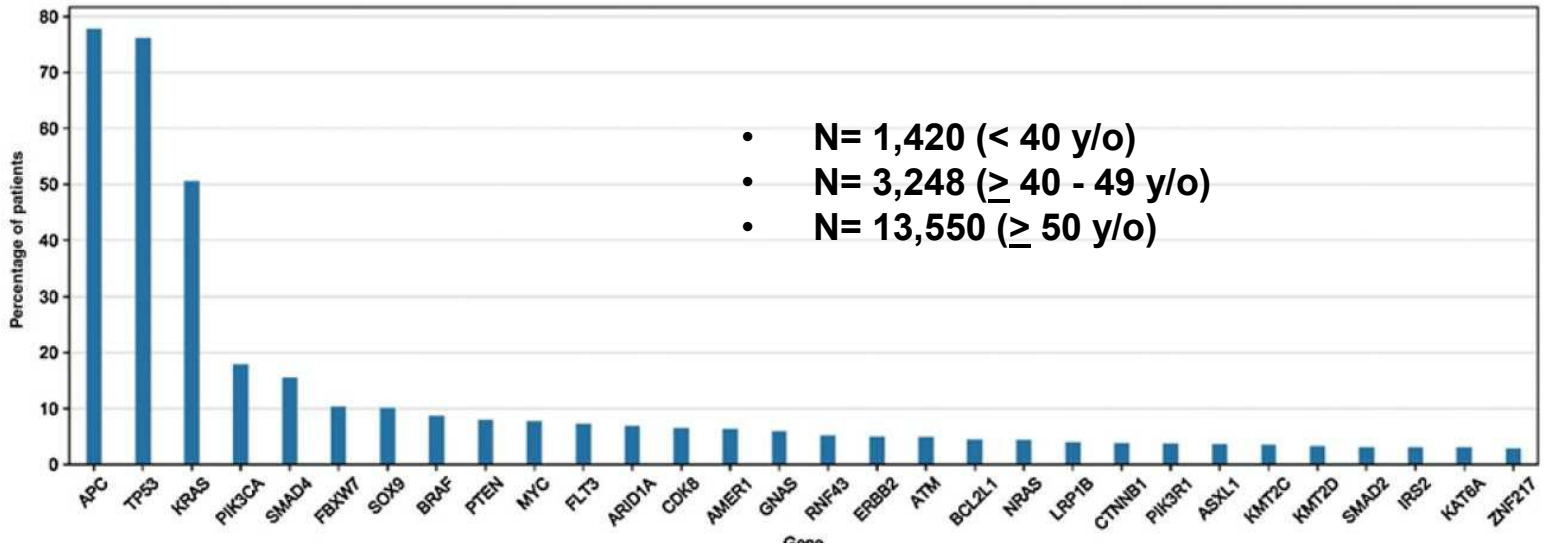
- Relative risk:
  - 1 sx: 1.94-fold (95% CI = 1.76 to 2.14)
  - 2 sx's: 3.59-fold (95% CI = 2.89 to 4.44),
  - 3x's: 6.52-fold (95% CI = 3.78 to 11.23)



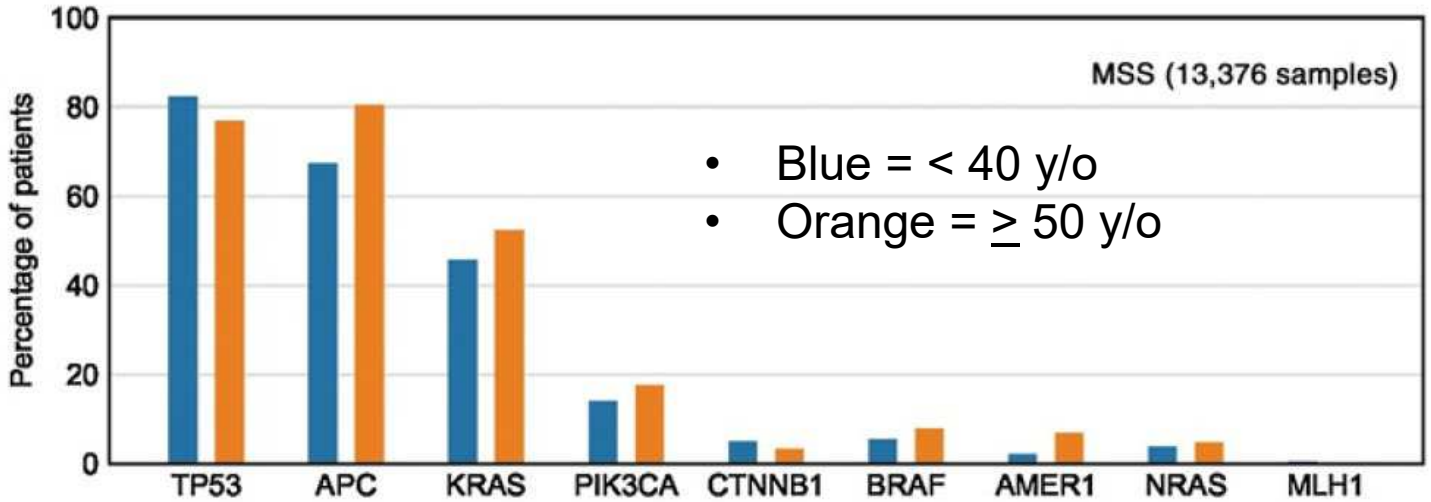
Fritz et al: JNCI, 2023

Are Molecular Alterations Different in Sporadic EOCRC?

Genomic Landscape (N=18,218 specimens)



- **N= 1,420 (< 40 y/o)**
- **N= 3,248 (≥ 40 - 49 y/o)**
- **N= 13,550 (≥ 50 y/o)**

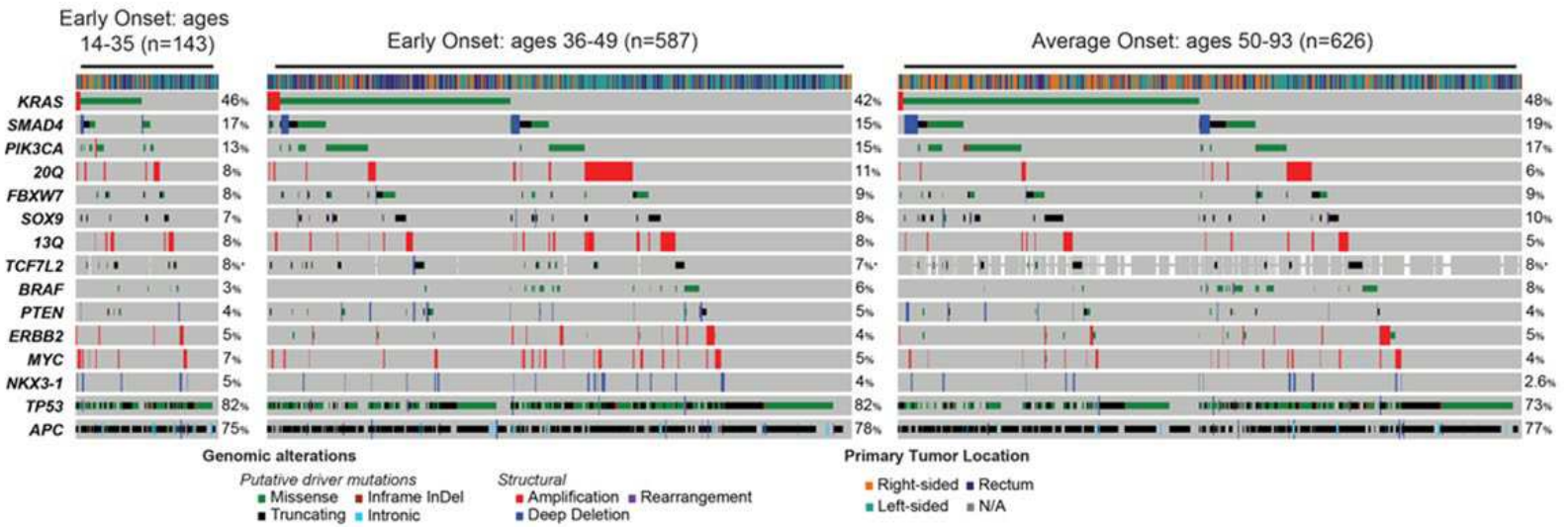


- Blue = < 40 y/o
- Orange = ≥ 50 y/o

Lieu… Eng, et al: Clin Can Res, 2019

MSKCC EOCRC vs. AOCRC: 2014-2019

Early Onset CRC	Comparisons	Average Onset CRC
EO sporadic CRC with clinical data (n=759)	Baseline Characteristics	AO sporadic CRC with clinical data (n=687)
EO sporadic MSS CRC (n=730)	Somatic Genomic Alterations	AO sporadic MSS CRC (n=626)
Metastatic EO sporadic MSS CRC (n=565)	Survival and Response	Metastatic AO sporadic MSS CRC (n=575)
EO CRC with germline data (n=458)	Germline Alterations	AO CRC with germline data (n=623)



No difference in early onset CRC:
Genomic alterations vs. average-age onset CRC (MSS)

Cercek et al: JNCI 2021

2023 ASCO ANNUAL MEETING

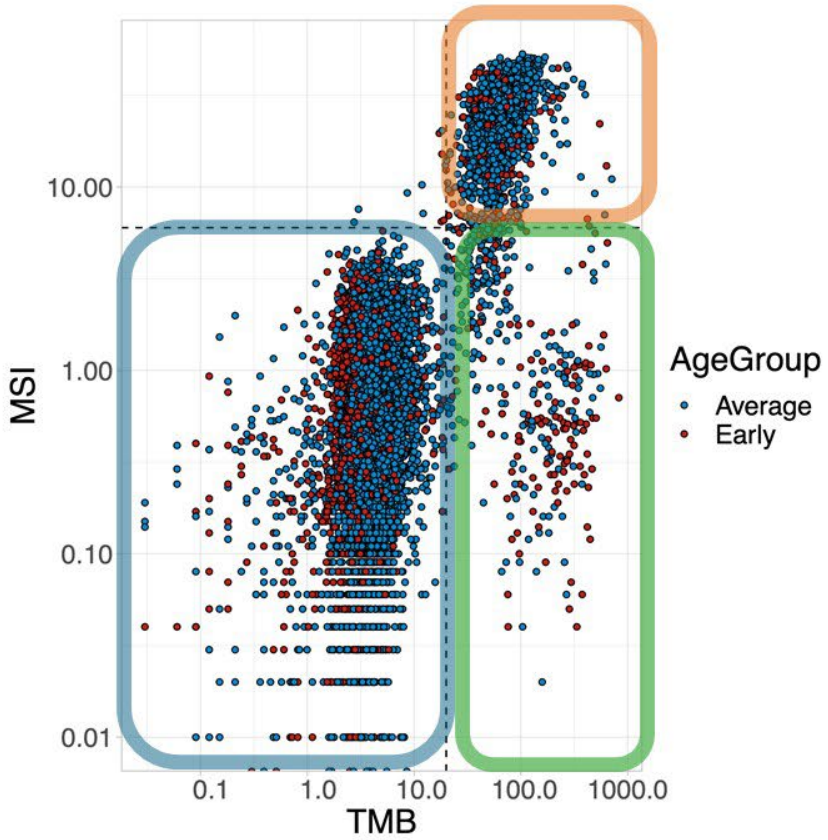
Evaluation of genomic alterations in early-onset versus average-onset colorectal cancer

Eric M. Lander[1], Samuel Rivero-Hinojosa[2], Vasily N. Aushev[2], Adham Jurdi[2], Minetta C. Liu[2], Cathy Eng[1]

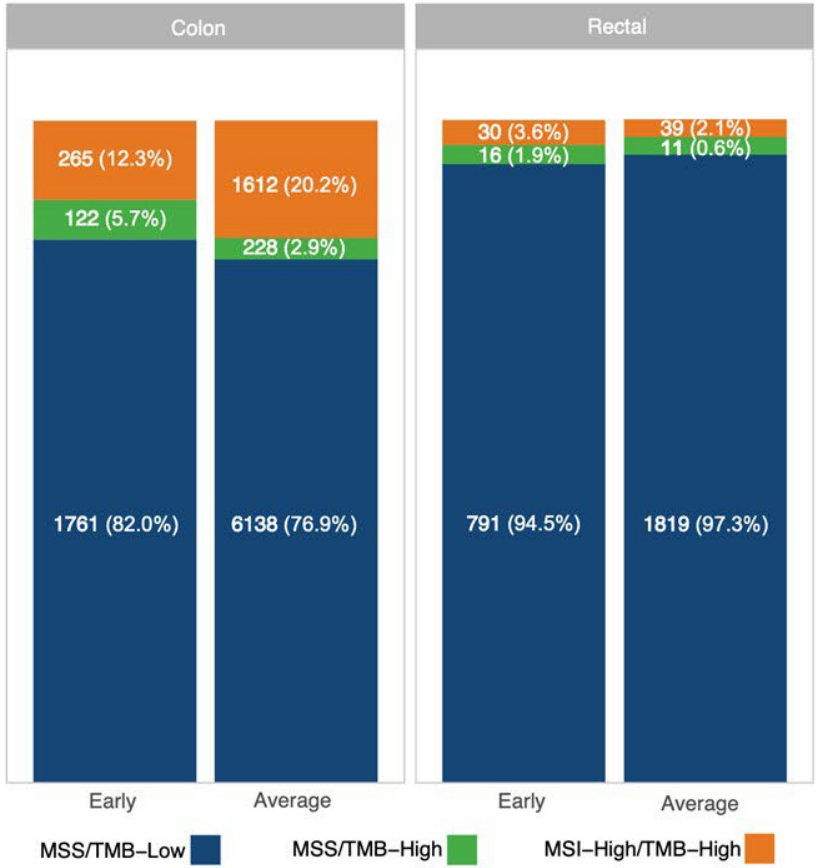
[1]Vanderbilt University Medical Center, Nashville, TN, USA; [2]Natera, Inc., Austin, TX, USA

PRESENTED BY: Eric M. Lander, MD

Results – Baseline genomic characteristics

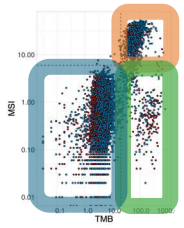


TMB-High is ≥ 20 Mut/Mb

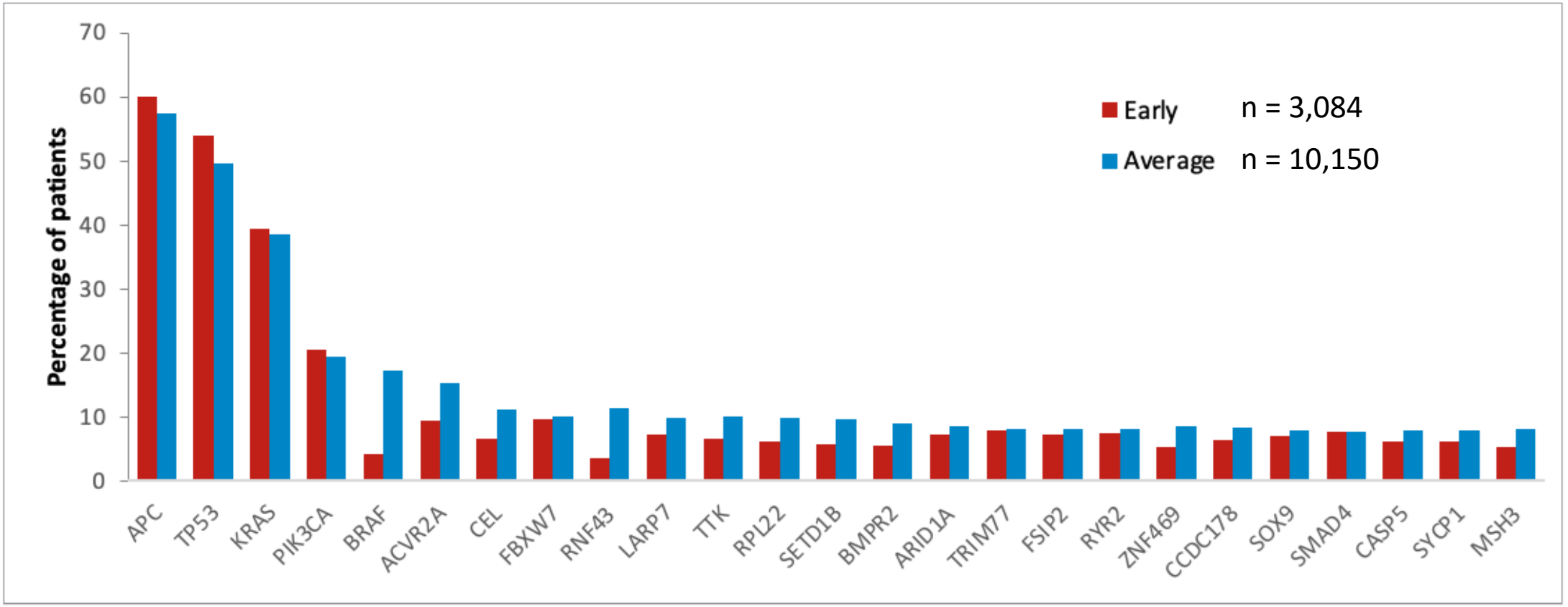


EOCRC was 3.2 times more likely to be MSS/TMB-High compared to AOCRC (p<0.001)

Results

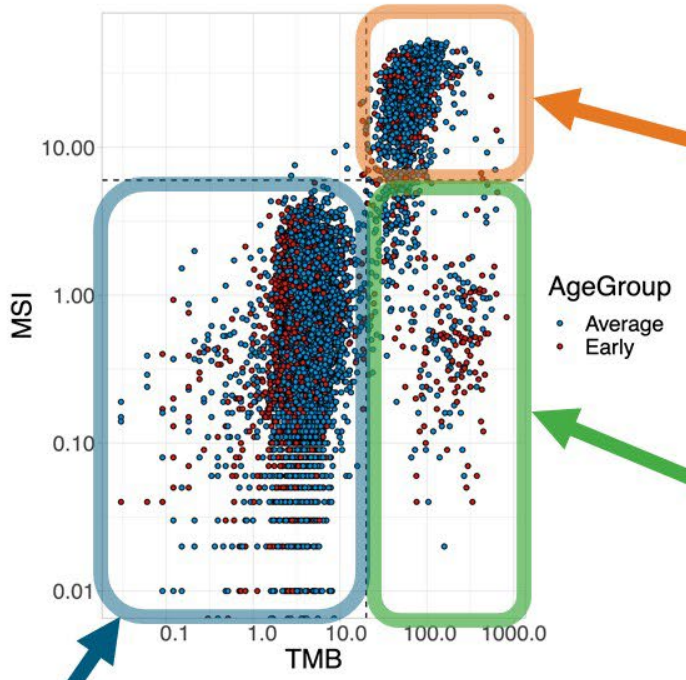


Overall cohort:
Mutational landscape similar compared to previously published studies



Key genomic differences between EO and AO

(significance: adjusted p-value < 0.05)



MSI-H/TMB-High: EO compared to AO has:

- More *KRAS* mutations (46% vs 15%)
- More *PIK3CA* mutations (47% vs 28%)
- More *ERBB2/3* mutations (16% and 13% vs 7% and 5%)
- Fewer *BRAF* mutations (8% vs 65%)
- Fewer *RNF43* mutations (25% vs 59%)

MSS/TMB-High: EO compared to AO has:

- More *POLE* mutations (65% vs 35%)
- Fewer *ACVR2A* mutations (32% vs 51%)

MSS/TMB-Low: No relevant differences

PRESENTED BY: Eric M. Lander, MD

WORLD CONGRESS ON Gastrointestinal Cancer

ESMO

Tumor mutational signatures in early-onset versus average-onset colorectal cancer

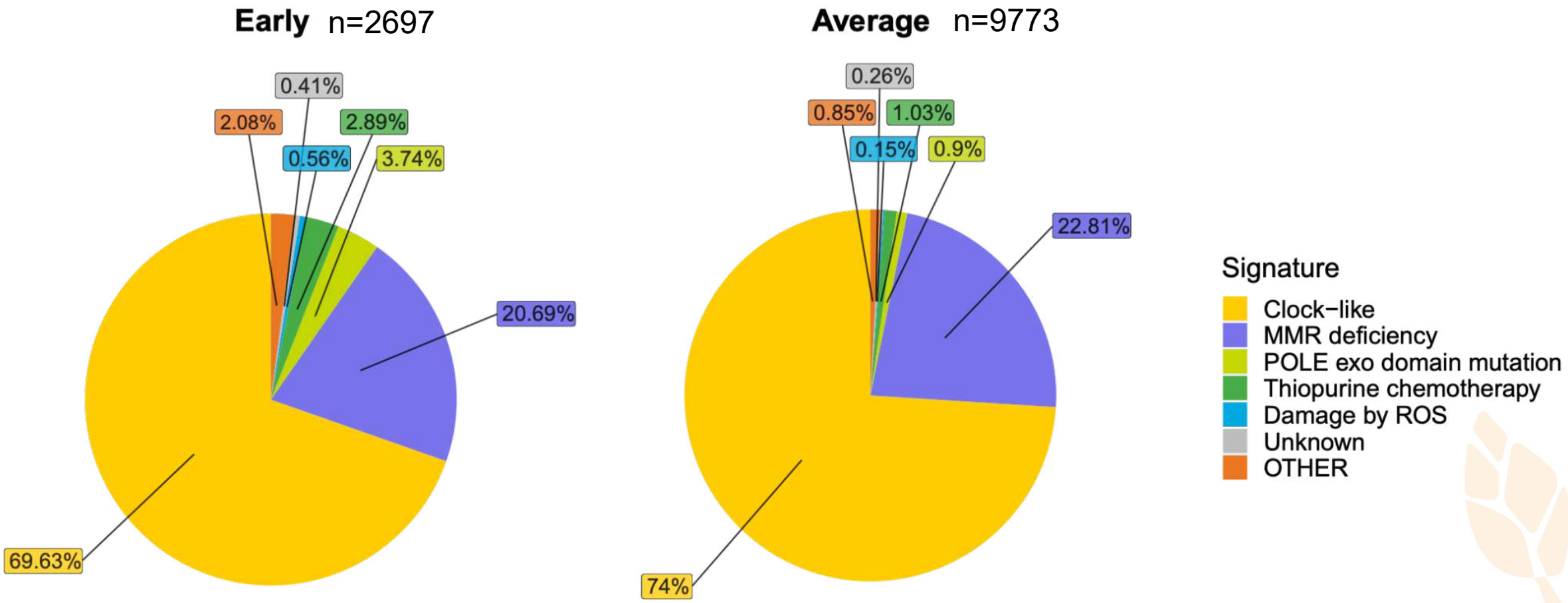
Eric M. Lander[1], Samuel Rivero-Hinojosa[2], Vasily N. Aushev[2], Minetta C. Liu[2], Adham Jurdi[2], Cathy Eng[1]

[1]Division of Hematology/Oncology, Vanderbilt-Ingram Cancer Center, Nashville, TN, USA
[2]Natera, Inc. Austin, TX, USA

VANDERBILT-INGRAM CANCER CENTER

Results – Overall Cohort

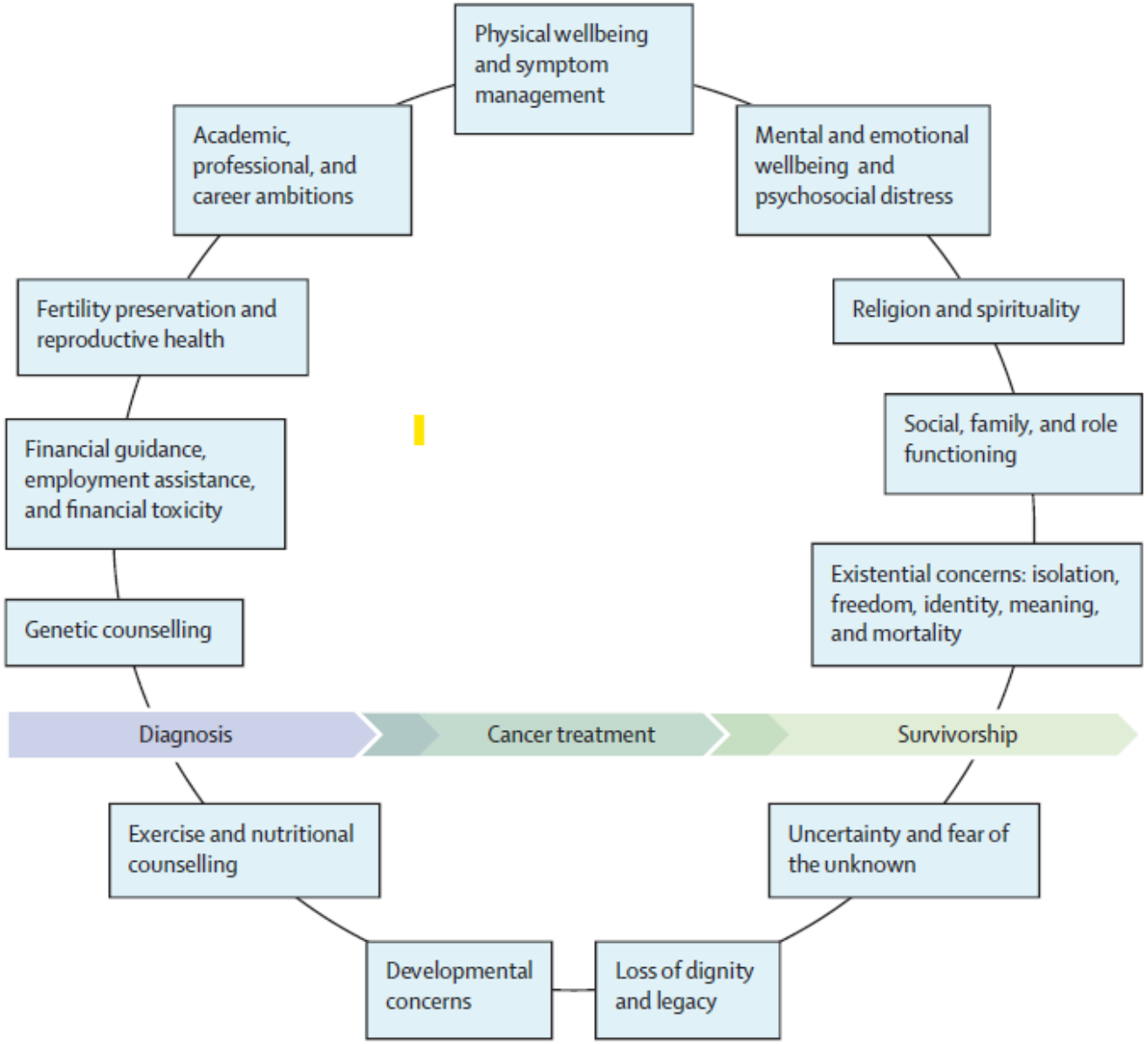
- POLE exonuclease domain signature 4.2 times (p<0.001) more likely in EOCRC.
- Thiopurine chemotherapy signature 2.8 times (p<0.001) more likely in EOCRC.
- Damage by ROS signature was 3.2 times (p<0.001) more likely in EOCRC.



Lander et al: WCGIC 2023

Addressing the Unmet Needs of EOCRC Patients

Optimizing the Care of EOCRC Patients



Eng et al: Lancet Onc 2022

National Colorectal Cancer Screening Recommendations

Revised Colorectal Cancer Screening Guidelines

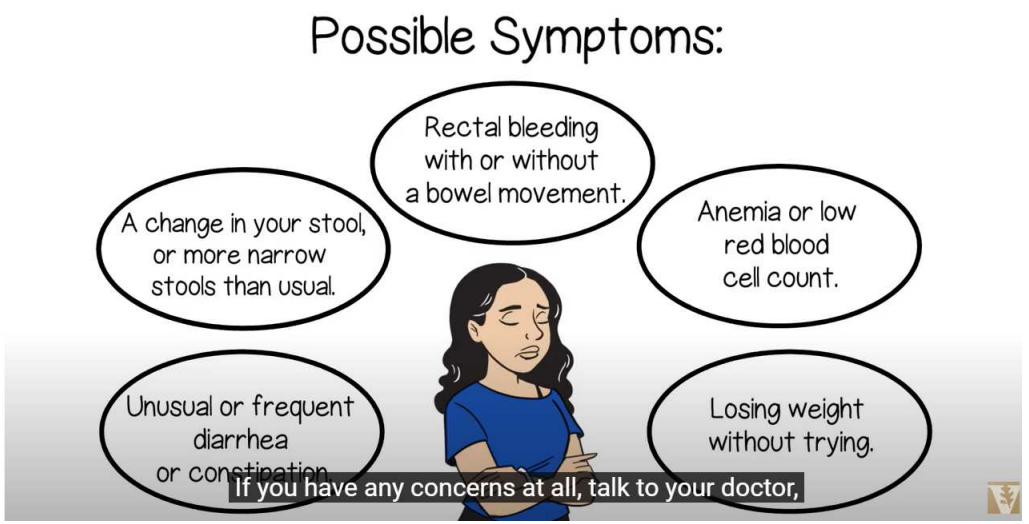
U.S. Preventive Services TASK FORCE

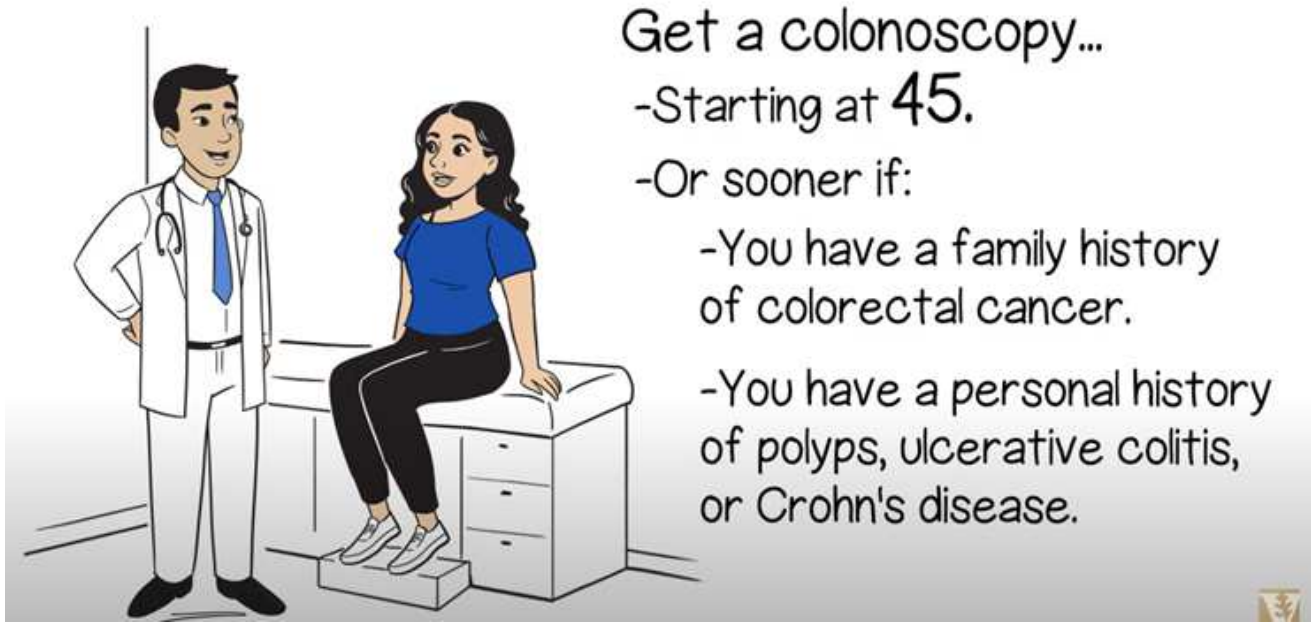
Recommendation Summary

Population	Recommendation	Grade
Adults aged 50 to 75 years	The USPSTF recommends screening for colorectal cancer in all adults aged 50 to 75 years. See the "Practice Considerations" section and Table 1 for details about screening strategies.	A
Adults aged 45 to 49 years	The USPSTF recommends screening for colorectal cancer in adults aged 45 to 49 years. See the "Practice Considerations" section and Table 1 for details about screening strategies.	B
Adults aged 76 to 85 years	The USPSTF recommends that clinicians selectively offer screening for colorectal cancer in adults aged 76 to 85 years. Evidence indicates that the net benefit of screening all persons in this age group is small. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the patient's overall health, prior screening history, and preferences.	C

https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/colorectal-cancer-screening

Vanderbilt-Ingram Cancer Center:
Impact of Education and Awareness on EOCRC



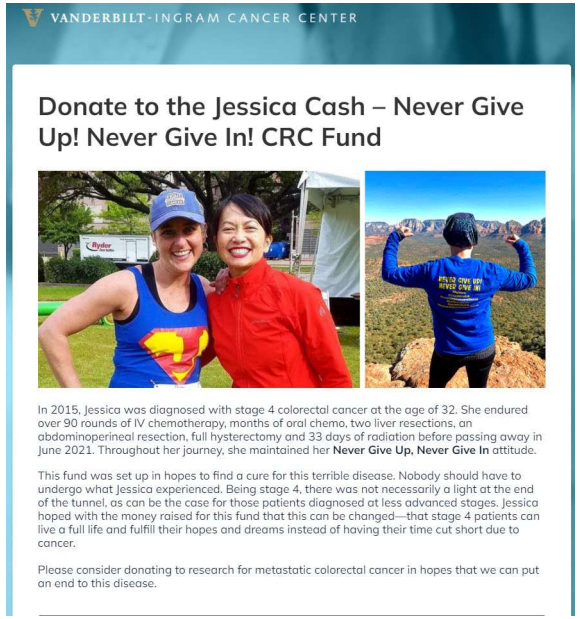


https://www.youtube.com/watch?v=nUh3V9an6So

In Memoriam: JC - “Cancer Thriver”

“When you die it does not mean you lose to cancer, you beat cancer by how you live, why you live, and in the manner in which you live.”
Stuart Scott

Grant and Philanthropic Support


VANDERBILT-INGRAM CANCER CENTER

Donate to the Jessica Cash – Never Give Up! Never Give In! CRC Fund

In 2015, Jessica was diagnosed with stage 4 colorectal cancer at the age of 32. She endured over 90 rounds of IV chemotherapy, months of oral chemo, two liver resections, an abdominoperineal resection, full hysterectomy and 33 days of radiation before passing away in June 2021. Throughout her journey, she maintained her **Never Give Up, Never Give In** attitude.

This fund was set up in hopes to find a cure for this terrible disease. Nobody should have to undergo what Jessica experienced. Being stage 4, there was not necessarily a light at the end of the tunnel, as can be the case for those patients diagnosed at less advanced stages. Jessica hoped with the money raised for this fund that this can be changed—that stage 4 patients can live a full life and fulfill their hopes and dreams instead of having their time cut short due to cancer.

Please consider donating to research for metastatic colorectal cancer in hopes that we can put an end to this disease.

colorectal cancer alliance

Melissa O. Waddey Cancer Discovery Grant

NASHVILLE WINE AUCTION

COLON CANCER COALITION

Mills Family

2ND ANNUAL 5K Live Like Lisa

Hope Family

Group Effort for Young Adult Cancers Program

www.youngadultswithcancer.com

THE HEIMERDINGER FOUNDATION

GILDA'S CLUB NASHVILLE

An Affiliate of the CANCER SUPPORT COMMUNITY

SURVIVOR FITNESS

AUSTIN HATCHER FOUNDATION for pediatric cancer

March 2023

Courtesy of Anjee Davis

Acknowledgements:

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- Christopher Cann
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- Eric Lander
- GI Program Clinical Teams