Session Ten

Panel
Early-Age Onset Colorectal Cancer: What's Experienced, What's Known, and What's Next?

American Cancer Society | NATIONAL COLORECTAL CANCER ROUNDTABLE

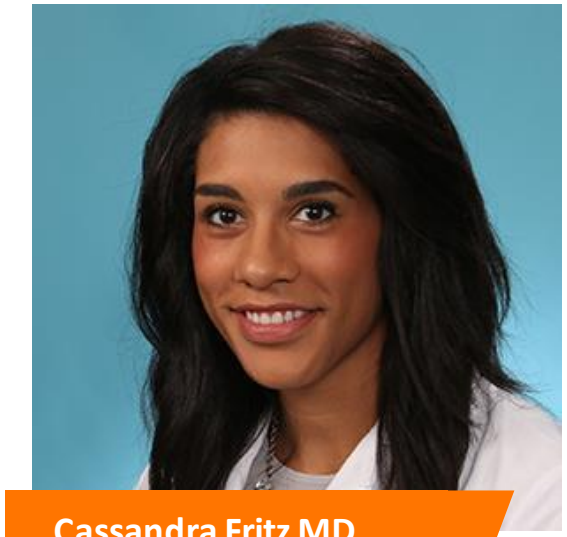
11:15 AM to 12:30 PM

Panel
Early-Age Onset Colorectal Cancer: What's Experienced, What's Known, and What's Next?

Moderator
Allison Rosen
MS

Suzy Reyes

Scott Kopetz
MD, PhD, FACP



Cassandra Fritz MD,
MPHS

Azucena (Suzy) Reyes

Suzy Reyes
Early-Age Onset Colorectal Cancer Survivor

Azucena (Suzy) Reyes

Cancer Survivor


AMERICAN


ALLERGY ALERT

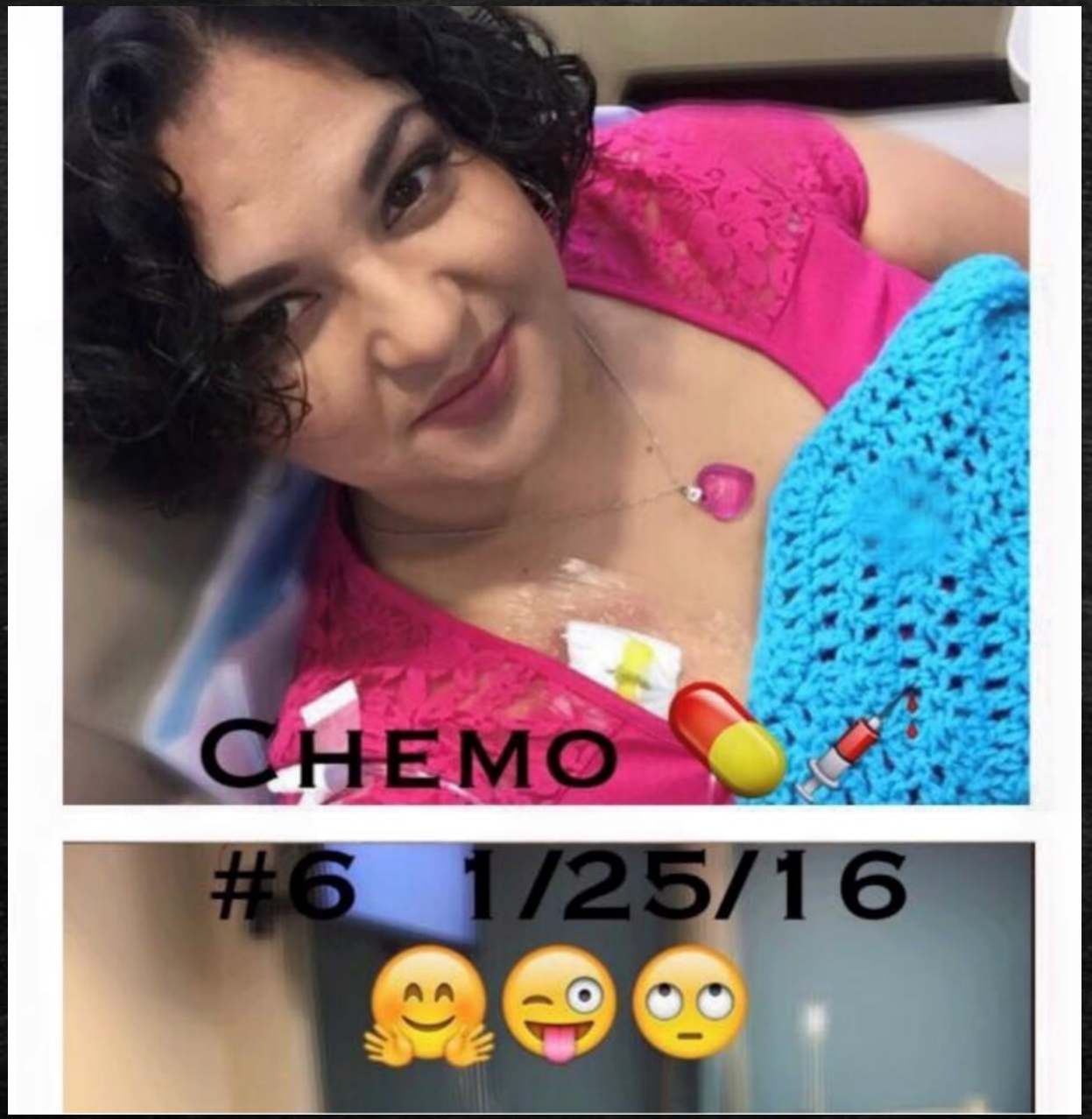

1st
Chemotherapy
1 down out of 12
11/16/2016


Chemotherapy
#2
November
30,2015

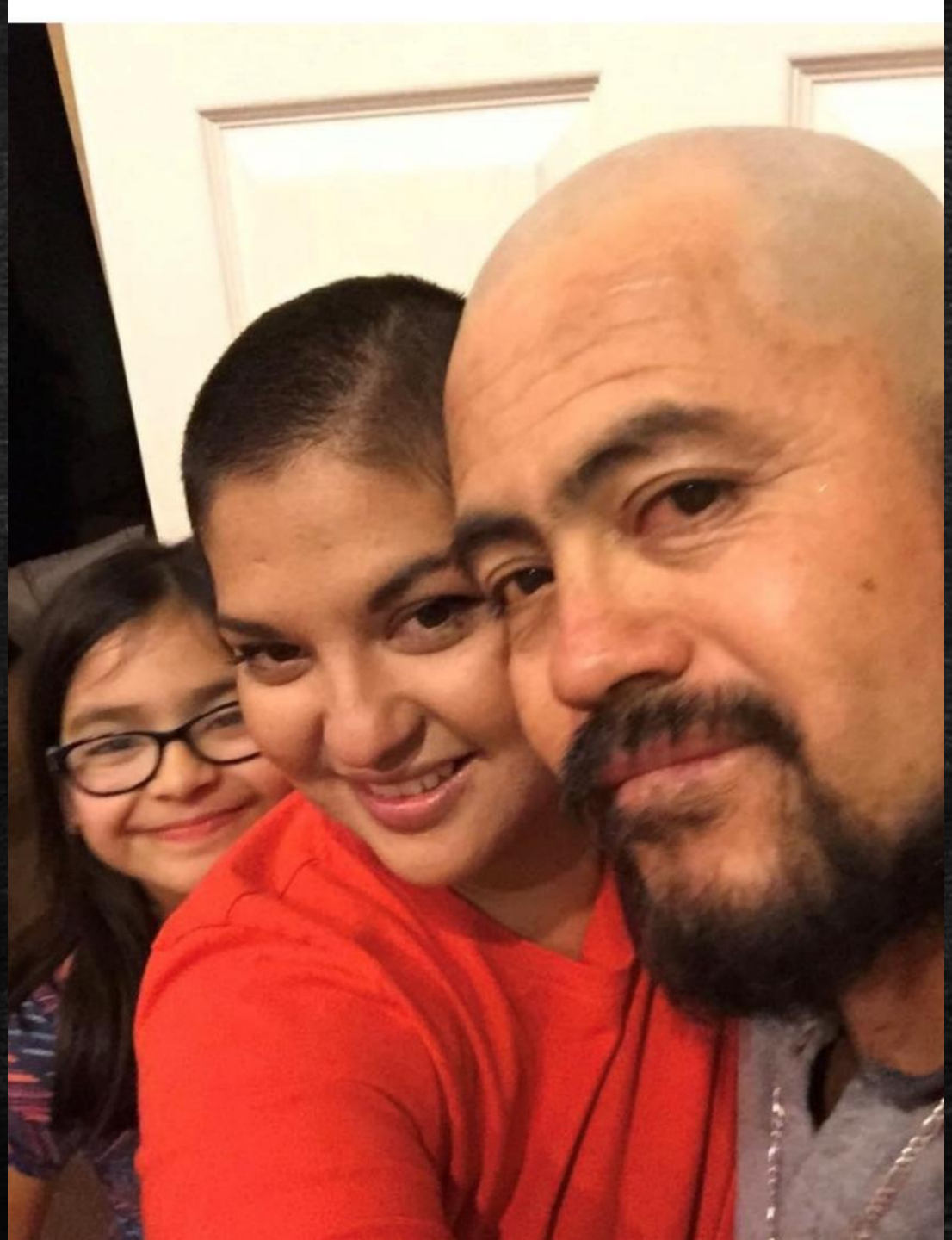

CHEMOTHERAPY
3 😜
12/14/2015💉


CHEMOTHERAPY
#4 😬🙄💊💉

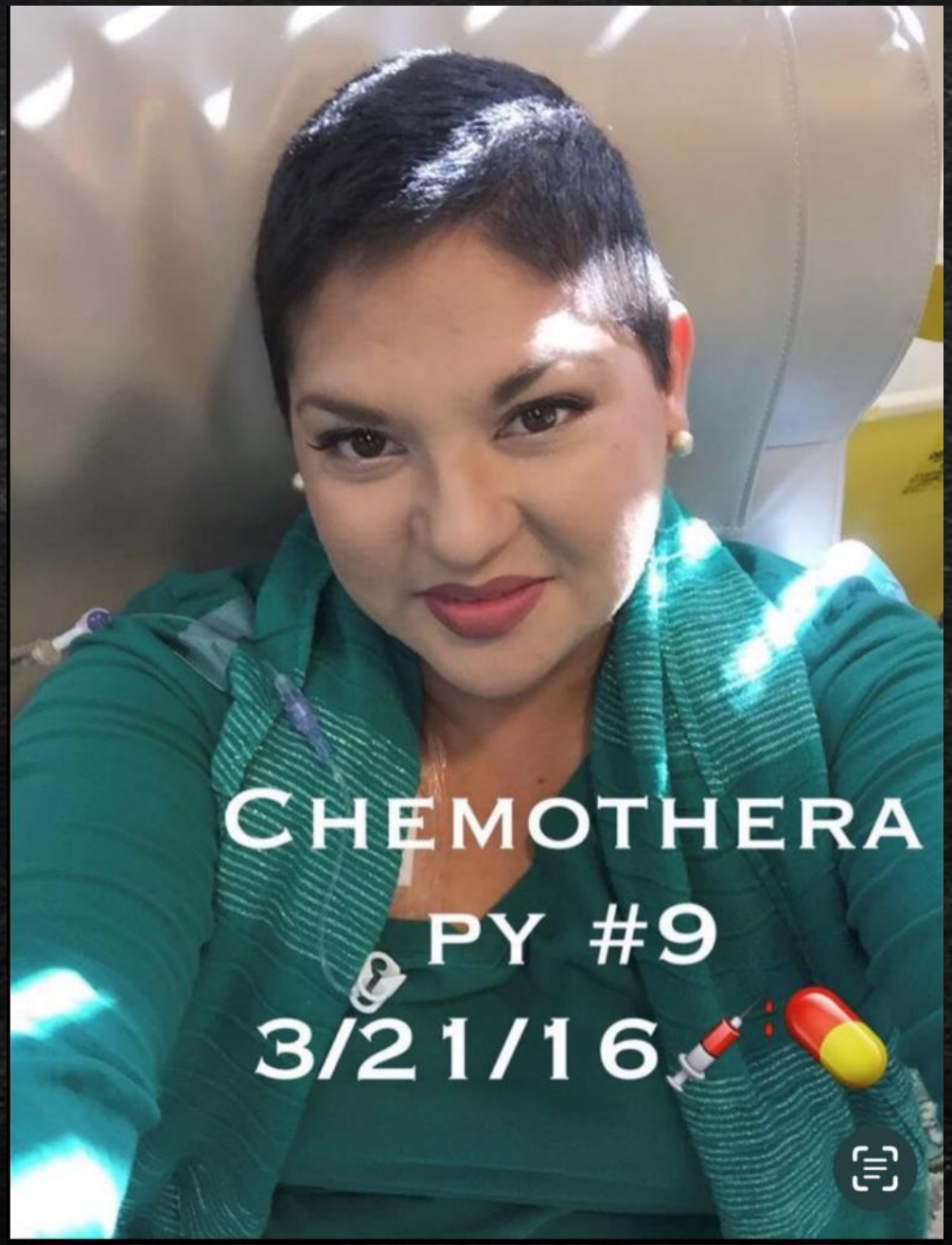

CHEMOTHERAPY
#5 💉💊😁
1/11/16


CHEMO
#6 1/25/16


CHEMOTHERAPY
#7 2/8/16



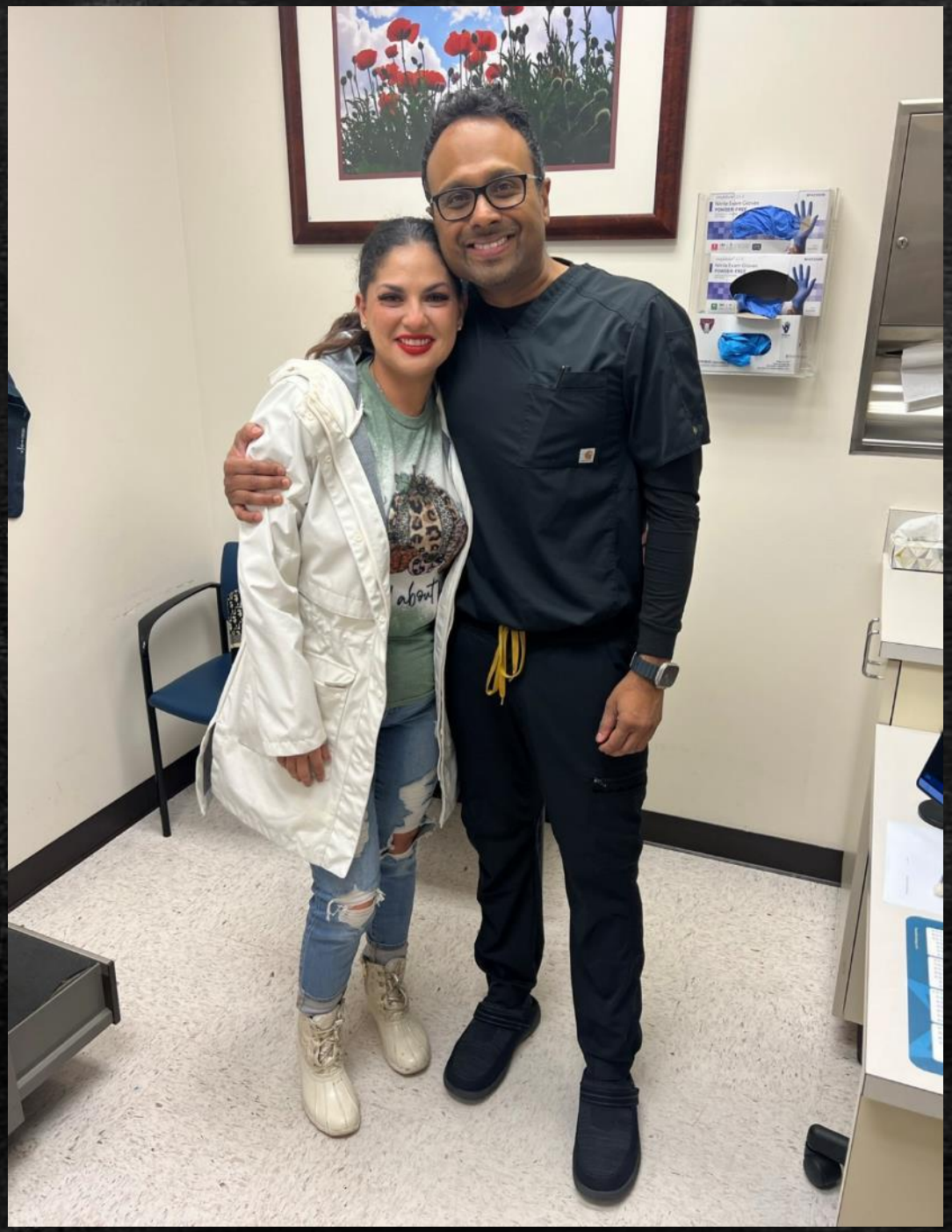

CHEMOTHERAPY # 8
2/22/16

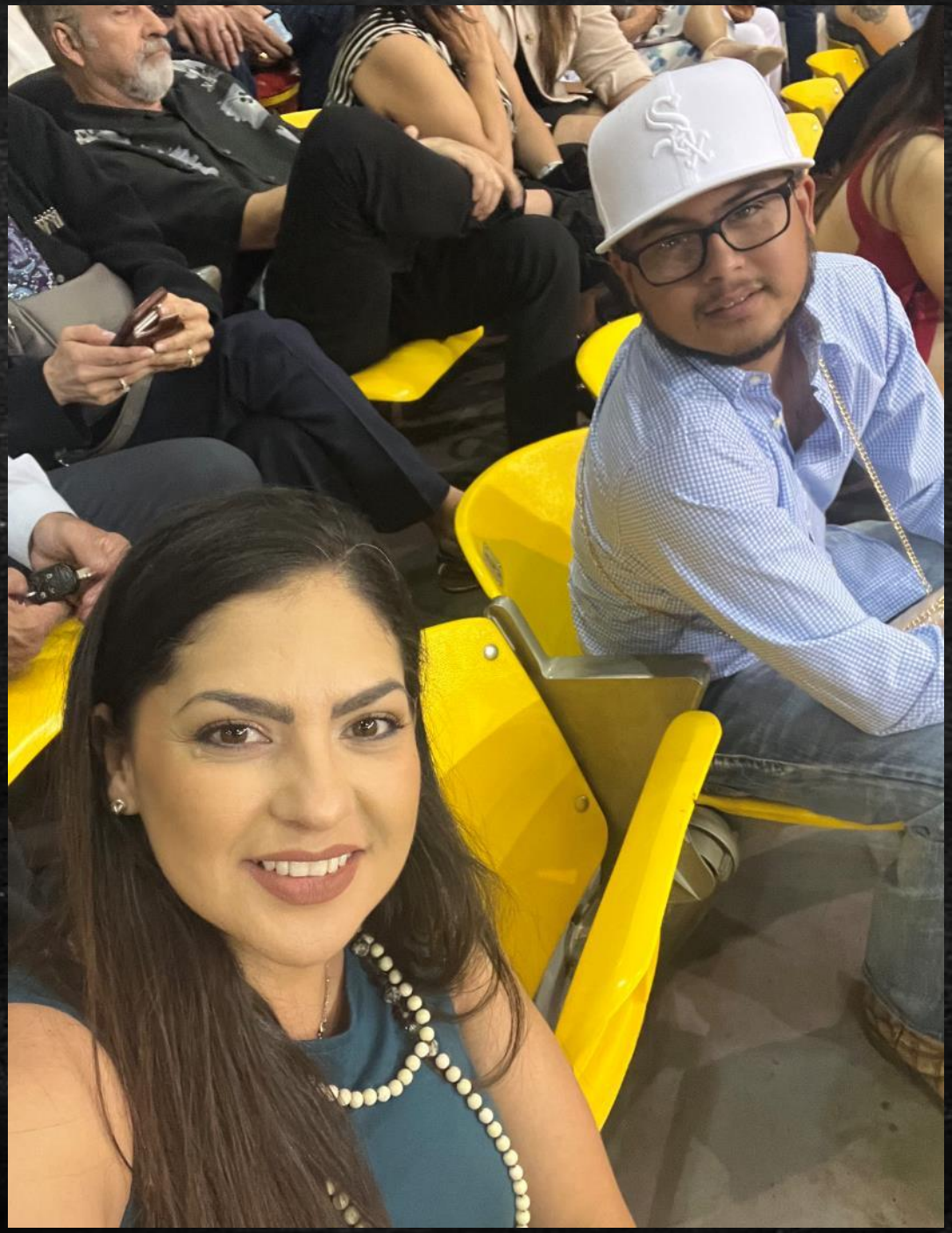

CHEMOTHERA
PY #9
3/21/16


CHEMOTHERAPY
#11
4/19/16 💉💊💪
😬
ARIBO
OLD BEARS


FINAL CHEMO
Ring the Bell...
...then
RUN LIKE HELL!
FINAL CHEMO RING THE
THEN RUN LIKE
HELL !!!
4/3/16


CANCER
FREE






21


Stitch

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Thank You

nccrt.org @NCCRTnews #80inEveryCommunity

Overview of Early-Onset Colorectal Cancer

Scott Kopetz, MD, PhD, FACP
Deputy Chair for Translational Research and Professor
Department of Gastrointestinal (GI) Medical Oncology, Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Overview of Early-Onset Colorectal Cancer

Scott Kopetz, MD, PhD

Department of Gastrointestinal Medical Oncology
MD Anderson Cancer Center

Topics

01

EPIDEMIOLOGY

The epidemiology of EOCRC globally and in the United States.

02

EXPOSOME

Exposures or risk factors potentially contributing to the rising risk of EOCRC.

03

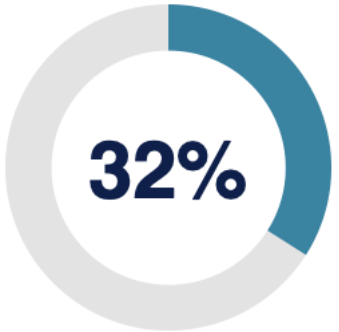
GENETICS & EPIGENETICS

Molecular aspects of EOCRC.

US Incidence

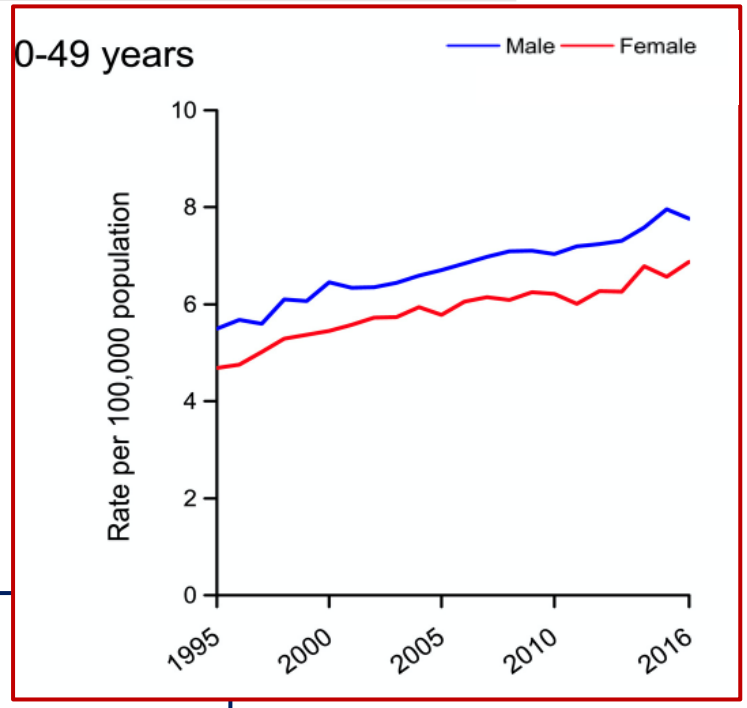
Incidence of EOCRC

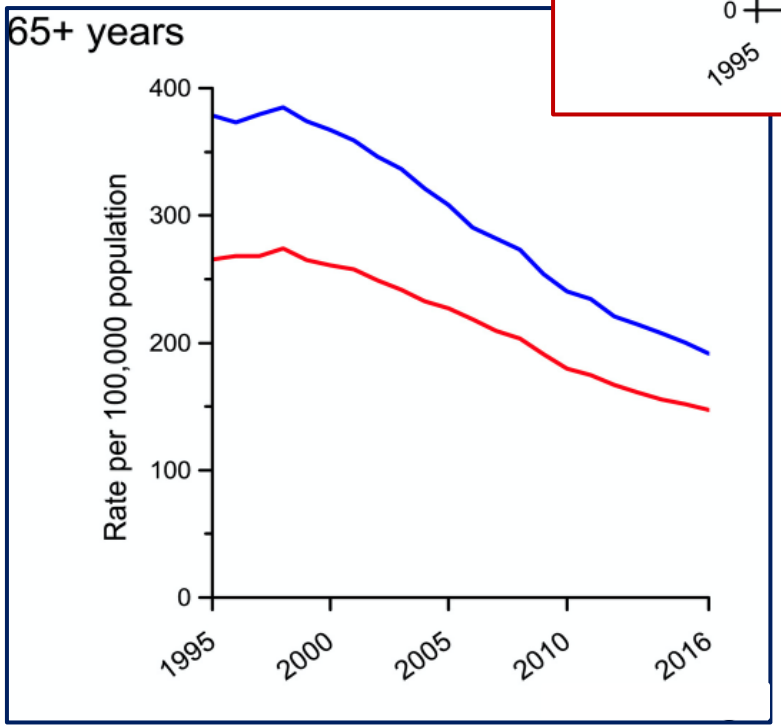
Incidence rate of EOCRC raised by more than 50% in both genders since 1994.



Incidence of LOCRC

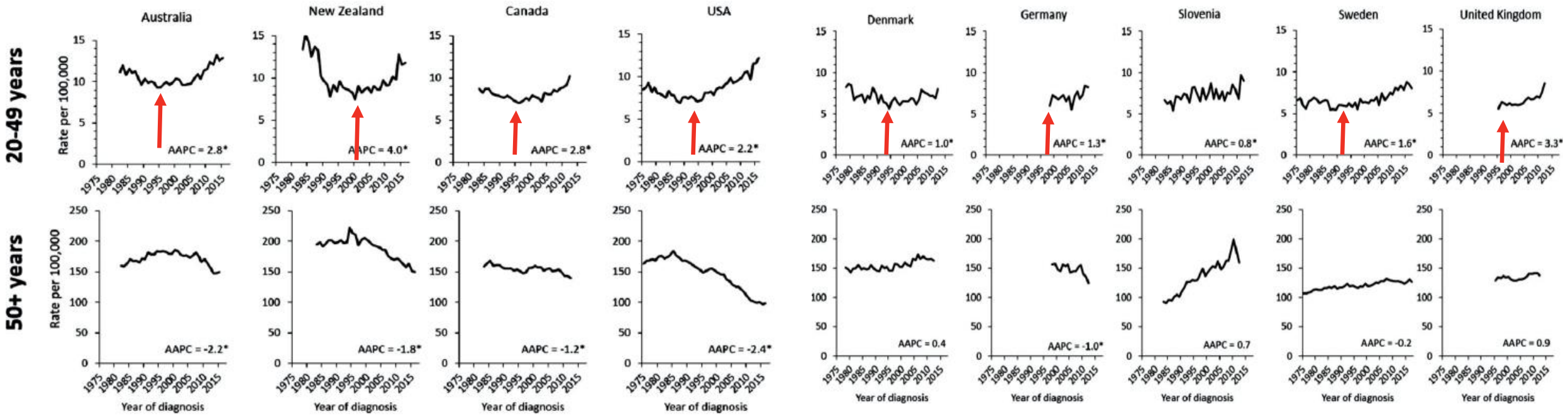
Incidence rate of LOCRC declined by around 34% in both genders since 2000.





Siegel RL, et al. CA Cancer J Clin' 2020

Global Prevalence: Europe, North America & Oceania



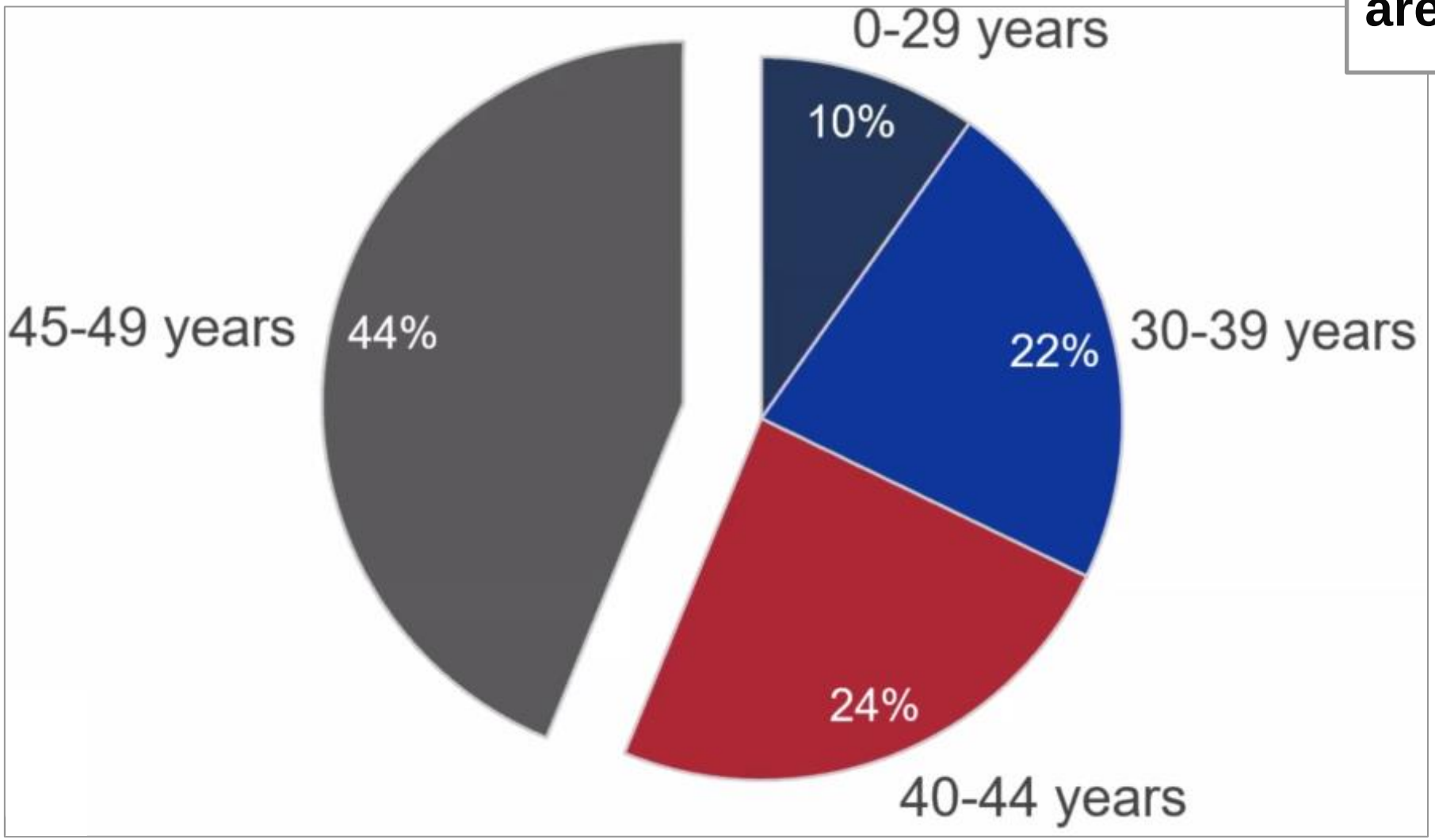
EOCRC incidence **increased** in 19 countries. **Nine** of which had stable or **declining** trends in older adults.

Average annual per cent change (AAPC) in colorectal cancer incidence by age during the most recent 10 years of available data.

Siegel RL, et al. Gut'19

EOCRC Age Distribution

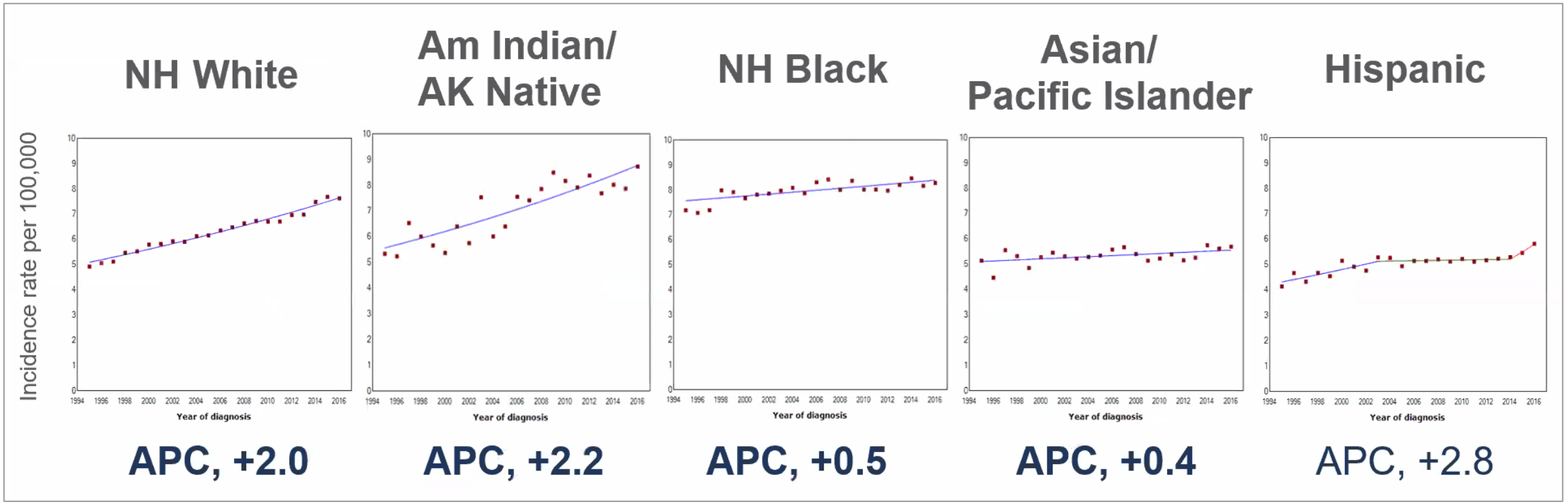
44% of EOCRC cases are 45-49 years old



Slide from Siegel RL, 2020

EOCRC by Race/Ethnicity

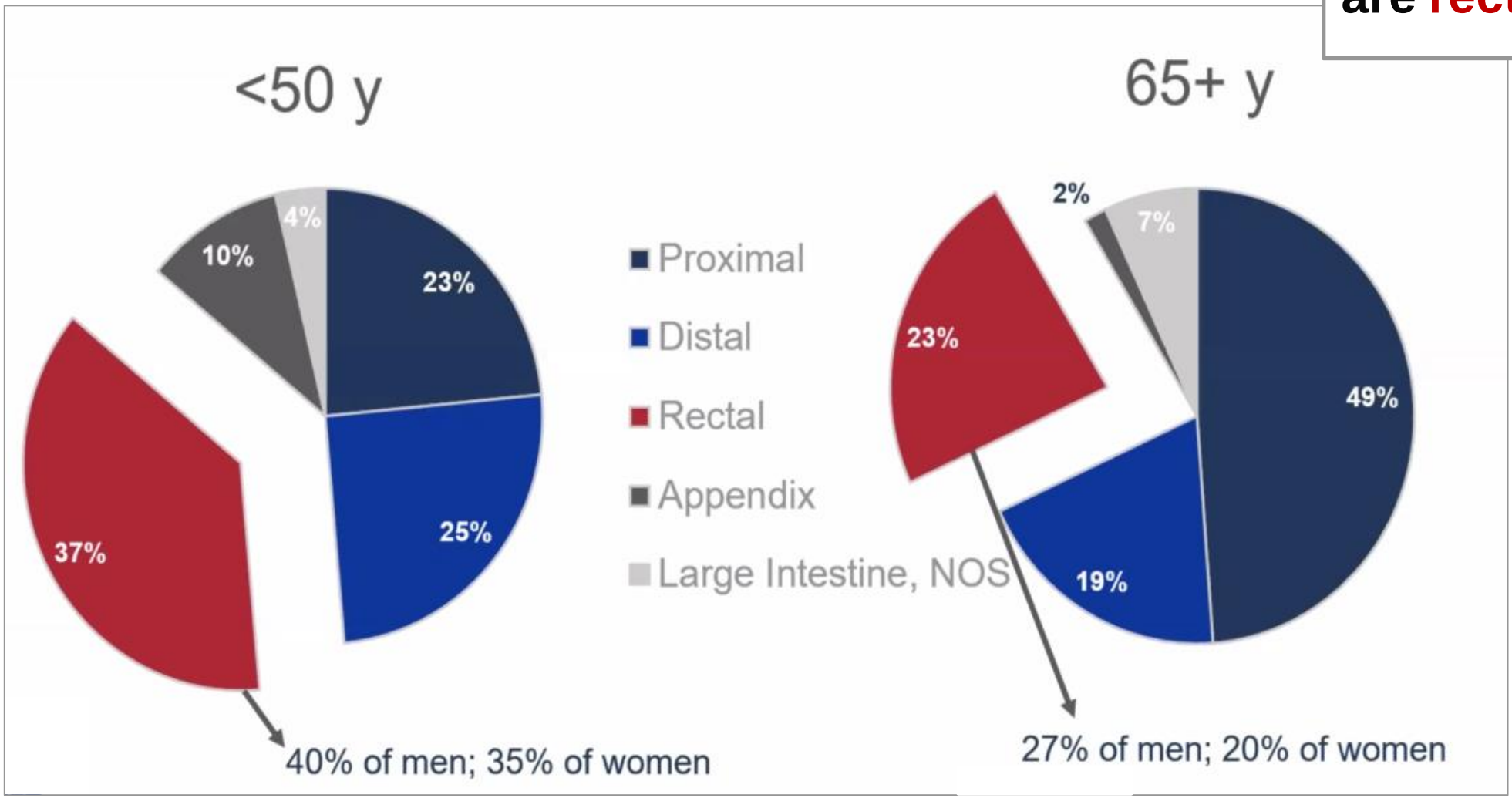
Annual per cent change (APC)
Bold = p<0.05



Siegel RL, et al. CA Cancer J Clin' 2020

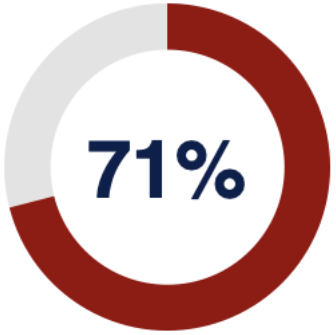
EOCRC Subsite

40% of EOCRC cases are rectal cancer



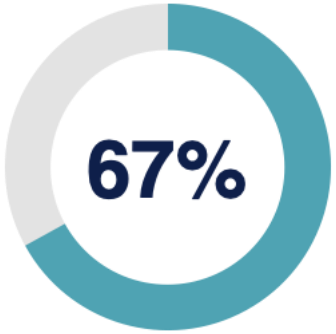
Slide from Siegel RL, 2020

EOCRC Clinical Diagnosis



Stage

Diagnosed at **stage III or IV.**

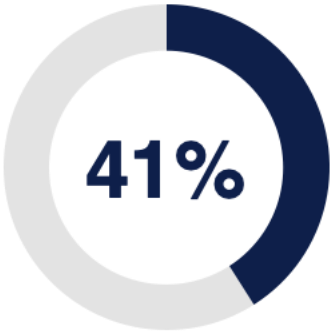


Diagnosis Time

Visited t**wo physician** at least before they get the diagnosis.

Family

Around 80% with young children



Diagnosis Period

Waited **six months** at least when they experienced symptoms before talking to a doctor

Colorectal Cancer Aliiance 2018

MD Anderson

AGENDA

01

EPIDEMIOLOGY

The epidemiology of EOCRC globally and in the United States.

02

EXPOSOME

Exposures or risk factors potentially contributing to the rising risk of EOCRC.

03

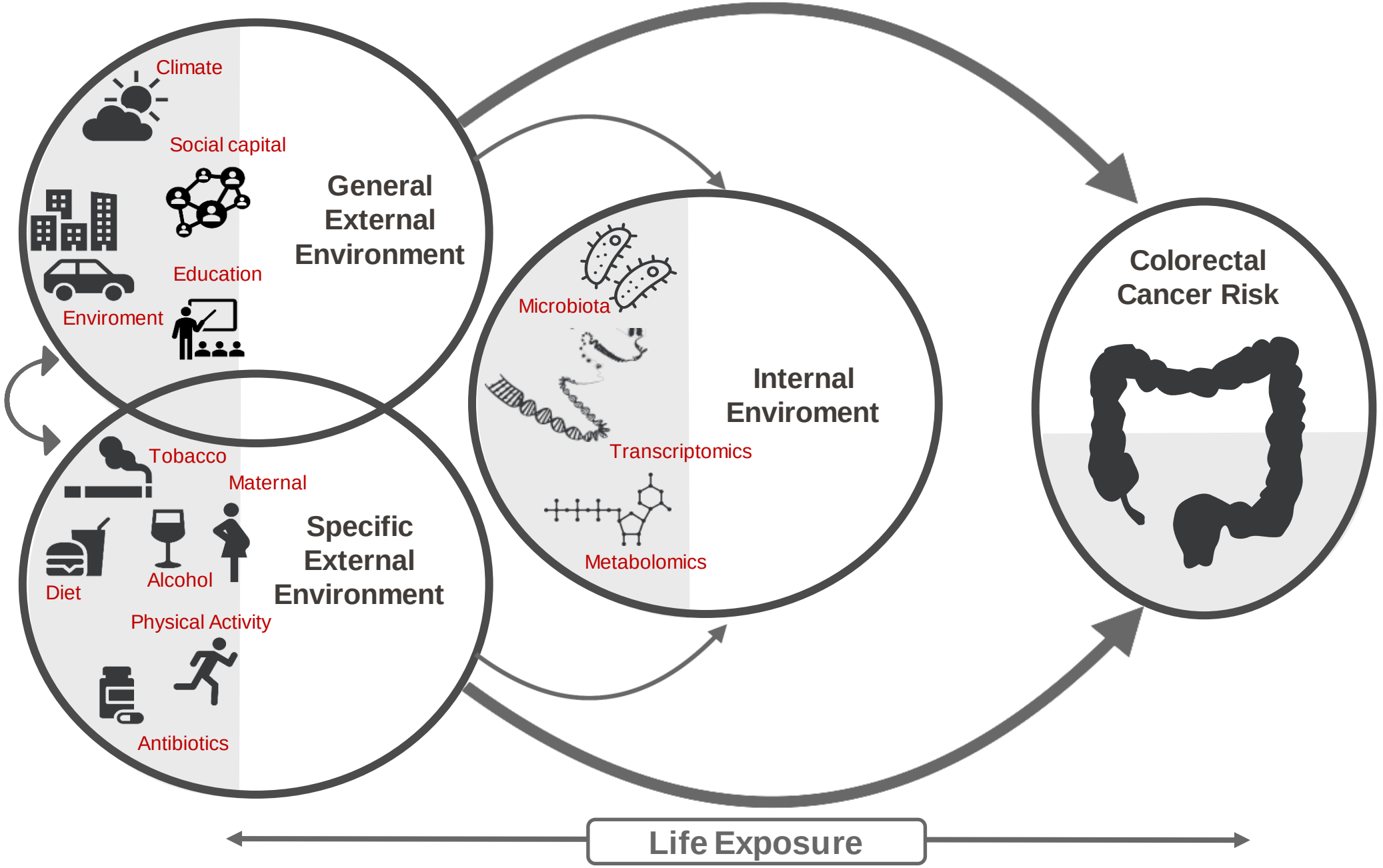
GENETICS & EPIGENETICS

Molecular aspects of EOCRC.

04

CONCLUSION

Remarks and recommendations


Climate
Social capital
General
External
Environment
Education
Enviroment
Tobacco
Maternal
Specific
External
Environment
Diet
Alcohol
Physical Activity
Antibiotics
Microbiota
Internal
Enviroment
Transcriptomics
Metabolomics
Colorectal
Cancer Risk
Life Exposure

Specific External Environment

Etiological factors	Level of evidence	Unit increase	RR (95% CI)	Temporal trend
Obesity	++	5 kg/m^2 in BMI	1.05 (1.03–1.07)	↑
Western dietary pattern	++	Highest vs lowest	1.12 (1.01–1.24)	Poorest in 2000s then stable
Processed meat	++	50 g per day	1.16 (1.08–1.26)	↔
Alcohol (as ethanol)	++	10 g per day	1.07 (1.05–1.09)	Peak in 1980s then ↓
Red meat	+	100 g per day	1.12 (1.00–1.25)	Peak in 1970s then ↓
Diabetes	+	Yes vs no	1.30 (1.20-1.40)	↑
Smoking	+	Current vs never	1.15 (1.00–1.32)	↓
Total physical activity	--	5 MET- hours per week	0.97 (0.94–0.99)	↔
Aspirin	--	75-1200 mg per day	0.76 (0.63–0.94)	↑
Total fiber	-	10 g per day	0.93 (0.87–1.00)	↑
Whole grain	-	90 g per day	0.83 (0.79–0.89)	↑
Total calcium	-	300 mg per day	0.92 (0.89–0.95)	↑

Keum *et al*, Nature Reviews Gastro, 2019; Daniel *et al*, Public Health Nutr, 2011; Menke *et al*, JAMA, 2015; Larson *et al*, JNCI, 2005; Albertson *et al*, Nutr J., 2016; Labarthe *et al*, Circulation 1996; Gahche *et al*, NCHS Data Brief, 2011

Table by Yin Cao

Microbiome

Early-life exposures

Mode of nutritional provision
- Breastfeeding
- Diet formula
- Pre-probiotic supplement

Mode of delivery
- Caesarean
- Vaginal

Environment
- Psychological and/or physical stress

Family environment and pets

Genetics

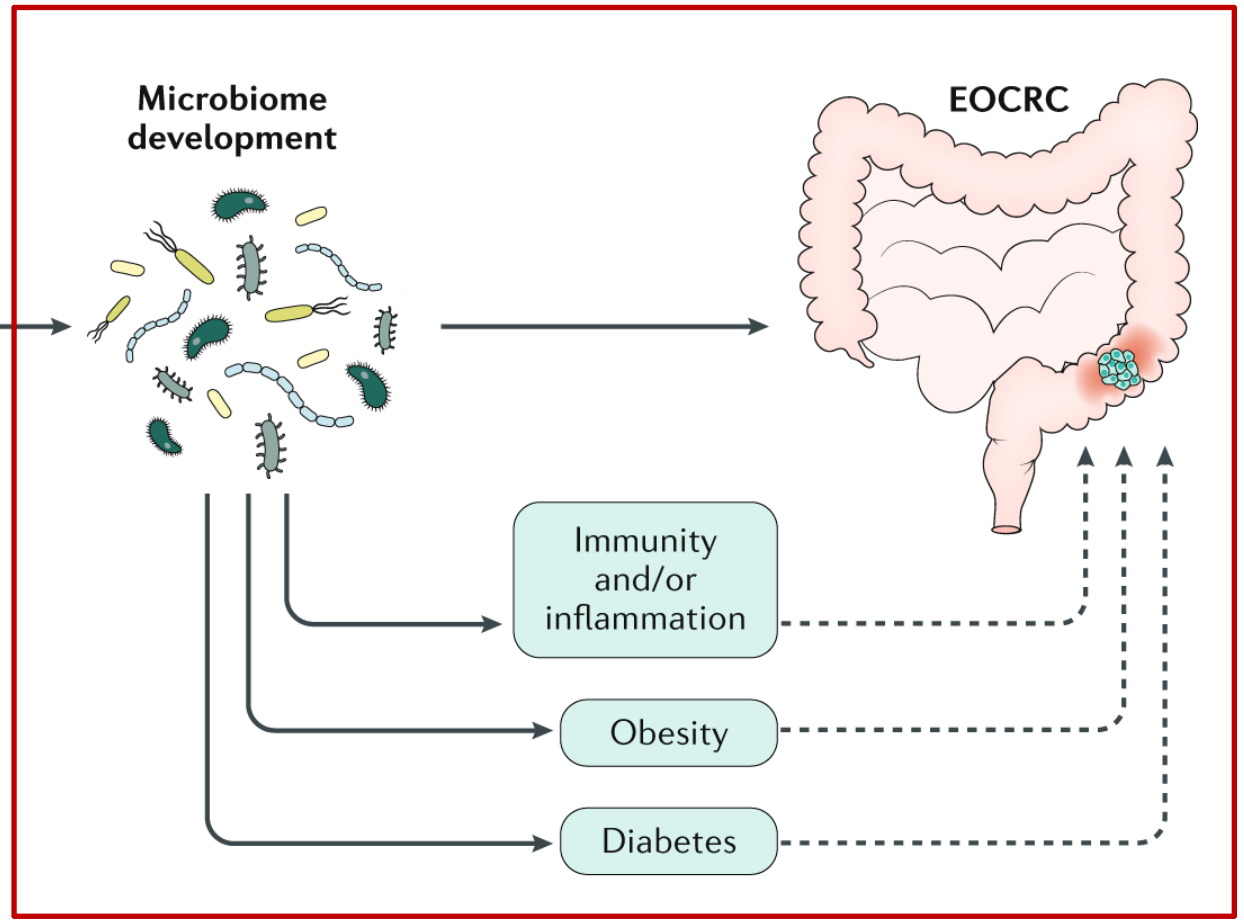
Antibiotics
- 2.7 courses by age 2 years
- 10.9 courses by age 10 years

Maternal infection, disease and/or medication

Maternal nutrition

Maternal stress

Exposomal elements
- Global westernization of diet
- Unhealthy cooking practices
- Red and processed meats
- Synthetic dyes
- MSG
- Titanium dioxide
- High-fructose corn syrup



Infancy → Childhood → Adulthood

Table by Yin Cao

Molecular Features: MD Anderson + AACR GENIE + Foundation Medicine

	MDACC Molecular Cohort	MDACC Tumor Registry Cohort	AACR Project GENIE Cohort	CMS Cohort
Patient Information	• N=1877 • Seen at MDACC from January 1, 2012 to September 1, 2016	• N=32507 • Seen at MDACC from January 1, 1980 to present	• N=1868 • Excluded patients from MDACC to prevent duplication of data	• Total N=626 • N=448 from TCGA N=178 from MDACC
Clinical Data	• Baseline clinical and pathologic characteristics	• Baseline clinical and pathologic characteristics	• Limited clinical and pathologic characteristics	• Limited clinical and pathologic characteristics
Molecular Data	• Mutational data available from 46- or 50-gene CLIA next-generation sequencing panel	• Unavailable	• Mutation data available from AACR Project GENIE database, which includes a mixture of next-generation sequencing platforms	• RNA expression data. • For TCGA patients, data were publicly available. • For MDACC patients, data were obtained with Affymetrix RNA expression arrays.
Cancer Stage(s)	• Stage IV	• Stages I-IV	• Majority stage IV	• Stages I-IV
Additional Data	• Comorbid predisposing condition information available for patients < 50 years			• Classification by CMS subtype

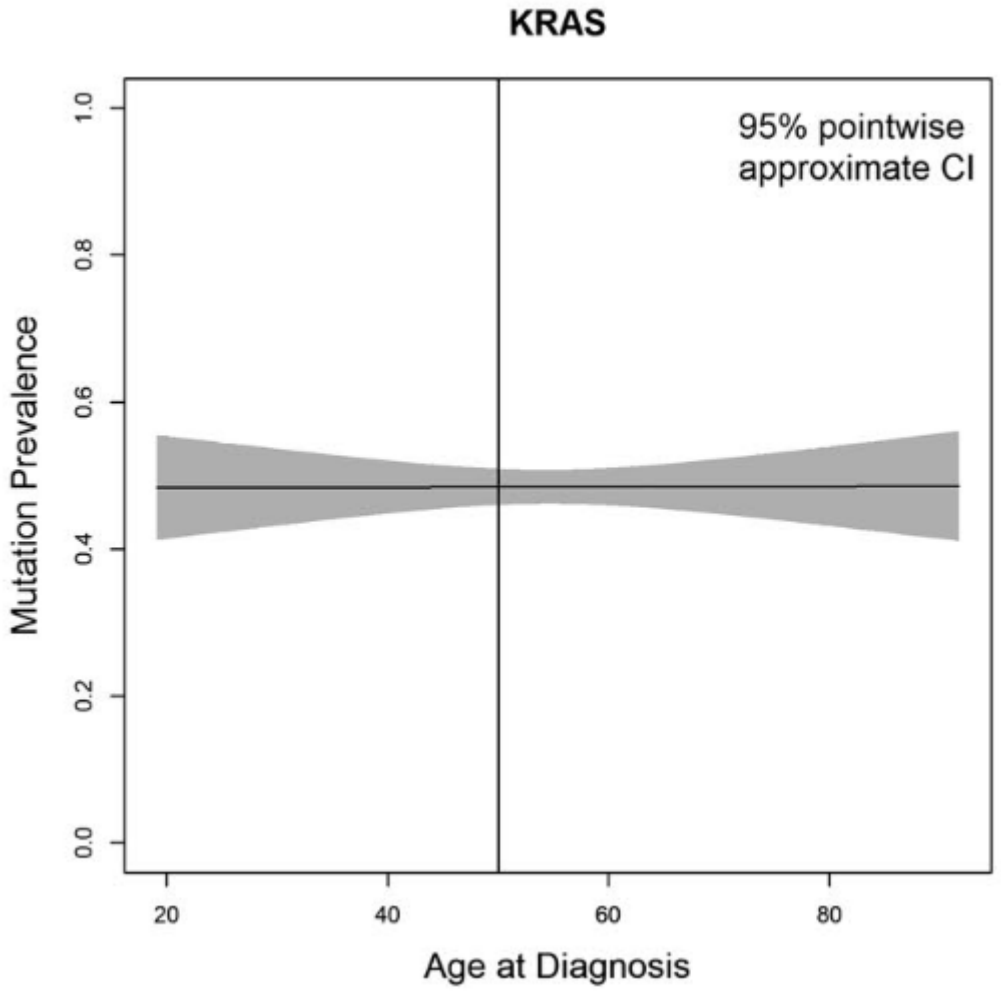
Foundation Medicine

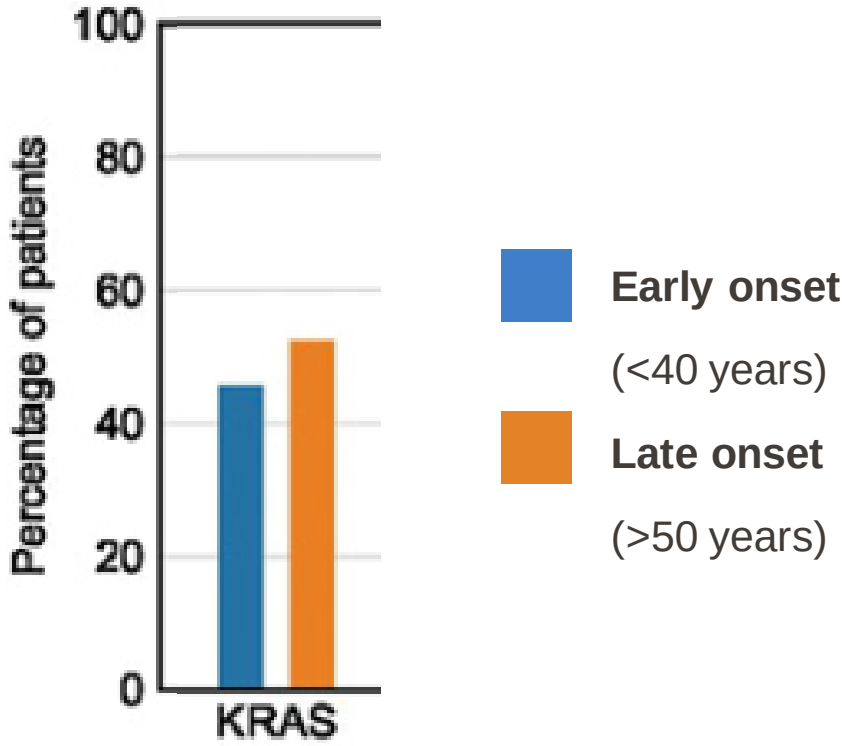
18,218 total patients

- 1,420 patients under the age of 40
- 3,248 between 40 and 49
- 13,550 age 50 and older

Willauer et al Cancer ’19, Lieu et al CCR ‘19

No significant difference in *KRAS*, *NRAS* mutations





Willauer et al Cancer '19, Lieu CCR '19

Foundation One molecular testing

Table 1. Significant alterations and alterations in genes of interest between cohorts using false discovery rate (FDR) in MSS colorectal cancer (CRC) and MSI-H colorectal cancer

	Alteration rates in the MSS cohort		
Gene	Rate observed in under 40 group (%)	Rate observed in 50 and over group (%)	FDR
TP53	82.3	76.7	1.56E−05
APC	65.8	79.7	4.84E−26
KRAS	45.6	52.4	1.56E−05
PIK3CA	14.1	17.5	0.002959601
CTNNB1	4	2.7	0.013488987
BRAF	5.2	7.7	0.002067048
FAM123B	2	6.8	1.35E−12
NRAS	3.7	4.6	0.171847712

Lieu et al CCR ‘19

Consensus Molecular Subtypes Differences: Higher CMS1

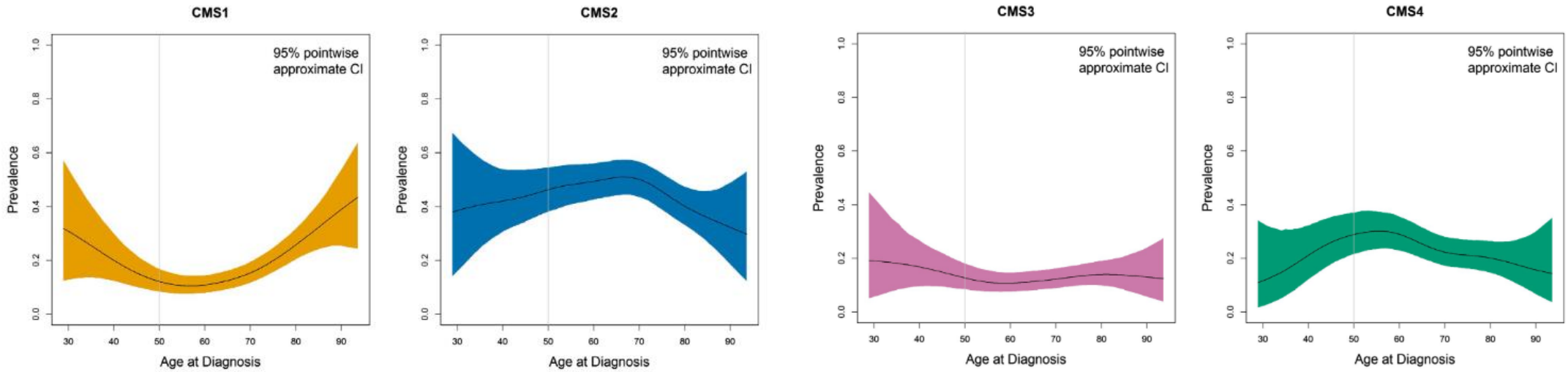


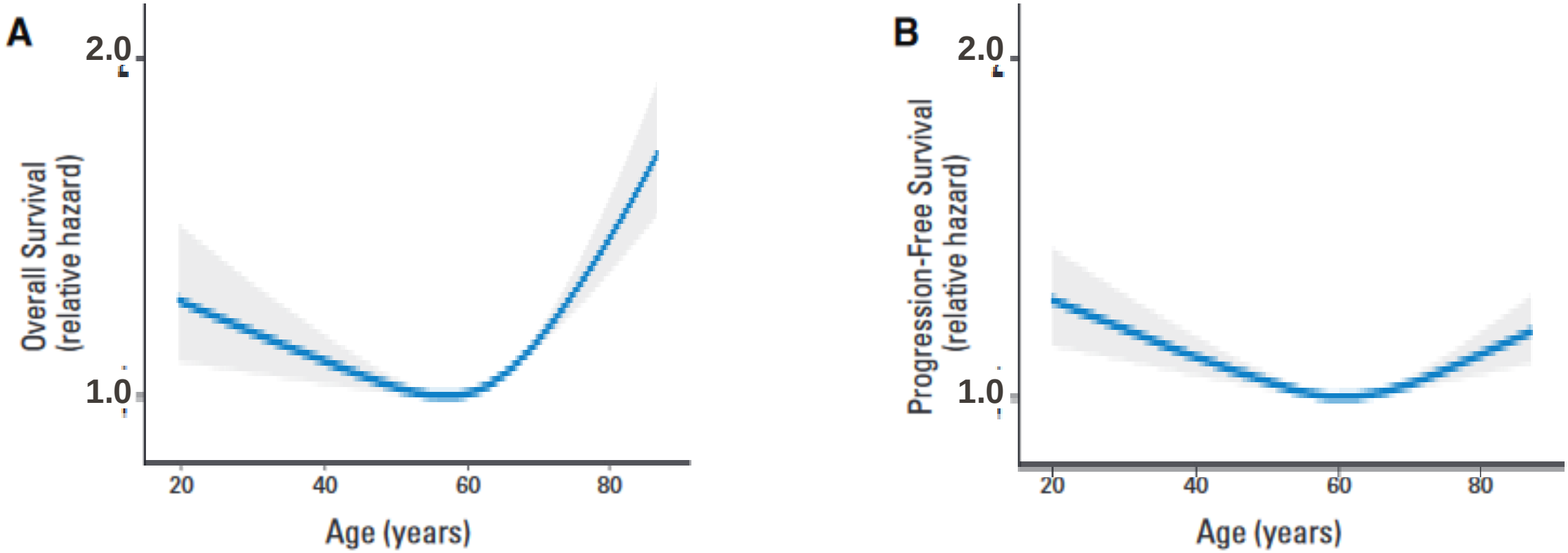
TABLE 1. Baseline Characteristics of the MDACC Molecular Cohort Classified by Age

	Age						
Characteristic	18-29 y	30-39 y	40-49 y	50-59 y	60-69 y	≥70 y	*P*
Patients, No. (%)	46 (2)	177 (9)	411 (22)	605 (32)	454 (24)	184 (10)	
MSI-H (n = 1525, 81% known), No. (%)	3 (7)	12 (8)	23 (3)	11 (2)	13 (4)	6 (4)	.038

High CMS1 despite low rates of MSI-H

Willauer et al Cancer '19

Overall survival and progression-free survival from diagnosis of mCRC is worse for EOCRC patients



20,003 patients from 24 first line studies of mCRC (ARCAD database)

Lieu et al JCO '14

Are we overtreating Young Adults with Colon Cancer?

More intense treatments with unmatched survival gains

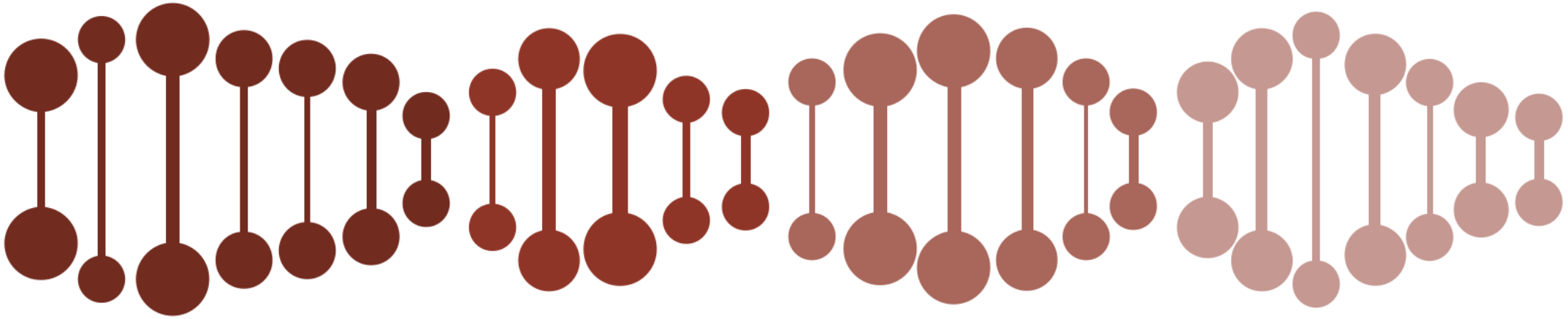
Table 2. Likelihood of Receiving Postoperative Systemic Chemotherapy and Multiagent Regimens for Young Adults (Ages 18-49 Years at Diagnosis) vs Older Adults (Ages 65-75 Years at Diagnosis) With Colon Cancers[a]

Patients Who Received Chemotherapy	Any Chemotherapy, No. (%)	Odds Ratio for Receiving Chemotherapy (95% CI)	Multiagent Regimens, No. (%)	Odds Ratio for Receiving Multiagent Regimen (95% CI)
Stage I				
Ages 65-75 y (n = 8991)	162 (1.8)	1 [Reference]	52 (43.0)	1 [Reference]
Ages 18-49 y (n = 1926)	109 (5.7)	2.88 (2.21-3.77)	43 (48.3)	1.38 (0.71-2.68)
Stage II Overall				
Ages 65-75 y (n = 11 011)	2748 (25.0)	1 [Reference]	773 (41.7)	1 [Reference]
Ages 18-49 y (n = 3083)	1732 (56.2)	3.93 (3.58-4.31)	670 (54.9)	1.71 (1.48-1.97)
Stage II Low Risk				
Ages 65-75 y (n = 4822)	923 (19.1)	1 [Reference]	313 (39.6)	1 [Reference]
Ages 18-49 y (n = 1636)	826 (50.5)	4.22 (3.70-4.81)	388 (52.5)	1.67 (1.34-2.09)

Kneuertz/You et al. *JAMA Surg 2015*

Slide from Nancy You

What We Need to Do?



01

Etiology

unknown to the majority of ~ **80%**

02

Risk Factor

No known major risk factor

03

Mechanism

No known differences in driver mechanisms

04

Evolution

Unknown in EOCRC

Multi-omics

Conclusion

- Early onset CRC is associated with unique clinical features and presentation
- Epidemiology suggests that this is not limited to US population, and that the impacts are across a diverse racial/ethnic groups.
- This rising incidence is in contrast to the gains being made in CRC prevention of screening age population
- Multiple etiologies have been proposed, but not yet clearly defined
- Molecular features are modestly different at the transcriptomic and mutational level, but do not provide clear clues yet
- Outcomes with treatment also vary, and yet overtreatment is a risk. Alignment of the treatments with the disease biology is needed

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Thank You

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Early-Onset Colorectal Cancer: Earlier Detection & Pathways to Prevention

Cassandra Fritz, MD, MPHS
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Early-Onset Colorectal Cancer: Earlier Detection & Pathways to Prevention

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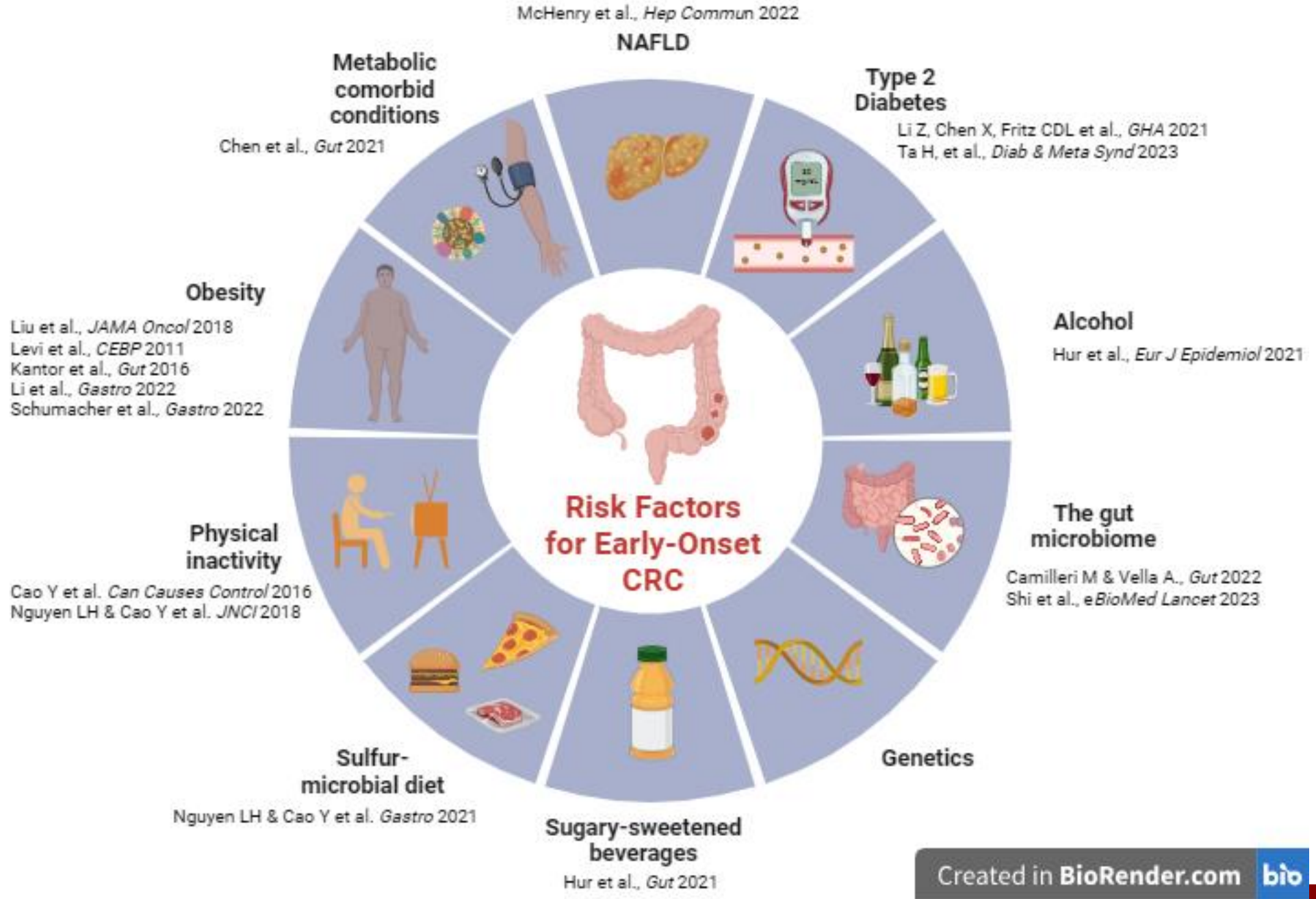
Assistant Professor of Medicine
Washington University in St. Louis

Department of Medicine
Division of Gastroenterology

No Financial Disclosures

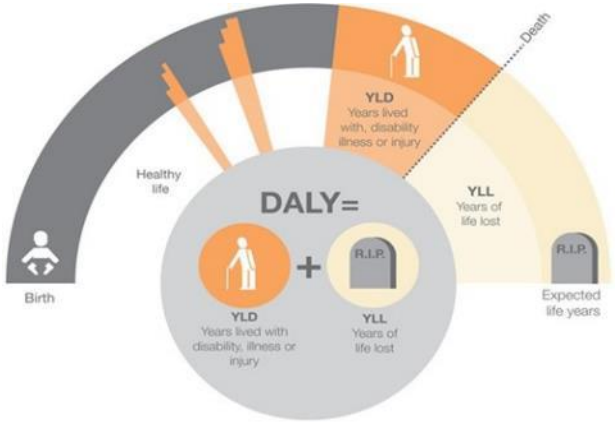
Outline

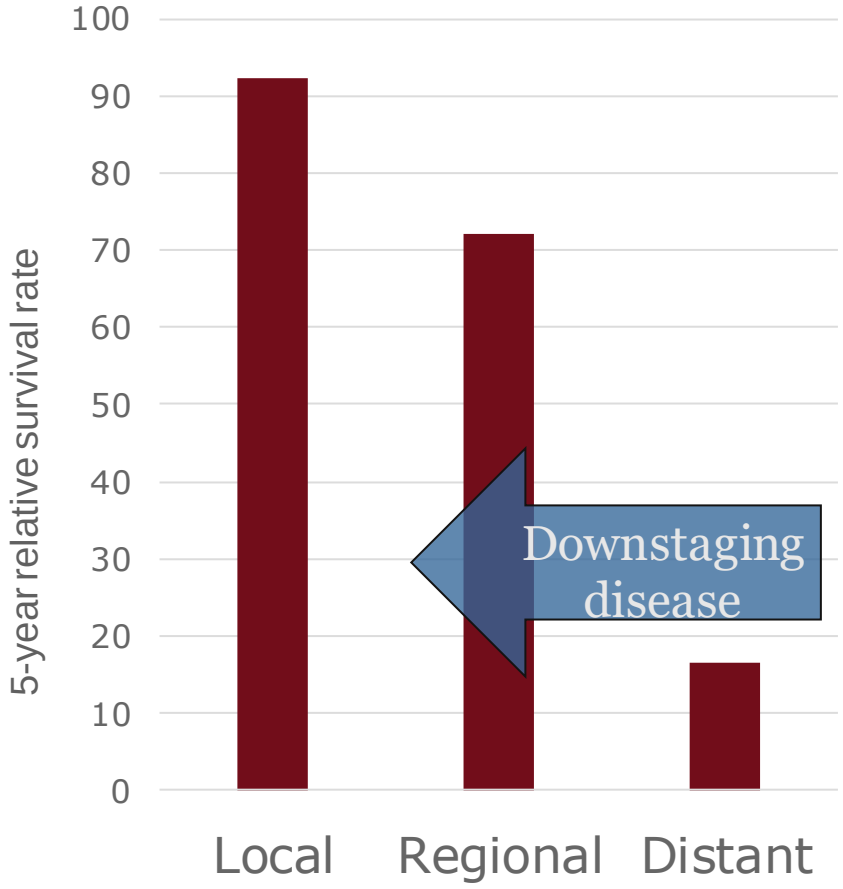
- Pathway to detection of early-onset colorectal cancer
- Signs and symptoms & Diagnostic intervals
- Opportunities for improvement
- Primary prevention


McHenry et al., Hep Commun 2022
NAFLD
Metabolic comorbid conditions
Chen et al., Gut 2021
Type 2 Diabetes
Li Z, Chen X, Fritz CDL et al., GHA 2021
Ta H, et al., Diab & Meta Synd 2023
Obesity
Liu et al., JAMA Oncol 2018
Levi et al., CEBP 2011
Kantor et al., Gut 2016
Li et al., Gastro 2022
Schumacher et al., Gastro 2022
Alcohol
Hur et al., Eur J Epidemiol 2021
Risk Factors for Early-Onset CRC
Physical inactivity
Cao Y et al. Can Causes Control 2016
Nguyen LH & Cao Y et al. JNCI 2018
The gut microbiome
Camilleri M & Vella A., Gut 2022
Shi et al., eBioMed Lancet 2023
Sulfur-microbial diet
Nguyen LH & Cao Y et al. Gastro 2021
Sugary-sweetened beverages
Hur et al., Gut 2021
Genetics
Created in BioRender.com

5-year Relative Survival of Early-onset Colorectal Cancer (20-49 years of age) by Stage at Diagnosis SEER 13, 1992-2013

- Morbidity and mortality are significant
- High mortality with later-stage disease
- Early-onset CRC is in the top 5 ranking cancers associated with high disability-adjusted life years (DALYs)

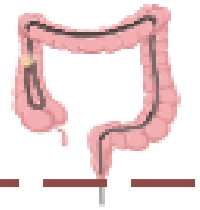




Cheng E. et al., JAMA Network Open. 2021
Zhao J. et al., BMJ Oncology 2023

Zaki T et al. CGH. 2023

From Symptoms to Detection

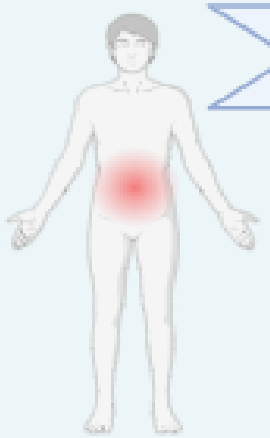


1 Patient notices symptoms

2 Patient reports symptoms to healthcare provider

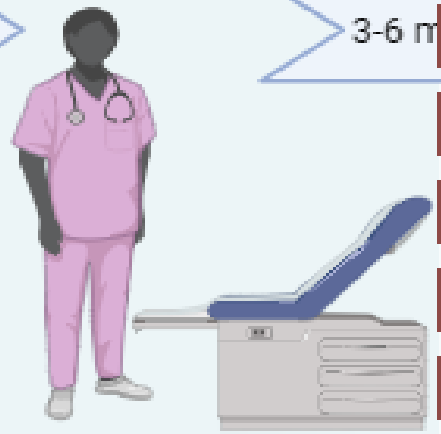
3 Provider has to activate a diagnostic pathway

4 Diagnosis of early-onset CRC



3-12 mo

- Patient needs to associate symptoms with CRC
- Not be afraid to access care
- Make an appointment (1-2 month delay)

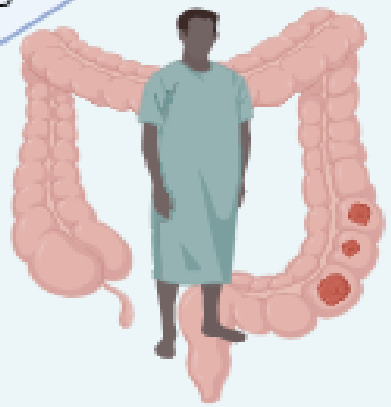


3-6 mo

- Provider has to associate concerning symptoms with CRC
- Navigate other competing issues
- Family history

1-2 mo

- Close the loop on symptoms
- Order a colonoscopy



- Receive a diagnosis of early-onset colorectal cancer

Signs and Symptoms of Early-Onset Colorectal Cancer

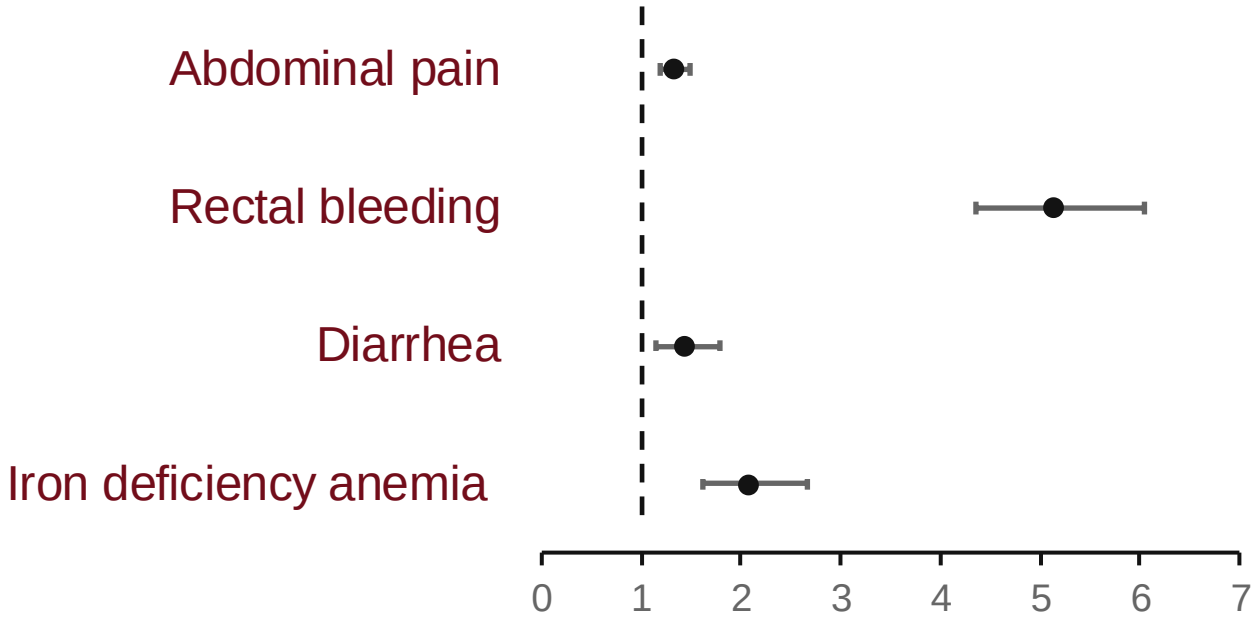
Objective: To identify signs & symptoms with early-onset CRC and report associated diagnostic intervals 3 months to 2 years before diagnosis.

Methods

- MarketScan commercial database including adults aged 18 to 49 years.
- Required at least 2 years of continuous enrollment prior to the index date (pathology diagnosis of CRC).
- Nested case-control study of 5075 incident early-onset CRC and 22378 matched controls.
- Multivariable logistic regressions
- Examined the median diagnostic intervals based on associated signs and symptoms.

Early signs/symptoms for Early-Onset CRC
Claims data, nested case-control, 2005-2016

4 Red-Flag Signs and Symptoms, 3mo to 2 years prior to index date



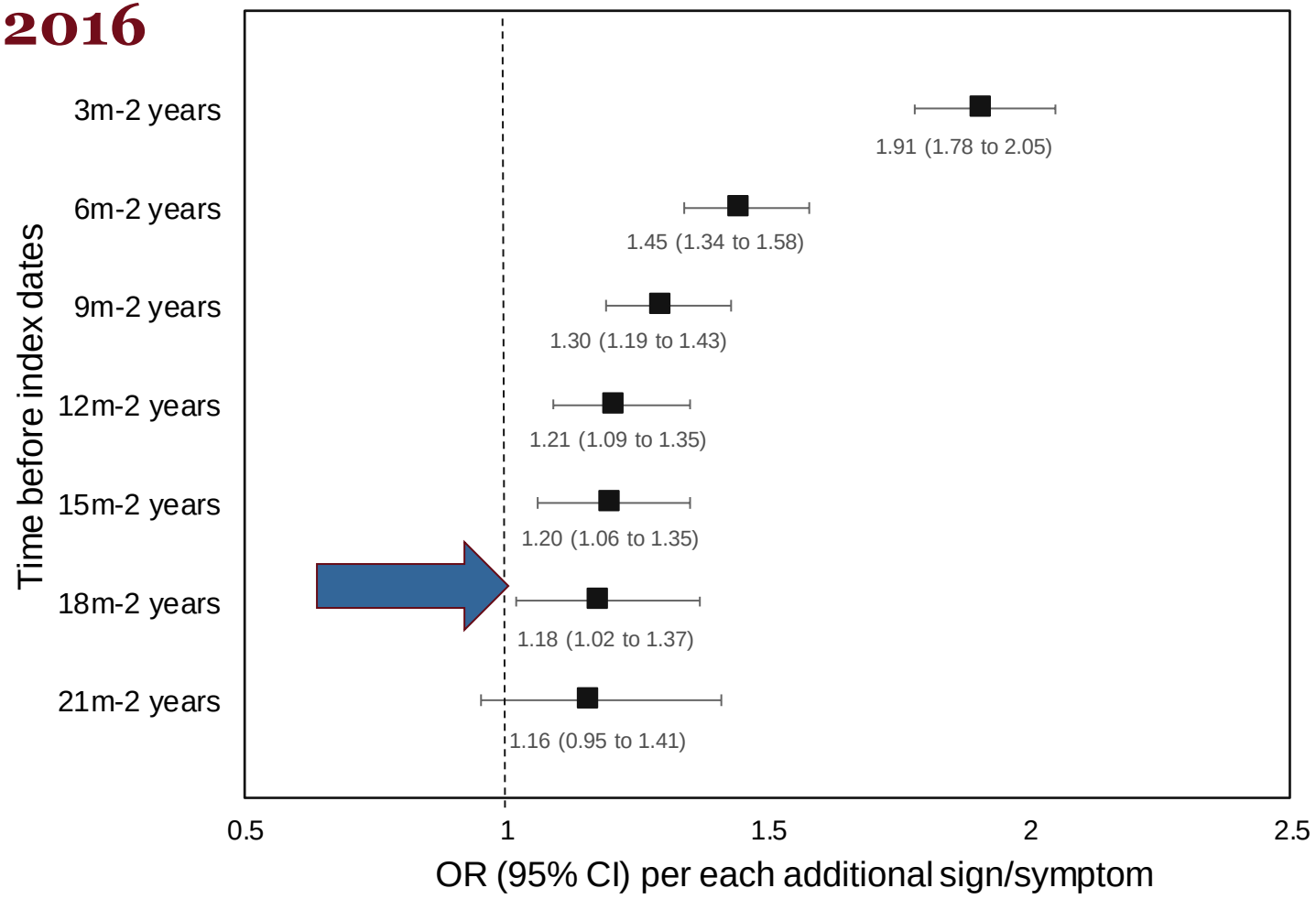
No. of red-flag signs/symptoms	OR (95% CI)
All participants	
0	1 (reference)
1	1.94 (1.76 to 2.14)
2	3.59 (2.89 to 4.44)
≥3	6.52 (3.78 to 11.23)
Per each additional sign/symptom	**1.91 (1.78 to 2.05)**
P_{trend}	<0.001

Fritz CDL & Otegbeye *et al*, JNCI 2023

Number of Red-flag Signs/Symptoms and Risk of Early-Onset Colorectal Cancer

3-month time intervals prior to the index date

Claims data, cases only, 2005-2016



Fritz CDL & Otegbeye *et al*, JNCI 2023

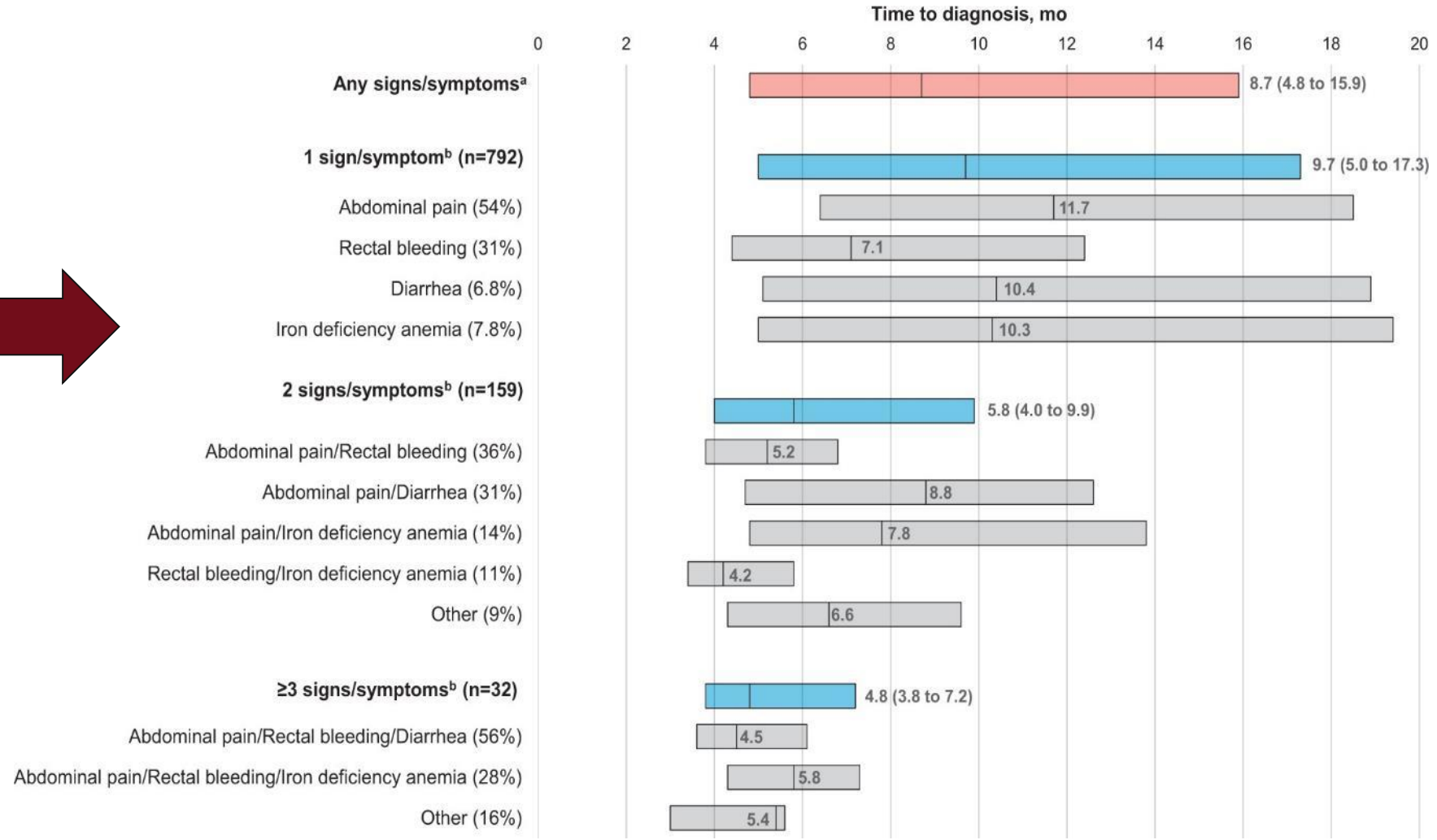
Duration of Signs and Symptoms in Young Adults Claims data, cases-only, 2005-2016

19%

of early-onset CRC cases reported their **first symptom > 3 months prior to diagnosis**

50%

of early-onset CRC cases reported their first symptom **< 3 months**

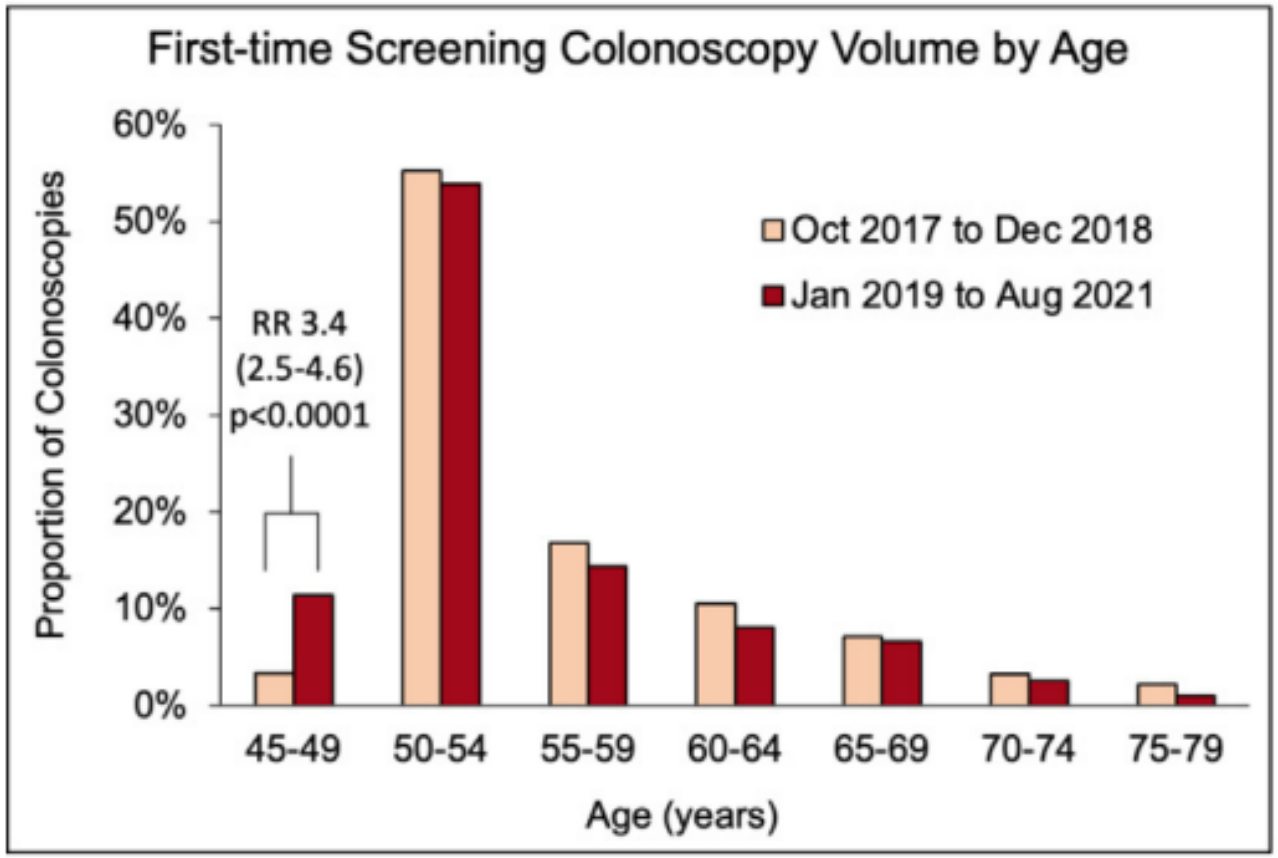


Current Prevention Approach

Lowered CRC screening age to 45 years

~50% of early-onset CRC cases are diagnosed <45 years

Screening in younger individuals has had slow uptake

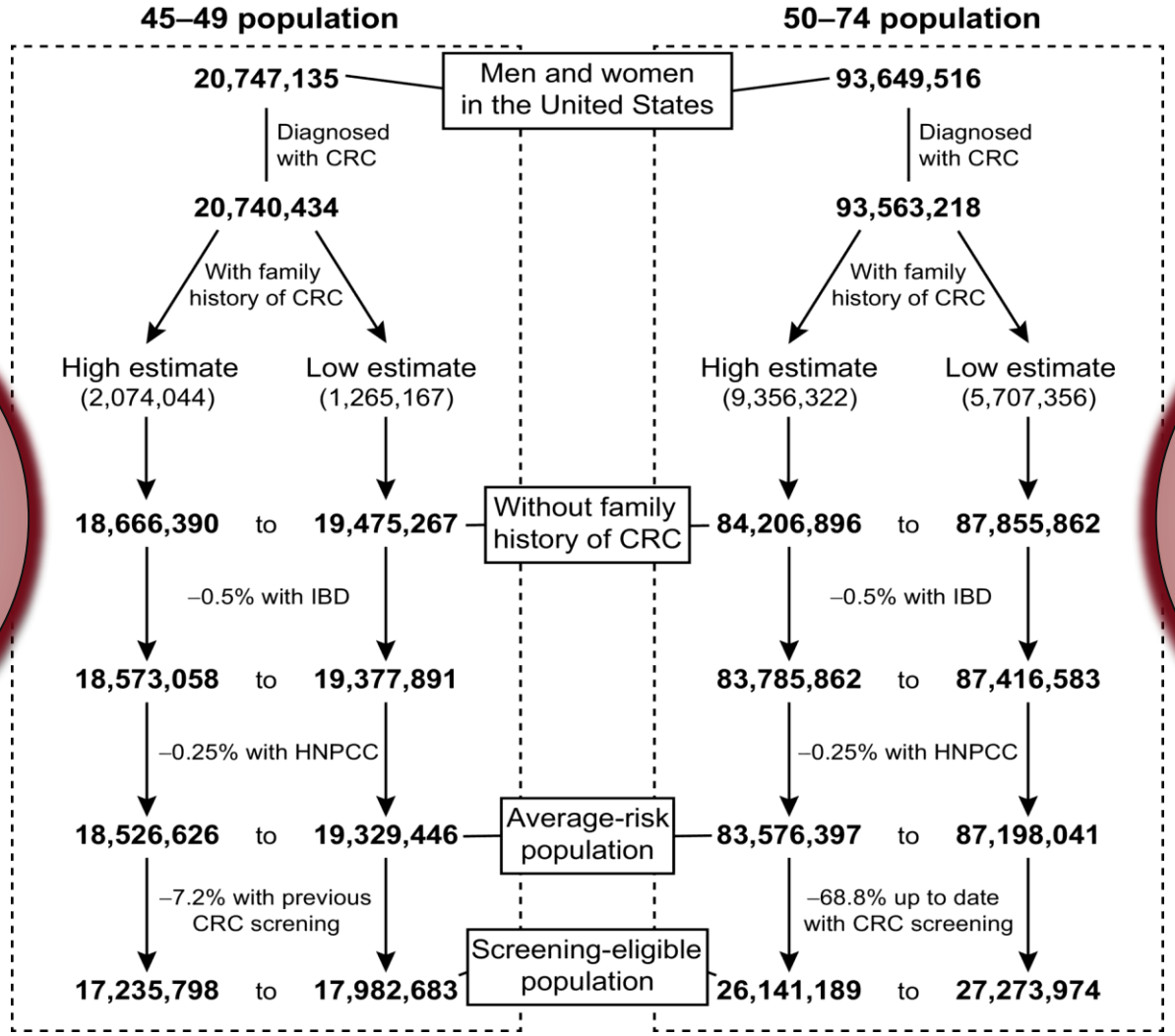


Wolf AMD *et al*, CA Cancer J Clin 2018
Davidson KW. JAMA 2021

Ladabaum U, et al. CGH 2022

Estimating the Screening-Eligible Population Size, Ages 45–74, at Average Risk to Develop CRC in the United States

~20 million people aged 45-49 years + 27 million 50-74 years



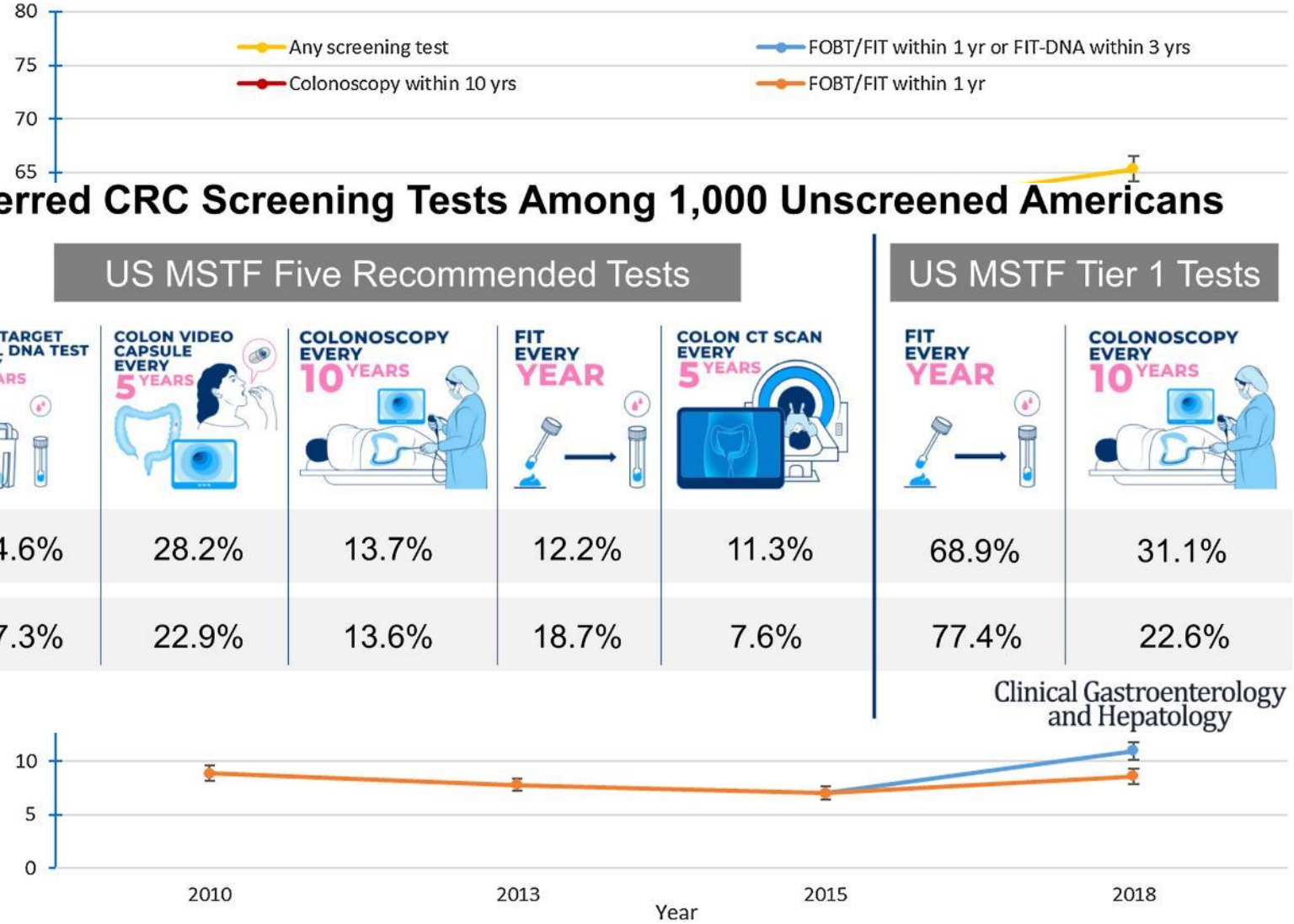
60% increase in the "average-risk" screening pool size

Piscitello A. et al. Cancer Prev Res. 2020

Do we have the resources?

Potentially, if we leverage stool-based testing

Screening for CRC in the U.S.: Time trend by type of test



Preferred CRC Screening Tests Among 1,000 Unscreened Americans

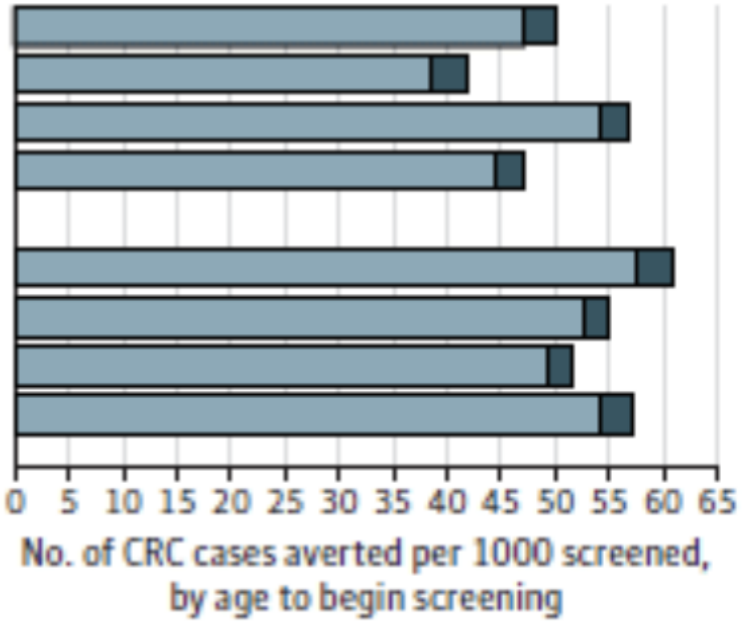
	US MSTF Five Recommended Tests					US MSTF Tier 1 Tests	
	MULTITARGET STOOL DNA TEST EVERY 3 YEARS	COLON VIDEO CAPSULE EVERY 5 YEARS	COLONOSCOPY EVERY 10 YEARS	FIT EVERY YEAR	COLON CT SCAN EVERY 5 YEARS	FIT EVERY YEAR	COLONOSCOPY EVERY 10 YEARS
40-49 yo	34.6%	28.2%	13.7%	12.2%	11.3%	68.9%	31.1%
≥50 yo	37.3%	22.9%	13.6%	18.7%	7.6%	77.4%	22.6%

Shapiro JA, et al. *Cancer Epidemiol Biomarkers* 2021
Makaroff KE et al. CGH 2022

Screening: No difference between colonoscopy vs. FIT for additional early-onset CRC cases averted

B Benefit: Estimated No. of CRC cases averted per 1000 individuals screened[a]

Screening modality and frequency	Mean CRC cases averted if start screening[b] At age 50 y	At age 45 y	Additional CRC cases averted if start screening at age 45 y
Stool tests			
FIT every year	47	50	3
HSgFOBT every year[c,d]	39	42	3
sDNA-FIT every year	54	57	3
sDNA-FIT every 3 y[d]	44	47	3
Direct visualization tests			
COL every 10 y	58	61	3
CT colonography every 5 y	53	55	2
Flexible SIG every 5 y	49	51	2
Flexible SIG every 10 y plus FIT every year	54	57	3



Knudsen AB. JAMA. 2021

Opportunity to leverage FIT for diagnostic pathways?

- Likely yes but we don't have the data for early-onset CRC population

Guideline from British Society of Gastroenterology: Using FIT in patients with signs and symptoms of suspected CRC

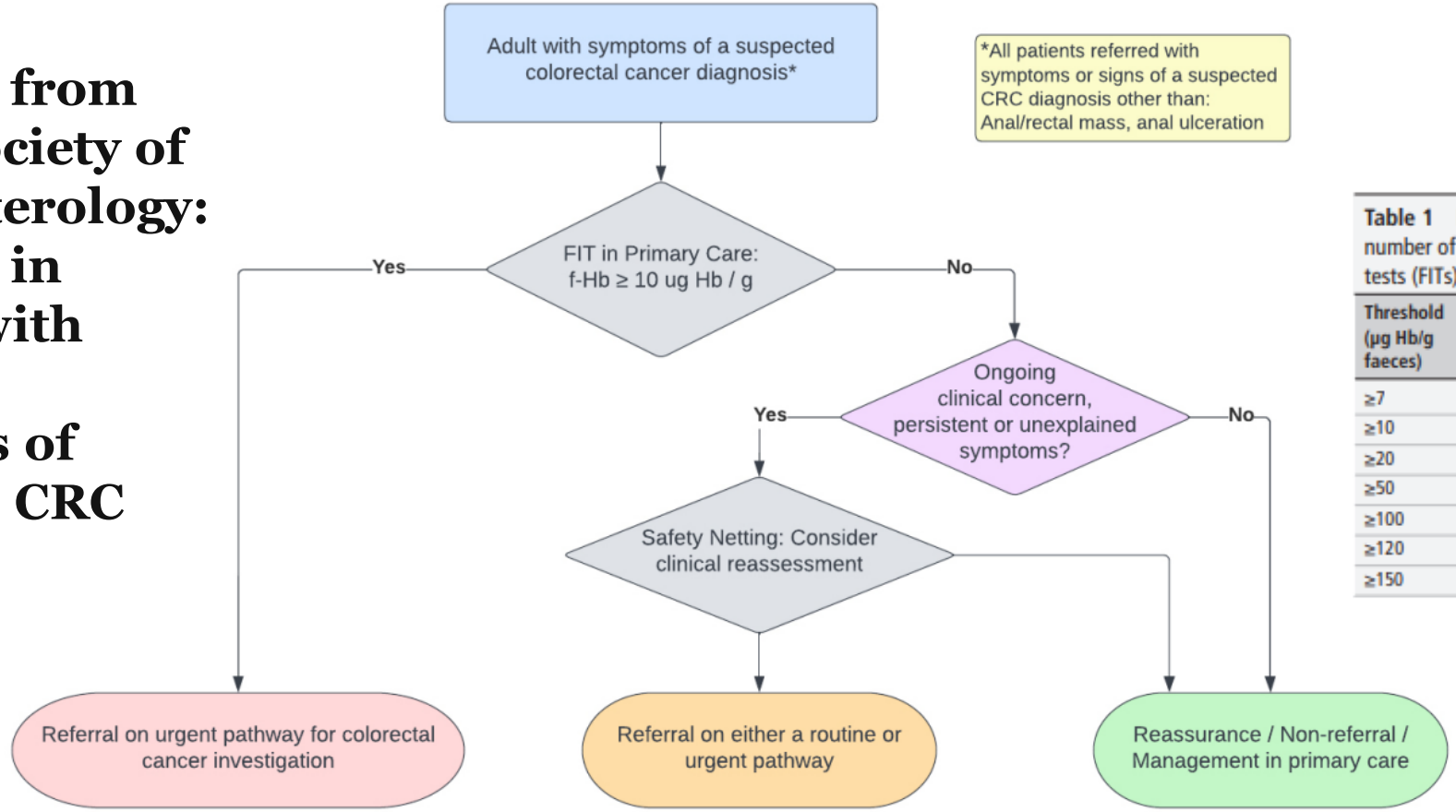


Table 1 Number needed to scope (NNS) to detect one cancer and number of missed cancers (NMC) per 1000 faecal immunochemical tests (FITs) at various thresholds of FIT[17]

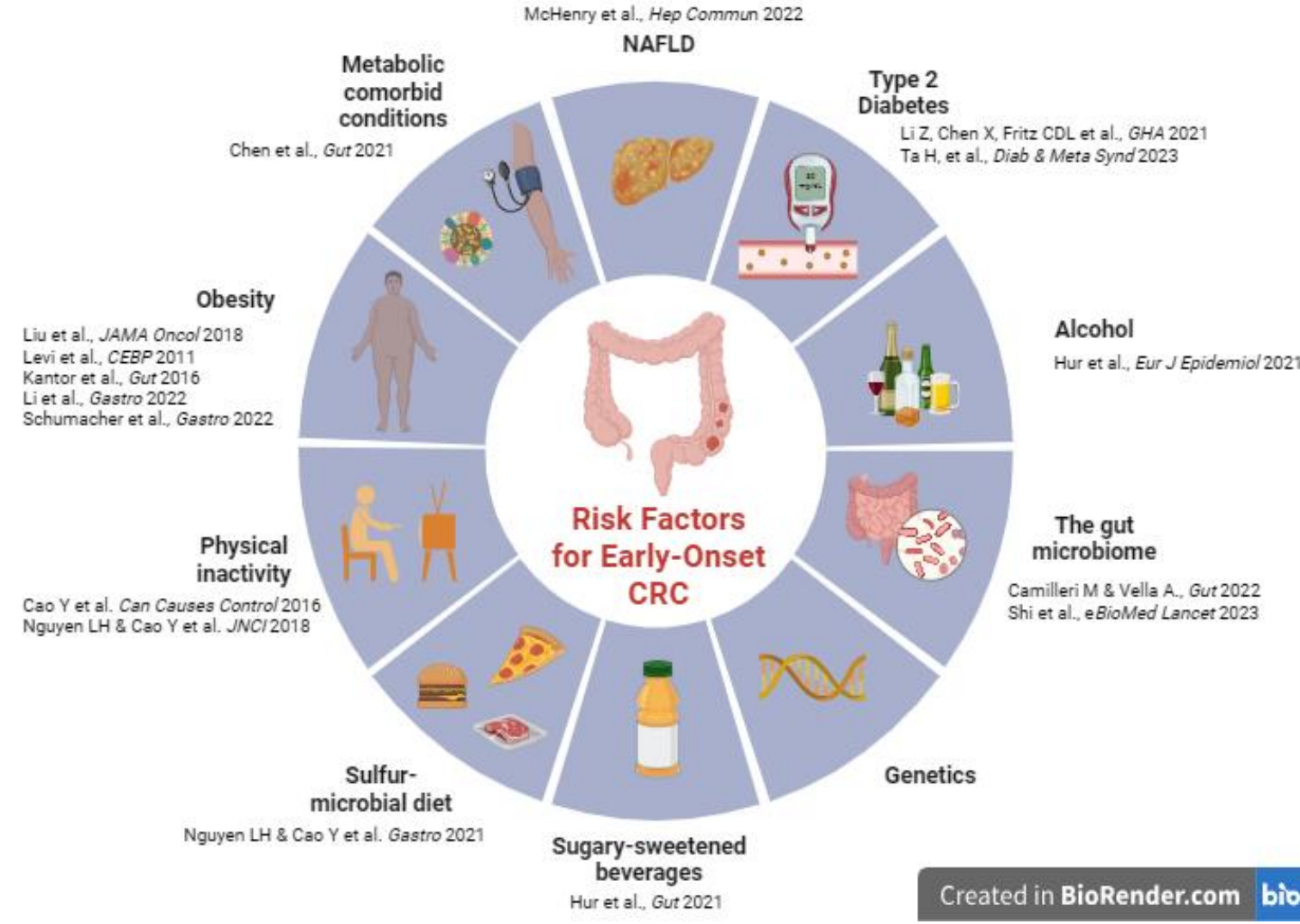
Threshold (µg Hb/g faeces)	Positive FITs n (%)	Negative FITs n (%)	Cancers detected n (%)	NNS to detect one cancer	NMC per 1000 FITs
≥7	111 (11)	889 (89)	10 (91)	11	1
≥10	96 (10)	904 (90)	10 (91)	10	1
≥20	71 (7)	929 (93)	9 (85)	8	2
≥50	44 (4)	956 (96)	8 (74)	6	3
≥100	30 (3)	970 (97)	7 (61)	5	4
≥120	28 (3)	972 (97)	6 (57)	5	5
≥150	25 (2)	975 (98)	6 (54)	4	5

Monahan KJ et al., Gut 2022

Primary Prevention

Mitigation of risk factors

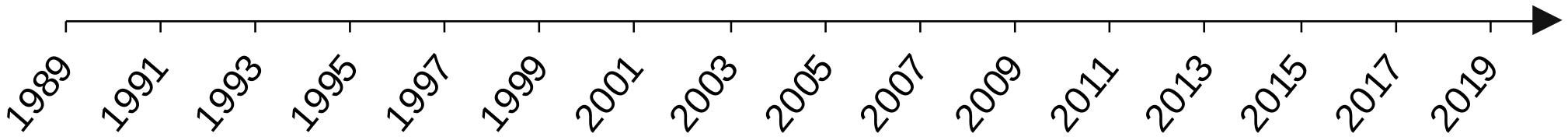
Chemopreventative agents



Methods: Study population

Nurses' Health Study II (NHSII): N=116,429 | age 25-42 in 1989

NSAID/aspirin every two years .



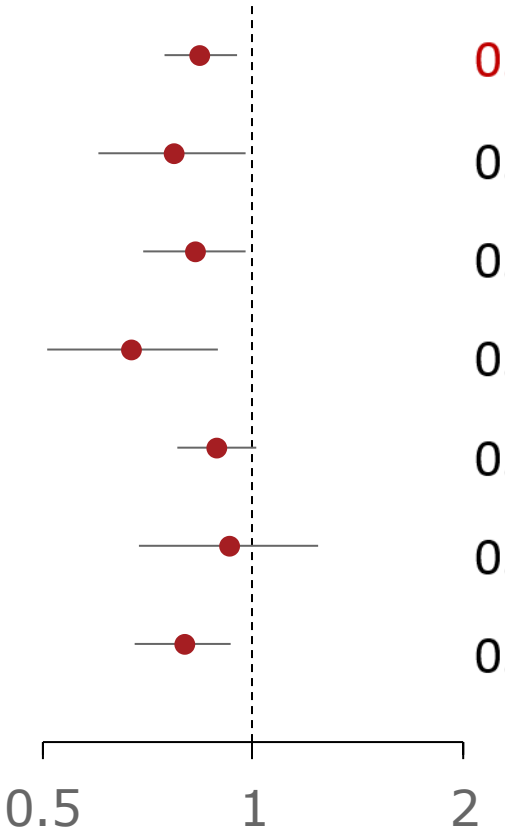
Lower endoscopy every two years

A sub-cohort of 32,058 women in NHS II with a lower endoscopy before age 50 between 1991-2015

- Excluded patients with CRC, inflammatory bowel disease, or missing medication info.

Regular use (2+times/week) of aspirin or NSAIDs and risk of early-onset adenoma, NHSII, 1991-2015

		No Regular Use (n=27795)	Regular Use (n=18732)	Multivariable OR (95% CI)	P het.
	Adenoma	777	470	0.84 (0.75-0.95)	
Malignant potential	High-risk	185	105	0.77 (0.60-0.98)	0.50
	Low-risk	401	245	0.83 (0.70-0.98)	
Histology	Villous	157	76	0.67 (0.51-0.89)	0.06
	Tubular	620	394	0.89 (0.78-1.01)	
Size	Large	120	80	0.93 (0.69-1.24)	0.51
	Small	455	269	0.80 (0.68-0.93)	



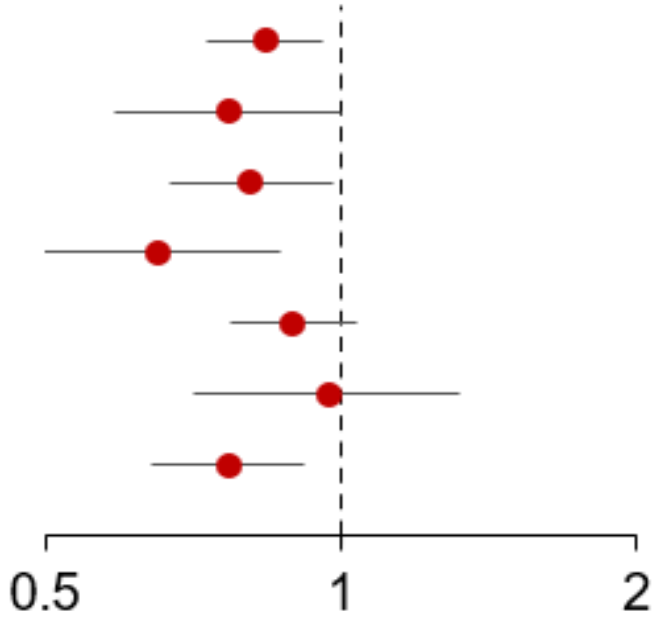
DO NOT POST

Fritz et al., unpublished

Regular use (2+times/week) of aspirin or NSAIDs and risk of early-onset adenoma, NHSII, 1991-2015

First endoscopy

		No Regular use N=18229	Regular use N=11890	Multivariable OR (95% CI)	*P* het.
	Adenoma	633	378	0.84 (0.73-0.96)	
Malignant potential	High-risk	158	90	0.77 (0.59-1.00)	0.58
	Low-risk	314	187	0.81 (0.67-0.98)	
Histology	Villous	144	67	0.65 (0.48-0.87)	0.04
	Tubular	489	311	0.89 (0.77-1.04)	
Size	Large	102	71	0.97 (0.71-1.32)	0.32
	Small	360	205	0.77 (0.64-0.92)	



Fritz et al., unpublished

Chemoprevention for early-onset CRC

Regular aspirin/NSAID use (2+ times/week) was associated with a lower risk of early-onset adenomas, especially those with advanced histology

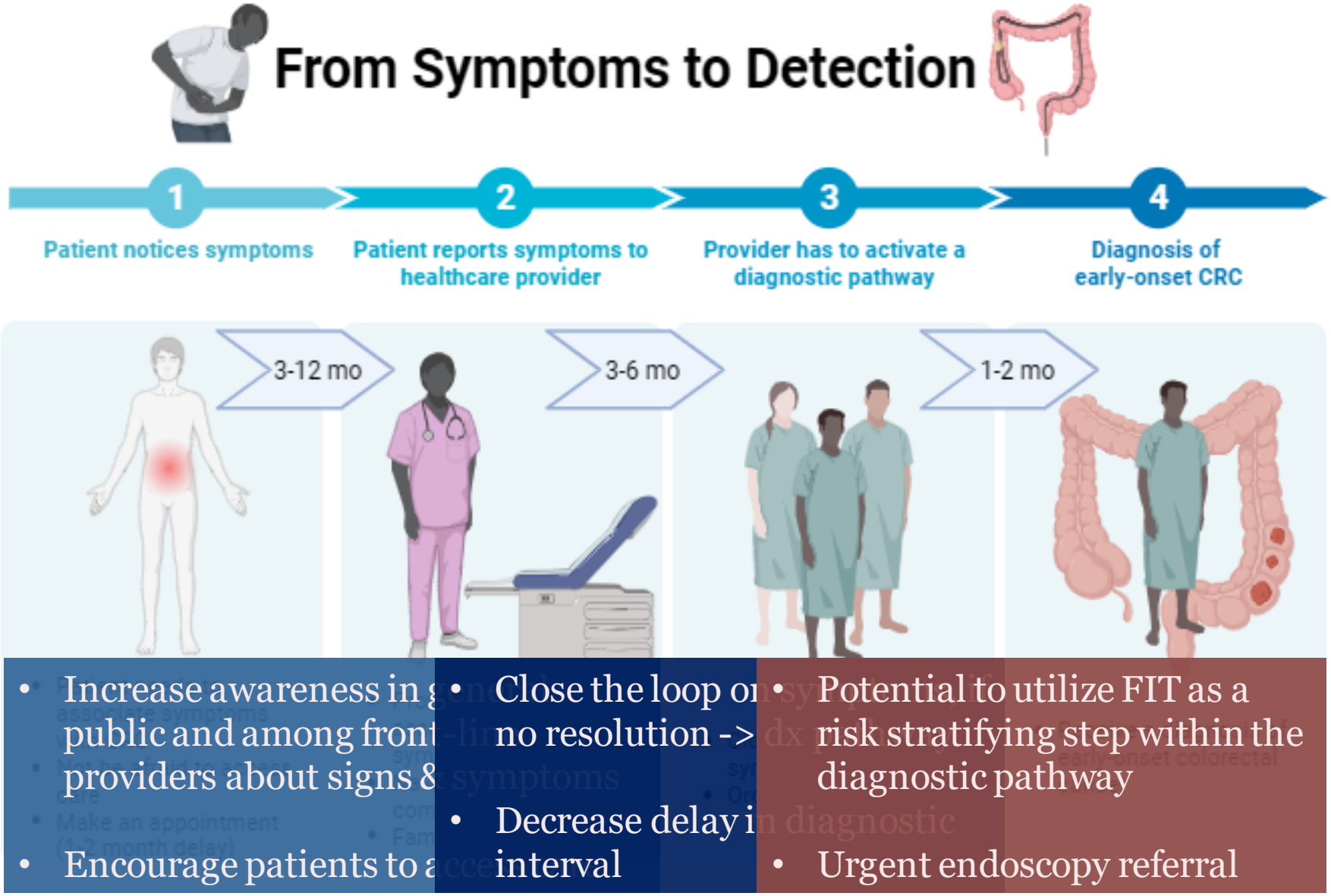
Evaluate aspirin/NSAIDs as promising agents for chemoprevention of early-onset CRC

- Gender, racial/ethnic diversity
- Dose and duration for young adults
- Precision-based strategies

Moving the needle on early-onset CRC

- Increased inclusion of minority populations into research and dissemination and implementation strategies
- Consider risk prediction models that incorporate family history, social vulnerability, risk factors, and genetics
- Change the conversation
  - Increase awareness of early-onset CRC & associated signs and symptoms
  - Targeting resources
  - System-level and population-level interventions

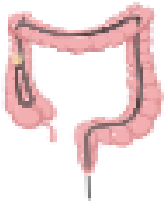
Conclusions



Conclusions

Prevention

From Symptoms to Detection



0 Prevention

1 Patient notices symptoms

2 Patient reports symptoms to healthcare provider

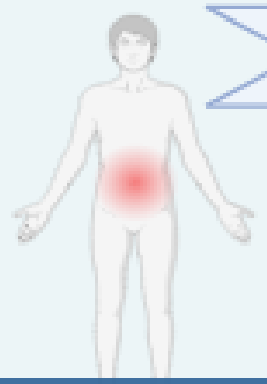
3 Provider has to activate a diagnostic pathway

4 Diagnosis of early-onset CRC

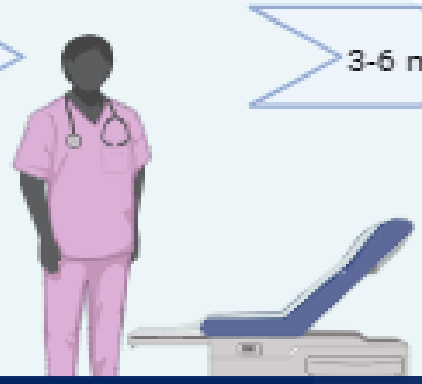
Risk factor mitigation

Chemoprevention

FIT for screening

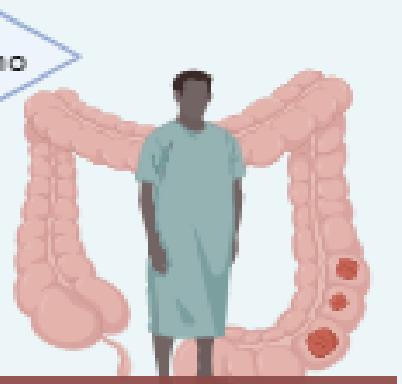


3-12 mo



3-6 mo

1-2 mo

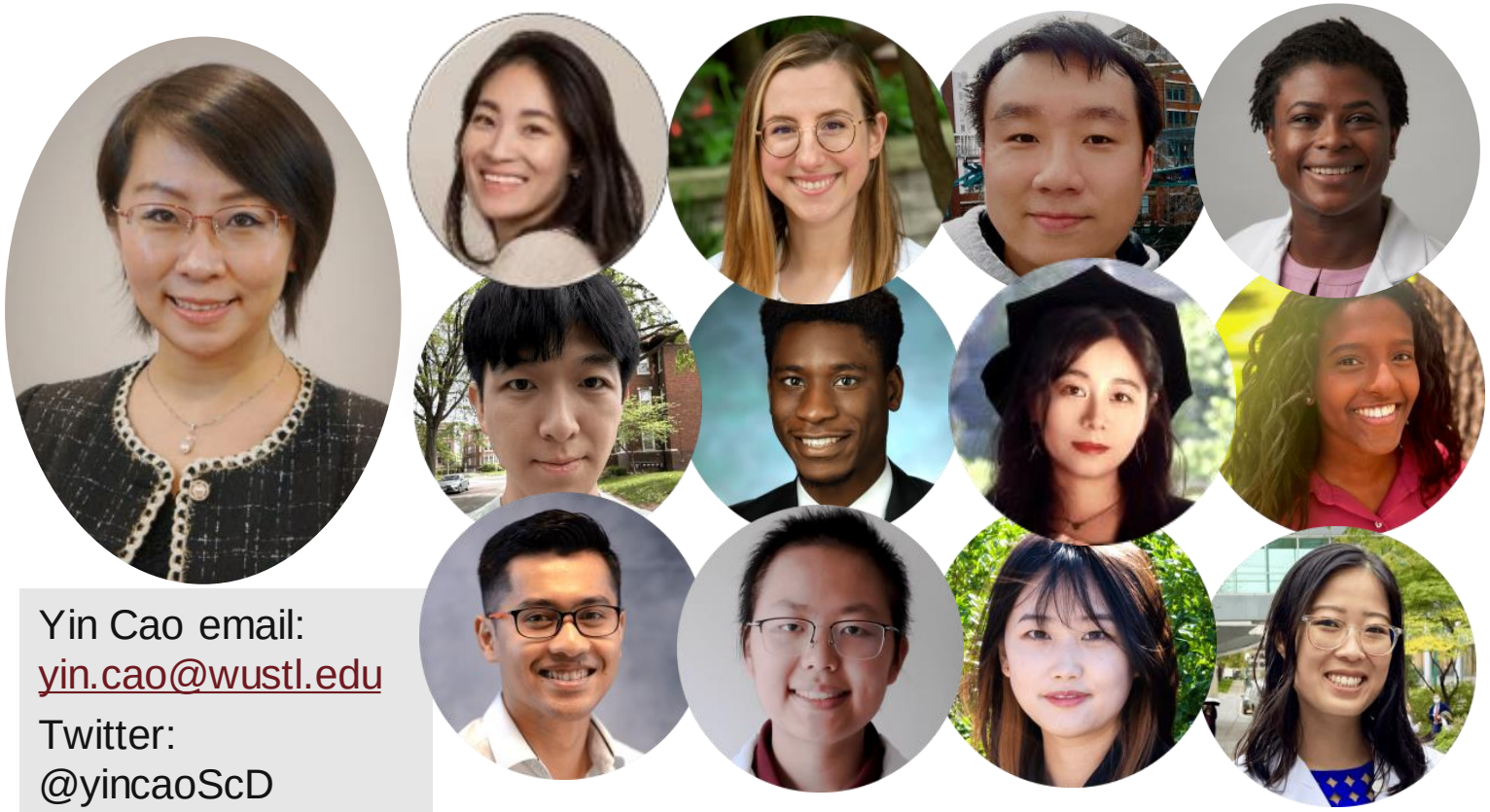


- Increase awareness in general public and among front line providers about signs & symptoms
- Encourage patients to access care

- Close the loop on symptoms, no resolution -> dx pathway
- Decrease delay in diagnostic interval

- Potential to utilize FIT as a risk stratifying step within the diagnostic pathway
- Urgent endoscopy referral

Acknowledgements



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Thank You

nccrt.org @NCCRTnews #80inEveryCommunity

American Cancer Society | NATIONAL COLORECTAL CANCER ROUNDTABLE

Q&A

Table Talk Questions

1. What can our organizations do to take what we've learned about lead time messaging and EAO CRC signs and symptoms to make an impact in our communities?
2. What are some success stories from organizations that have specifically targeted EAO CRC awareness and processes that lead to timely diagnosis?