Early Onset Colorectal Cancer
How Much Do We Know?

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Disclosures

None

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Objectives:

- Review recent trends in early onset CRC incidence and mortality
- Identify risk factors for early onset CRC
- Explore ways to optimize screening and prevention

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Definition:

- Age < 50
- Doesn't correspond to biologically or pathophysiologically different disease entities
- Intuitive cut off based on historical recommendations to initiate screening at this age

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Incidence and Mortality

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CRC Incidence:

- Third most common cancer worldwide
- Second leading cause of cancer related mortality
- Early-onset CRC (EO-CRC) accounts for 10% of all new diagnosis of CRC
- Estimated that 23% of rectal cancers and 11% of colon cancers will be diagnosed in people younger than 50 years of age by 2030

Bray et al. CA Cancer J Clin (2018)
Stoffel et al. Gastroenterology (2020)

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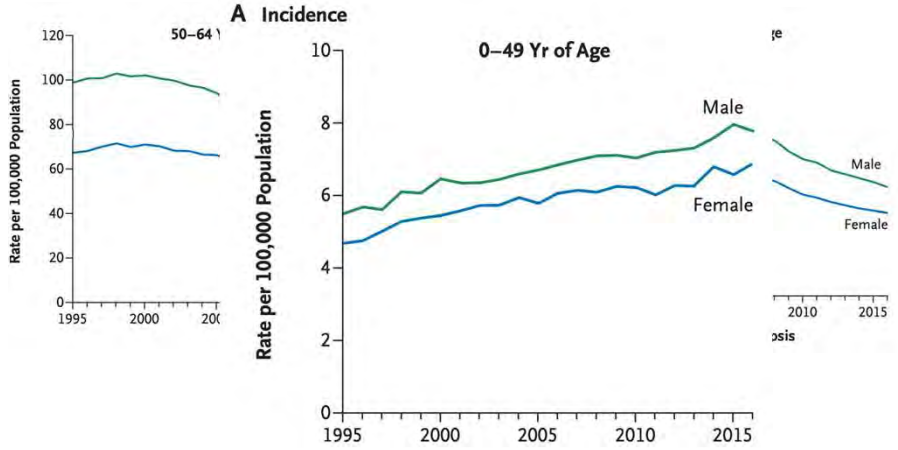
EO-CRC Incidence:



Sinicrope , NEJM (2022)

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EO-CRC incidence by US state:

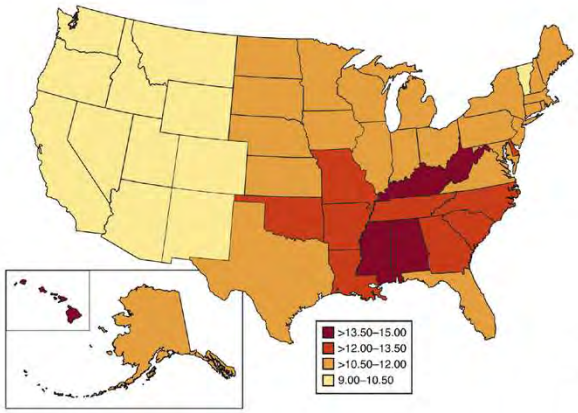

Figure 1. Incidence rates of early-onset CRC (aged 20–49 years) by US state, National Program of Cancer Registries, 2001–2015.

Stoffel et al. Gastroenterology (2020)

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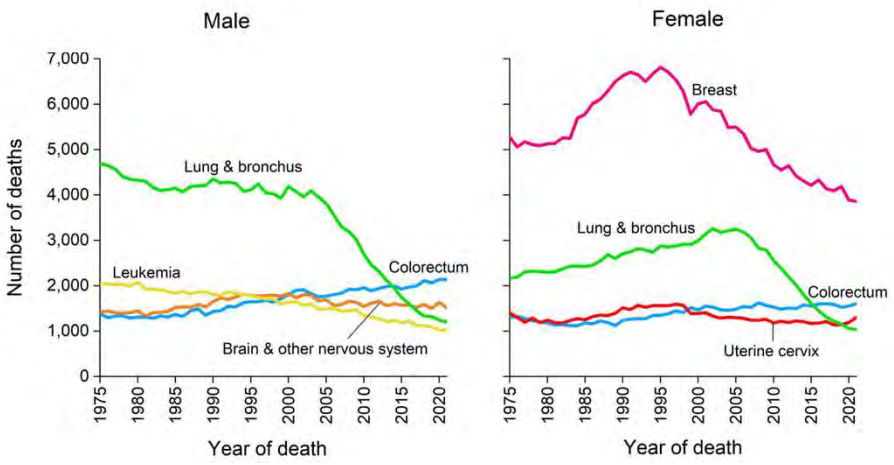
EO-CRC Mortality:

Age birth-49



Siegal et al. Cancer statistics. CA CancerJClin.2024

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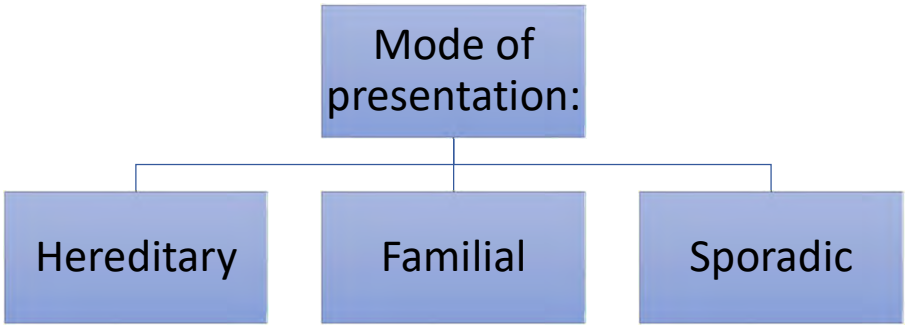

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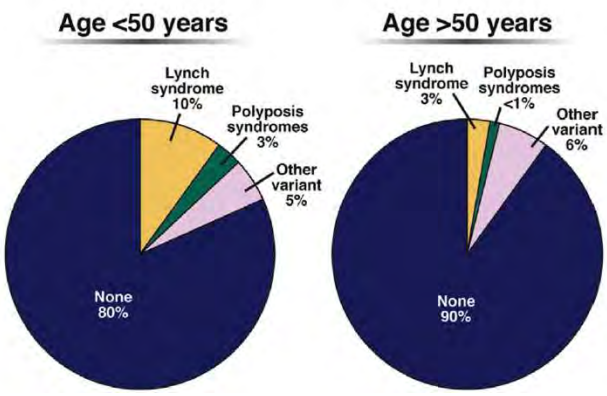
Hereditary:



Lynch syndrome	Polyposis syndromes	Other pathogenic variants	
		High penetrance	Moderate/low penetrance
MLH1	*APC*	*BRCA1*	*CHEK2*
MSH2	*MUTYH*	*BRCA2*	*ATM*
MSH6	*SMAD4*	*TP53*	*NBN*
PMS2	*BMPR1A*	*PALB2*	*BARD1*
	PTEN	*CDKN2A*	*BRIP1*
	POLE		

Stoffel et al. Gastroenterology(2020)

Daca Alvarez et al. Cells(2021)

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Hereditary:

Studies have consistently demonstrated that many individuals who harbor pathogenic or likely pathogenic germline cancer susceptibility gene variants have *clinical histories that **fail** to fulfill **traditional, syndrome specific guidelines**, have **atypical clinical phenotypes** that apriori would not fit into the syndrome's classical phenotype.*

Daca Alvarez et al. Cells(2021)

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Delphi Initiative for Early-Onset Colorectal Cancer (DIRECt) International Management Guidelines

A. All eoCRC patients should be offered multi-gene panel germline genetic testing and genetic counseling for those with a positive germline finding.

Germline genetic testing for CRC patients diagnosed younger than age 50 should include at a minimum:
APC, BMPR1A, EPCAM, MLH1, MSH2, MSH6, MUTYH, POLD1, POLE, PMS2, PTEN, SMAD4, STK11, and *TP53.*

Where available and not cost-prohibitive testing should also include:
BRCA1, BRCA2, ATM, CHEK2, PALB2, and possibly, but less prevalent,
BRIP1, BARD1, CDKN2A, CDH1, RAD51C, and *RAD51D.*
AXIN2, GREM1, MLH3, MSH3, MBD4, NTHL1, RNF43, and *RPS20.*

Cavestro et al. Clinical Gastroenterology and Hepatology (2023)

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Familial:

- 28% (range: 13–33%) have family history of CRC
- ↑risk FDR (2x)
- ↑ ↑ younger onset CRC and multiple affected members

Daca Alvarez et al. Cells(2021)
Boardman at al. CGH (2020)
Stoffel et al. Gastroenterology (2018)

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Practice Guideline	Criteria	Recommendation
Joint Guideline by ACS, USMSTF,[a] and American College of Radiology, 2008[5]	CRC or advanced adenoma in 2 FDRs at any age OR CRC or adenoma in a single FDR aged <60 y	Colonoscopy every 5 y beginning 10 y prior to age of diagnosis of FDR or age 40 y
	CRC or adenoma in single FDR diagnosed at age ≥60 y OR CRC in 2 SDRs at any age	Begin screening at age 40 y with any test
USMSTF 2017[6,b]	CRC or advanced adenoma in 2 FDRs at any age OR CRC or advanced adenoma in a single FDR aged <60 y	Colonoscopy every 5 y beginning 10 y prior to age of diagnosis of FDR or age 40 y
	CRC or advanced adenoma in single FDR diagnosed at age ≥60 y	Begin screening at age 40 y with any test
NCCN 2017[7,c]	CRC in ≥1 FDR with CRC diagnosed at any age	Colonoscopy at age 40 y or 10 y before earliest diagnosis of CRC, repeat every 5-10 y
Canadian Association of Gastroenterology, endorsed by the American Gastroenterological Association[8]	CRC in ≥2 FDRs	Colonoscopy every 5 y at age 40 y or 10 y younger than age of diagnosis of earliest diagnosed FDR, whichever is earlier
	CRC in 1 FDR	Colonoscopy every 5-10 y at age 40-50 y or 10 y younger than age of diagnosis of FDR, whichever is earlier; FIT every 1-2 y is suggested as second-line option
	≥1 FDR with documented advanced adenoma	No recommendation for a preferred test; colonoscopy or FIT both are options; colonoscopy every 5-10 y at age 40-50 y or 10 y younger than age of diagnosis of FDR, whichever is earlier; FIT every 1-2 y is suggested as second-line option
Cancer Council Australia 2018[9]	CRC in 1 FDR diagnosed at age <55 y or in 2 FDRs at any age, or in 1 FDR and at least 2 SDRs with CRC at any age	FIT every 2 y from age 40-49 y and colonoscopy every 5 y from age 50-74 y
	≥3 FDRs or SDRs with CRC, with at least 1 diagnosed at age <55 y or ≥3 FDRs with CRC at any age	FIT every 2 y from age 35-44 y and colonoscopy every 5 y from age 45-74 y

Gupta et al. Cancer (2020)

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Original Article

Potential Impact of Family History–Based Screening Guidelines on the Detection of Early-Onset Colorectal Cancer

Criteria	Sensitivity	Specificity
ACS 2008[a]	25%	90%
NCCN 2017	21%	92%
USMSTF 2017	21%	92%
CAN 2018	21%	92%

Sensitivity and Specificity of Family History based criteria issued by ACS, NCCN, USMSTF, and CAN for identifying patients aged 40-49 years with early onset CRC

Gupta et al. Cancer (2020)

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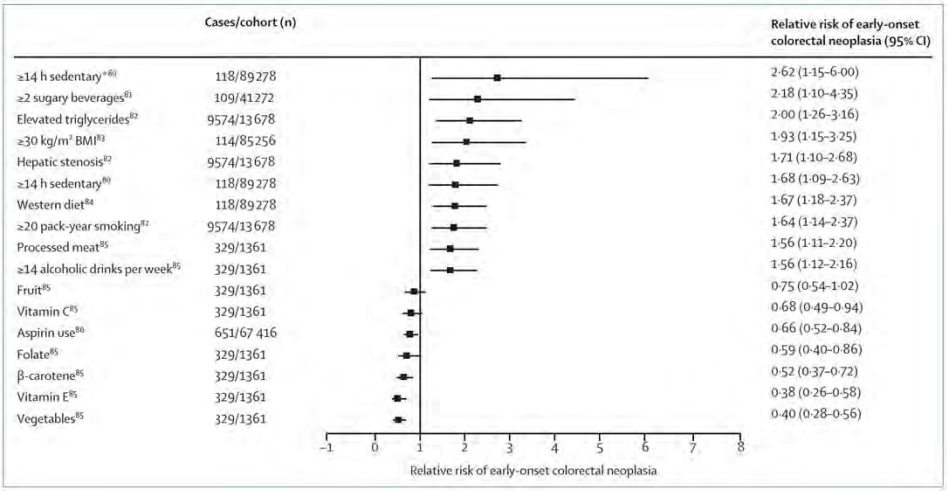
Sporadic: Risk factors (Diet and Lifestyle)



There is insufficient evidence to recommend earlier CRC screening based on these factors.

Patel et al. Lancet Gastroenterol Hepatol (2022)

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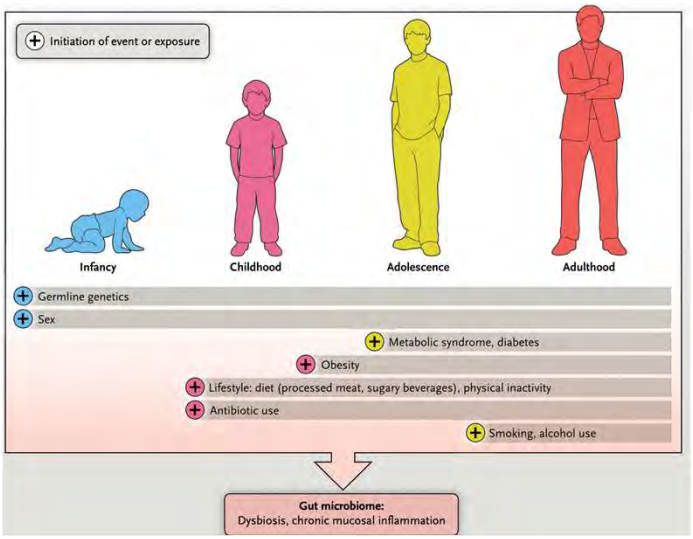
Sporadic: Gut microbiota



Sinicrope , NEJM (2022)

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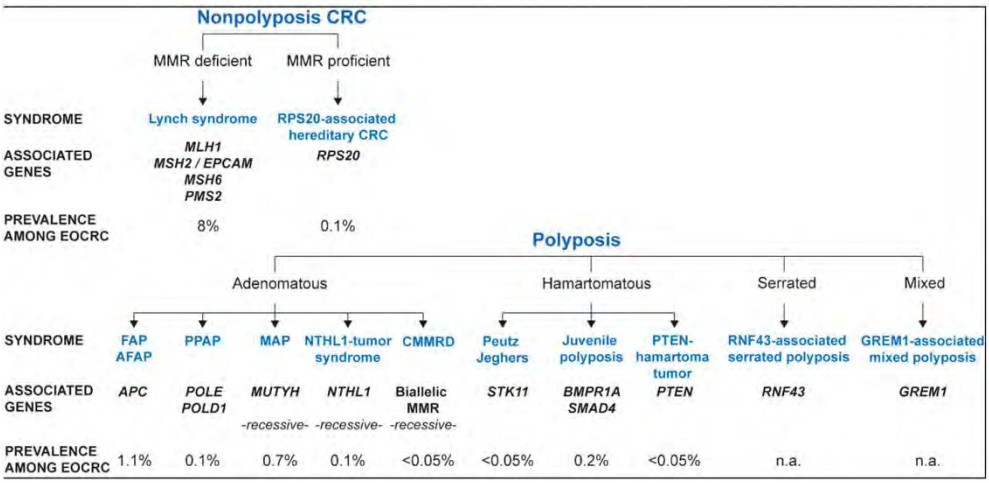
Inherited and familial component



Alvarez et al. Cells (2021)

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Molecular Pathogenesis:

The molecular profile of sporadic EO-CRC
 # Late Onset CRC

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Molecular Profile :

- The molecular profile of sporadic early-onset tumors is distinct from late-onset CRC
  - ↑
  - MMR deficient but most are chromosome and microsatellite stable
  - ↓
  - APC and BRAF mutations
  - ↑
  - CTNNB1
  - Global hypomethylation of DNA
  - ↑
  - POLE (high tumor mutation burden)
  - ↓
  - NRF2 (role in preventing toxicity and accumulation of ROS)
  - Higher proportion of the CMS1 subtype

Burnett-Hartman et al. Gastroenterology (2021)

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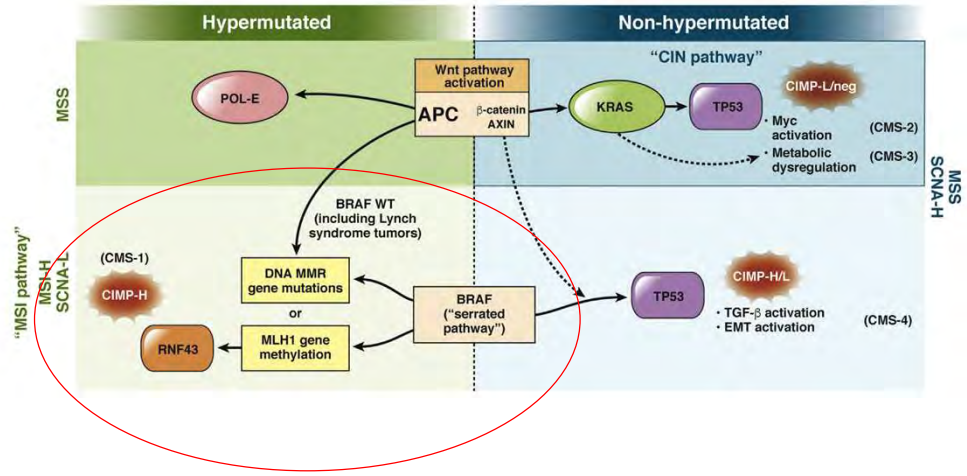

- It also includes neoplasms with markers of inflammation and of immune response

?? →

Long standing colon inflammation related to pathogenesis

Stoffel et al. Gastroenterology (2020)
Nguyen et al. Gastroenterology (2020)

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Clinical phenotype

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Clinical Phenotype:

	Early-onset colorectal cancer (age <50 years)	Late-onset colorectal cancer (age ≥50 years)
Presenting with symptoms, %	85·0–95·6[33·36]	33·9–79·0[34,37]
Incidental or screen detected, %	1·6–5·2[34,38]	3·4–14·6[34,38]
Duration of symptoms, days	243[38]	154[38]
Time to diagnosis, days	152–217[38,39]	29·5–87[38,39]
Family history of colorectal cancer, %	13·8–33·5[32,38,40,41]	8·3–19·3[32,38,40]
Location, %		
Right colon	16·2–39·9[32–34,32,38,40,42–50]	28·5–53·5[32,40,44–46,50,51]
Left colon	24·0–53·0[32,33,38,42–48]	28·9–48·5[34,38,40,44–46]
Rectal	23·5–49·1[32–34,32,38,42–44,46–48]	20·0–35·2[34,32,38,44–46]
Histology, %		
Mucinous	8·1–15·0[34,42,43,45,47,48,50,51]	4·7–16·0[34,45,50,51]
Signet ring	1·0–13·0[34,42,43,45,47,50,52]	0·9–4·0[34,45,50,53,54]
Poor or no differentiation	7·2–27·9[34,42,43,48,50,51]	3·2–18·9[34,50,51,53]
Stage, %		
Early	11·0–47·0[32–34,40,42,43,46,47–50]	37·5–69·7[33,34,38,40,46,50]
Late	58·4–89·0[32–34,32,38,40,42,43,47–50]	30·3–62·5[33,34,32,38,40,46,50]

Table 1: **Clinical and pathologic features of colorectal cancer diagnosed in patients younger than 50 years and in those 50 years and older**

- Rectal bleeding (most common)
- Abdominal pain
- Change in bowel habits
- Unexplained weight loss
- Anemia

Patel et al. Lancet Gastroenterol Hepatol (2022)

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Screening and Prevention

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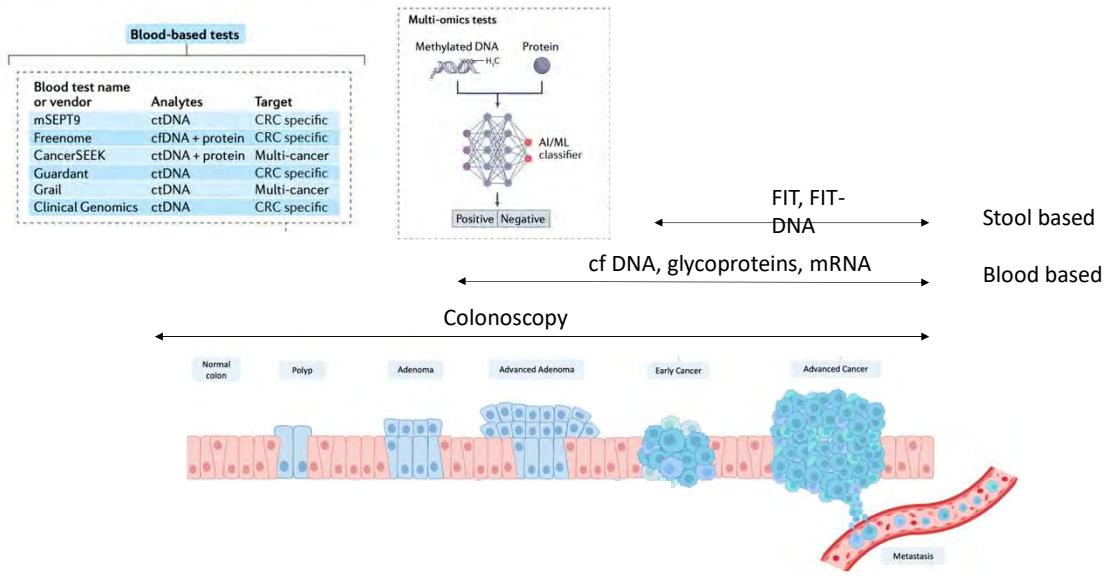

Shaukat et al. Nature Reviews Gastroenterology and Hepatology (2022)

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	Sensitivity	Specificity
FIT	79%	94%
mts DNA	92%	87%
Blood based	48.2-68%	80-91.5%
Colon capsule (polyps > 6mm)	88%	82%
CT colonography (polyps > 6mm)	73-98%	81-91%

Shaukat et al. Nature Reviews Gastroenterology and Hepatology (2022)

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Delphi Initiative for Early-Onset Colorectal Cancer (DIRECt) International Management Guidelines

D.3: Which test(s) should be used to evaluate eoCRC signs and symptoms? A diagnostic colonoscopy is recommended for evaluation of alarming symptoms and signs of eoCRC.

- ✓ Higher risk of false negatives with FIT
- ✓ FIT use may prolong diagnostic delays
- ✓ FIT may be useful for patients with vague symptoms (ie, not alarming)

Cavestro et al. Clinical Gastroenterology and Hepatology (2023)

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Early detection and prevention : *How can we do better?*

1- Prompt symptom evaluation:

- Considerable **delays** from symptom onset to diagnosis (delays in seeking care, barriers to accessing care, **medical provider dismissal** or misattribution and **delayed evaluation of symptoms**)

2- Improving screening in high-risk population

Early screening initiation based on family history has been the primary precision screening strategy
Around 30% of patients with EO-CRC has positive family history of colon cancer

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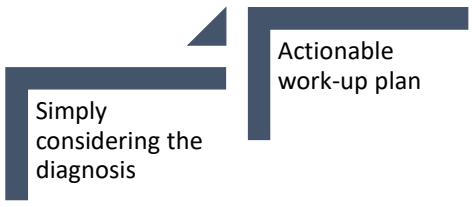
Early detection and prevention: *How can we do better?*

1- Prompt symptom evaluation:

Considerable **delays** from symptom onset to diagnosis (delays in seeking care, barriers to accessing care, **medical provider dismissal** or misattribution and **delayed evaluation of symptoms**)



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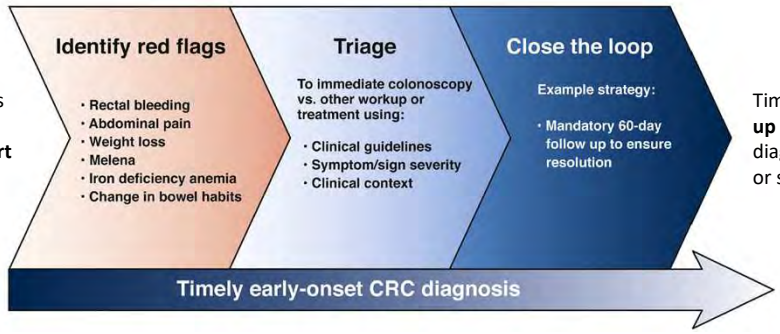
Recognize red flag signs and symptoms with including **EO-CRC as part of the differential diagnosis**



Timely, systematic **follow up** to either confirm a diagnosis other than CRC or symptom resolution

Burnett-Hartman et al. Gastroenterology (2021)

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Early detection and prevention: *How can we do better?*

2- Improving screening in high-risk population:

- Better recognition of CRC genetic syndromes
- Complete documentation of family history of **CRC and advanced adenomas** including **age** of cancer onset/advanced adenoma in relative
- All EO-CRC patients are now referred for genetic assessment to allow for high-risk surveillance and predictive genetic testing for relatives

Gupta et al. Cancer (2020)

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Take home messages

- Early onset colorectal cancer is on the rise
- Think about it
- Family history of all cancer diagnosis is key
- We still have a long way ahead

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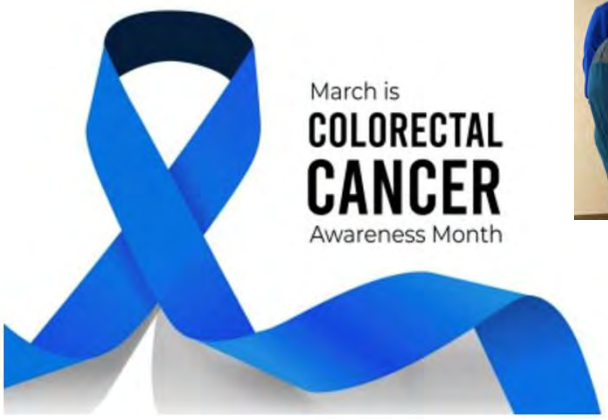

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