Panel: Return to Cancer Screenings Post Covid Colon Cancer

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Disclosure of Conflicts of Interest

Reid M. Ness, MD, MPH has the following financial relationships to disclose:

Speaker - Guardant Health, Inc.

Updates in Screening Recommendations for Colorectal Cancer

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RISK ASSESSMENT FOR COLORECTAL CANCER

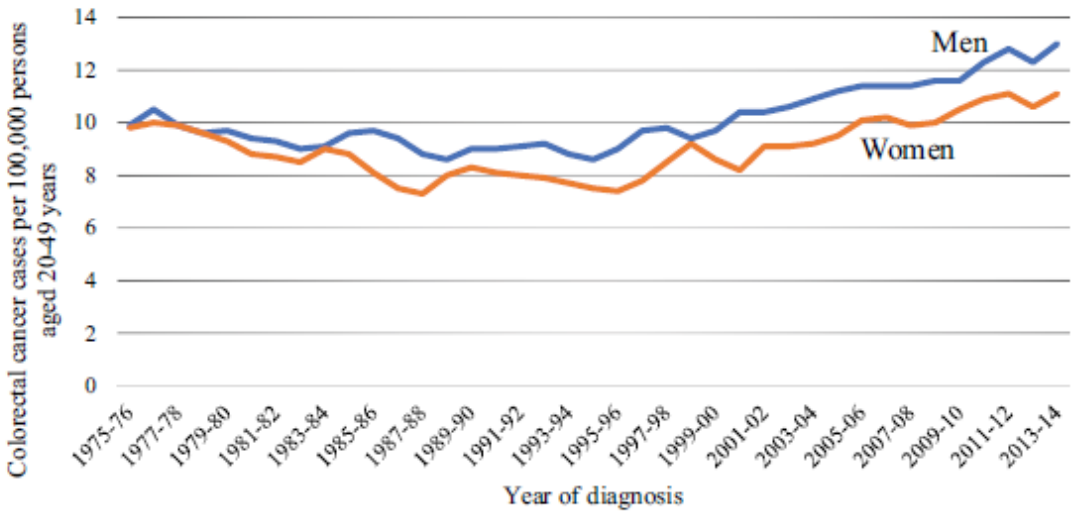
Average risk:

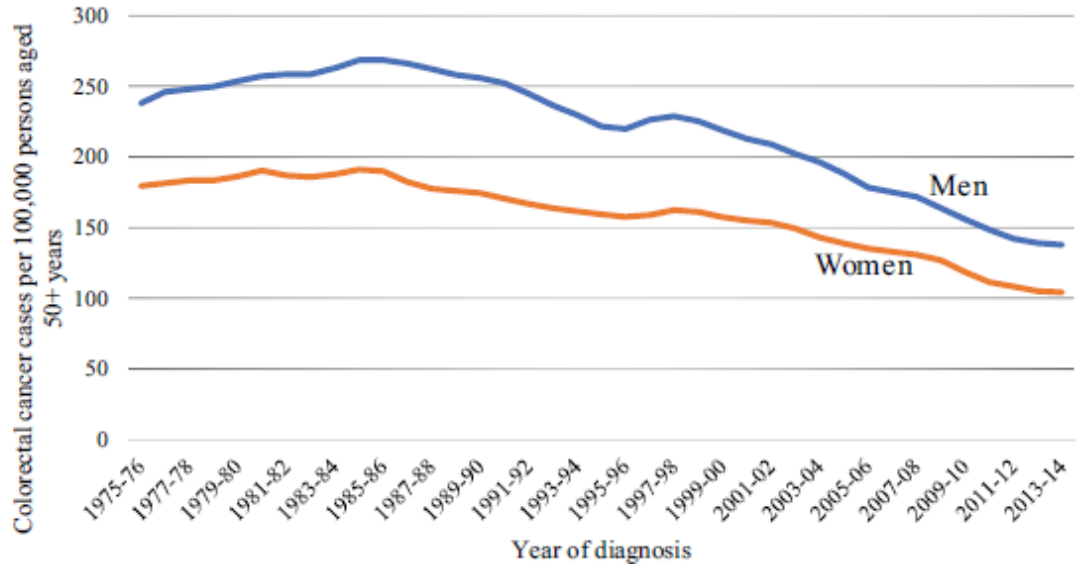
- Age ≥45 years[a]
  - Because there are multiple options for screening, the choice of a particular screening modality should include a conversation with the patient concerning their preference and availability.
- No personal history of adenoma or sessile serrated polyp (SSP)[b] or CRC
- No personal history of inflammatory bowel disease (IBD)
- No personal history of high-risk CRC genetic syndromes
- No personal history of cystic fibrosis
- Negative family history for CRC in first-, second-, or third-degree relatives
- Negative family history for confirmed advanced adenoma (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology) or an advanced SSP[b,c] (≥1 cm, any dysplasia) in first-degree relatives.[d]

→ See Average-Risk Screening and Evaluation (CSCR-3)

Increased risk:

- Personal history
  - Adenoma or SSP[b] → See Follow-up of Clinical Findings: Polyp Found at Colonoscopy (CSCR-5)
  - CRC → Diagnosis of Colorectal Cancer (CSCR-7)
  - IBD (ulcerative colitis, Crohn's colitis) → See Increased Risk Screening Based on Personal History of Inflammatory Bowel Disease (CSCR-8)
  - Cystic fibrosis → See Increased Risk Based on Personal History of Cystic Fibrosis (CSCR-11)
- Positive family history → See Increased Risk Based on Positive Family History (CSCR-12)





Wolf, CA Cancer J Clin 2018; 68:250-281

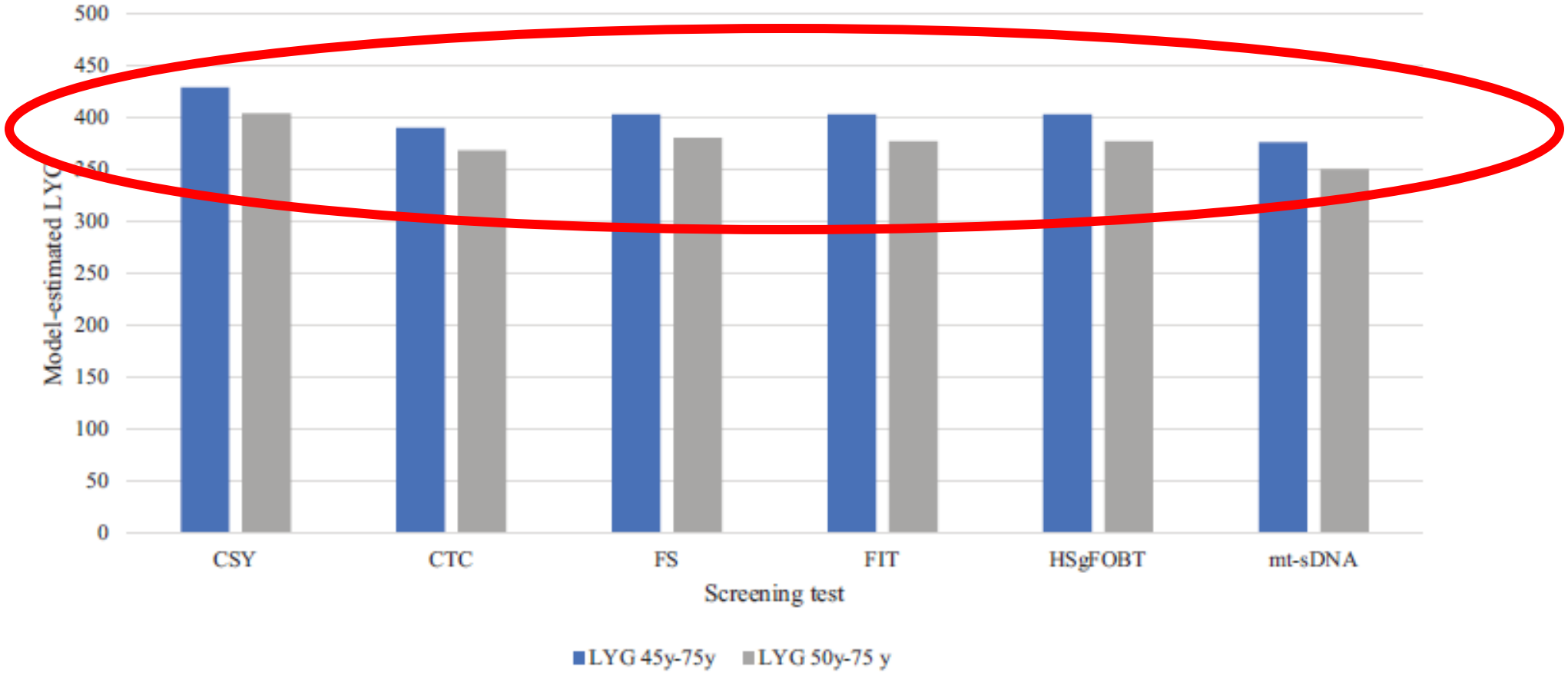
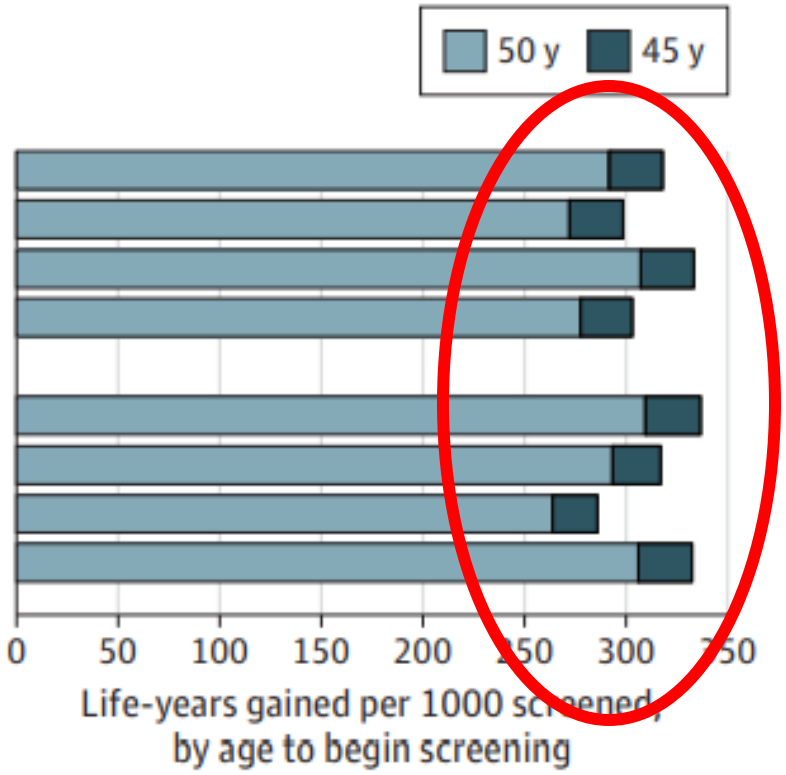


FIGURE 5. Model-Estimated Life-Years Gained (LYG) from Colorectal Cancer Screening Starting at Age 45 Years Versus 50 Years, per 1000 Screened Over a Lifetime. CSY indicates colonoscopy; CTC, computed tomography colonography; FSIG, flexible sigmoidoscopy; FIT, fecal immunochemical test; gFOBT, guaiac-based fecal occult blood test; LYG, life-years gained; mt-sDNA, multitarget stool DNA. Adapted from: Peterse EFP, Meester RGS, Siegal RL, et al. The impact of the rising colorectal cancer incidence in young adults on the optimal age to start screening: microsimulation analysis I to inform the American Cancer Society colorectal cancer screening guideline. *Cancer*. 10.1002/cncr.31543 [epub ahead of print].[34]

Peterse, Cancer 2018;124:2964-73

A Benefit: Estimated life-years gained per 1000 individuals screened[a]

Screening modality and frequency	Mean life-years gained if start screening[b]		Additional life years gained if start screening at age 45 y
	At age 50 y	At age 45 y	
Stool tests			
FIT every year	292	318	26
HSgFOBT every year[c,d]	272	298	26
sDNA-FIT every year	307	333	26
sDNA-FIT every 3 y[d]	278	303	25
Direct visualization tests			
COL every 10 y	310	337	27
CT colonography every 5 y	293	317	24
Flexible SIG every 5 y	264	286	22
Flexible SIG every 10 y plus FIT every year	306	332	26



USPSTF, JAMA 2021;325:1965-1977

Clinician Summary of USPSTF Recommendation

Screening for Colorectal Cancer

May 2021

What does the USPSTF recommend?

A Grade

For adults aged 50 to 75 years:

Screen all adults aged 50 to 75 years for colorectal cancer.

B Grade

For adults aged 45 to 49 years:

Screen adults aged 45 to 49 years for colorectal cancer.

C Grade

For adults aged 76 to 85 years:

Selectively screen adults aged 76 to 85 years for colorectal cancer, considering the patient's overall health, prior screening history, and patient's preferences.

To whom does this recommendation apply?

Adults 45 years and older who do not have signs or symptoms of colorectal cancer and who are at average risk for colorectal cancer (ie, no prior diagnosis of colorectal cancer, adenomatous polyps, or inflammatory bowel disease; no personal diagnosis or family history of known genetic disorders that predispose them to a high lifetime risk of colorectal cancer [such as Lynch syndrome or familial adenomatous polyposis]).

USPSTF, JAMA 2021;325:1965-1977

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RISK ASSESSMENT FOR COLORECTAL CANCER (CONT.)

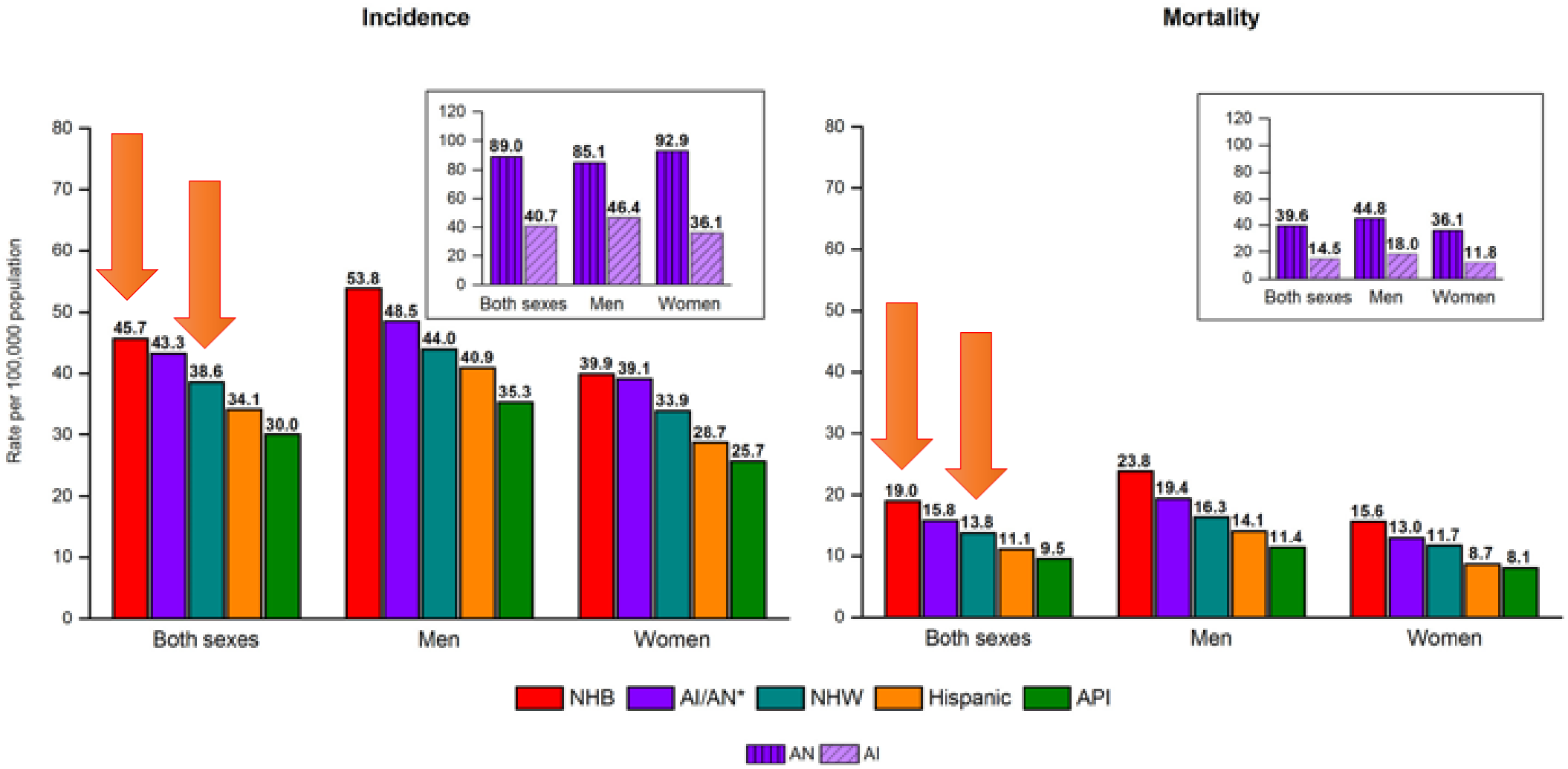
Evaluation of alarm symptoms in patients <45 years:
Half of the patients who present with early-onset CRC (<50 years of age) are <45 years of age[e] and many have signs and symptoms of CRC such as iron deficiency anemia, rectal bleeding, or a change in bowel habits. Individuals with these symptoms warrant prompt evaluation with a colonoscopy regardless of age unless they recently underwent colonoscopy.

- The majority of early-onset CRCs appears to be sporadic. Nonetheless, the possibility of an inherited cancer syndrome should be investigated given the higher incidence of inherited CRC syndromes in younger compared to older patients.

High-risk genetic syndromes with predisposition to colorectal cancer:
- Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC])
- Polyposis syndromes
  - Classical familial adenomatous polyposis
  - Attenuated familial adenomatous polyposis
  - *MUTYH*-associated polyposis
  - Peutz-Jeghers syndrome
  - Juvenile polyposis syndrome
  - Serrated polyposis syndrome (rarely inherited)
- Cowden syndrome/PTEN hamartoma tumor syndrome
- Li-Fraumeni syndrome

→ See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal

→ See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic



Siegel, CA Cancer J Clin 2020; 70:145-164

Model-Recommendable Screening Strategies for 2 Scenarios of CRC Risk

Model	Test Class	Scenario 1: Stable CRC Risk[a]				Scenario 2: Increased CRC Risk[b]			
		White Females	Black Females	White Males	Black Males	White Females	Black Females	White Males	Black Males
MISCAN	COL	50-75, 10	45-75, 10	50-75, 10	45-75, 10	45-75, 10	45-75, 10	45-75, 5	45-75, 10
	Stool	FIT 50-75, 1	FIT 45-75, 1	FIT 50-75, 1	FIT 45-75, 1	FIT 45-75, 1	FIT 45-75, 1	—	FIT 45-75, 1
	SIG	—	—	—	—	45-75, 5	45-75, 5	—	45-75, 5
	CTC	50-75, 5	45-75, 5	50-75, 5	45-75, 5	45-75, 5	45-75, 5	—	45-75, 5

Meester, Cancer 2018;124:2974–2985

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INCREASED RISK BASED ON POSITIVE FAMILY HISTORY
(Not meeting criteria for consideration of a hereditary cancer syndrome or appropriate testing for a hereditary cancer syndrome non-diagnostic or not done)[yy]

FAMILY HISTORY CRITERIA	SCREENING[bbb]	
≥1 first-degree relative with CRC at any age	Colonoscopy beginning at age 40 y or 10 y before earliest diagnosis of CRC	Repeat every 5 y[zz,bbb,ccc,ddd] or if positive, repeat per colonoscopy findings
Second- and third-degree relatives with CRC at any age	Colonoscopy beginning at age 45 y[zz]	Repeat every 10 y or if positive, repeat per colonoscopy findings
First-degree relative with confirmed advanced adenoma(s) (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology, TSA), or advanced SSPs (≥1 cm, any dysplasia) at any age [aaa,eee,fff]	Colonoscopy beginning at age 40 y or at age of onset of adenoma in relative, whichever is first	Repeat every 5–10 y[bbb,ccc] or if positive, repeat per colonoscopy findings

CRITERIA FOR THE EVALUATION OF LYNCH SYNDROME

- Known LS pathogenic variant in the family
- Personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC diagnosed at any age[a] (See LS-A)
- An individual with colorectal or endometrial cancer and any of the following:
  - Diagnosed <50 y
  - A synchronous or metachronous LS-related cancer[b] regardless of age
  - 1 first-degree or second-degree relative with an LS-related cancer[b] diagnosed <50 y
  - ≥2 first-degree or second-degree relatives with an LS-related cancer[b] regardless of age
- Family history[c] of any of the following:
  - ≥1 first-degree relative with a colorectal or endometrial cancer diagnosed <50 y
  - ≥1 first-degree relative with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer[b] regardless of age
  - ≥2 first-degree or second-degree relatives with LS-related cancers,[b] including ≥1 diagnosed <50 y
  - ≥3 first-degree or second-degree relatives with LS-related cancers[b] regardless of age
- Increased model-predicted risk for Lynch syndrome
  - An individual with a ≥5% risk of having an MMR gene pathogenic variant based on predictive models (ie, $PREMM_5$, MMRpro, MMRpredict)
    - ◊ Individuals with a personal history of colorectal and/or endometrial cancer with a $PREMM_5$ score of ≥2.5% should be considered for multi-gene panel testing.
    - ◊ For individuals without a personal history of colorectal and/or endometrial cancer, some data have suggested using a $PREMM_5$ score threshold of ≥2.5% rather than ≥5% to select individuals for MMR genetic testing. Based on these data, it is reasonable for testing to be done based on the ≥2.5% score result and clinical judgment. Of note, with the lower threshold, there is an increase in sensitivity, but a decrease in specificity.

→ See Strategies For Evaluating LS (LS-2)

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Second- and third-degree relatives with CRC at any age	Colonoscopy beginning at age 45 y[zz]	Repeat every 10 y or if positive, repeat per colonoscopy findings
First-degree relative with confirmed advanced adenoma(s) (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology, TSA), or advanced SSPs (≥1 cm, any dysplasia) at any age [aaa,eee,fff]	Colonoscopy beginning at age 40 y or at age of onset of adenoma in relative, whichever is first	Repeat every 5–10 y[bbb,ccc] or if positive, repeat per colonoscopy findings

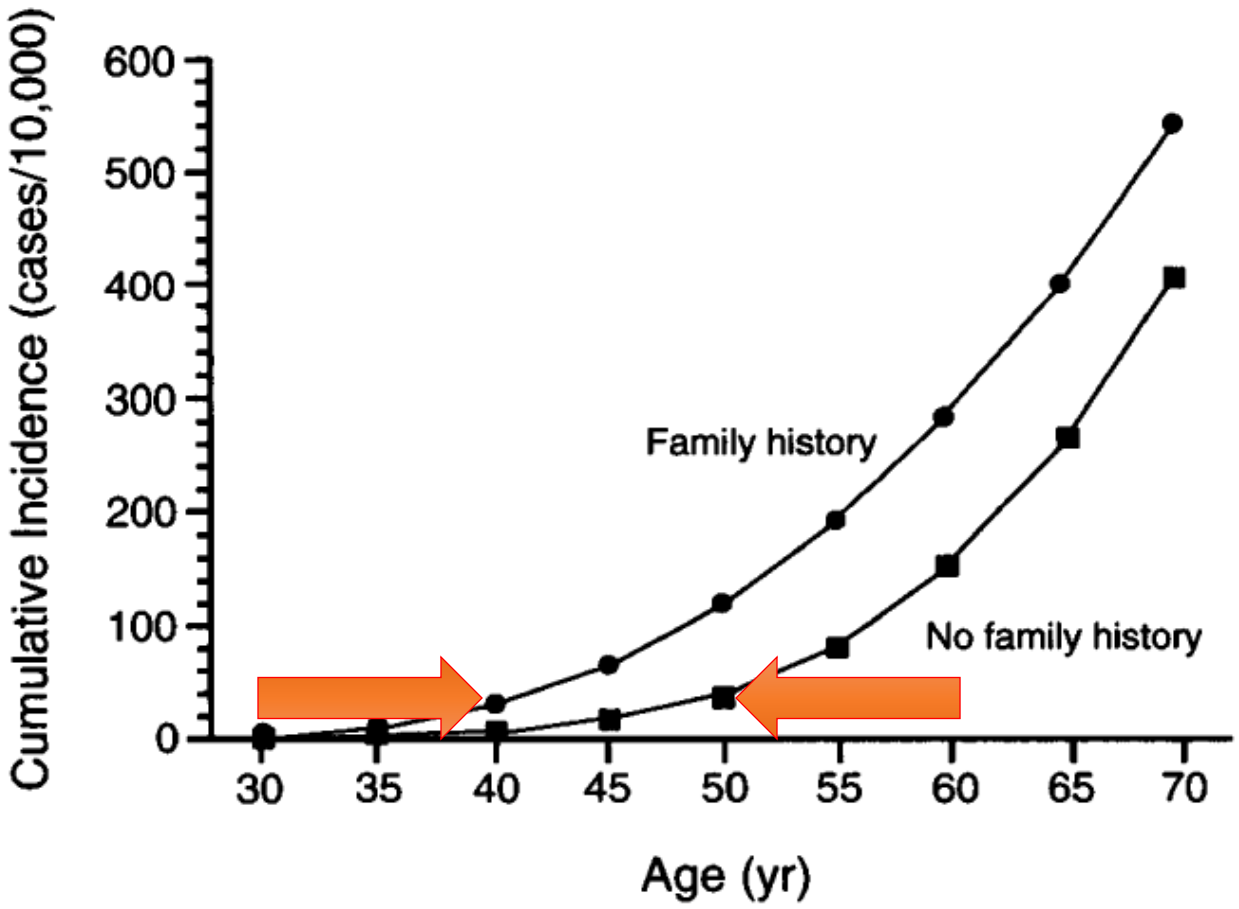
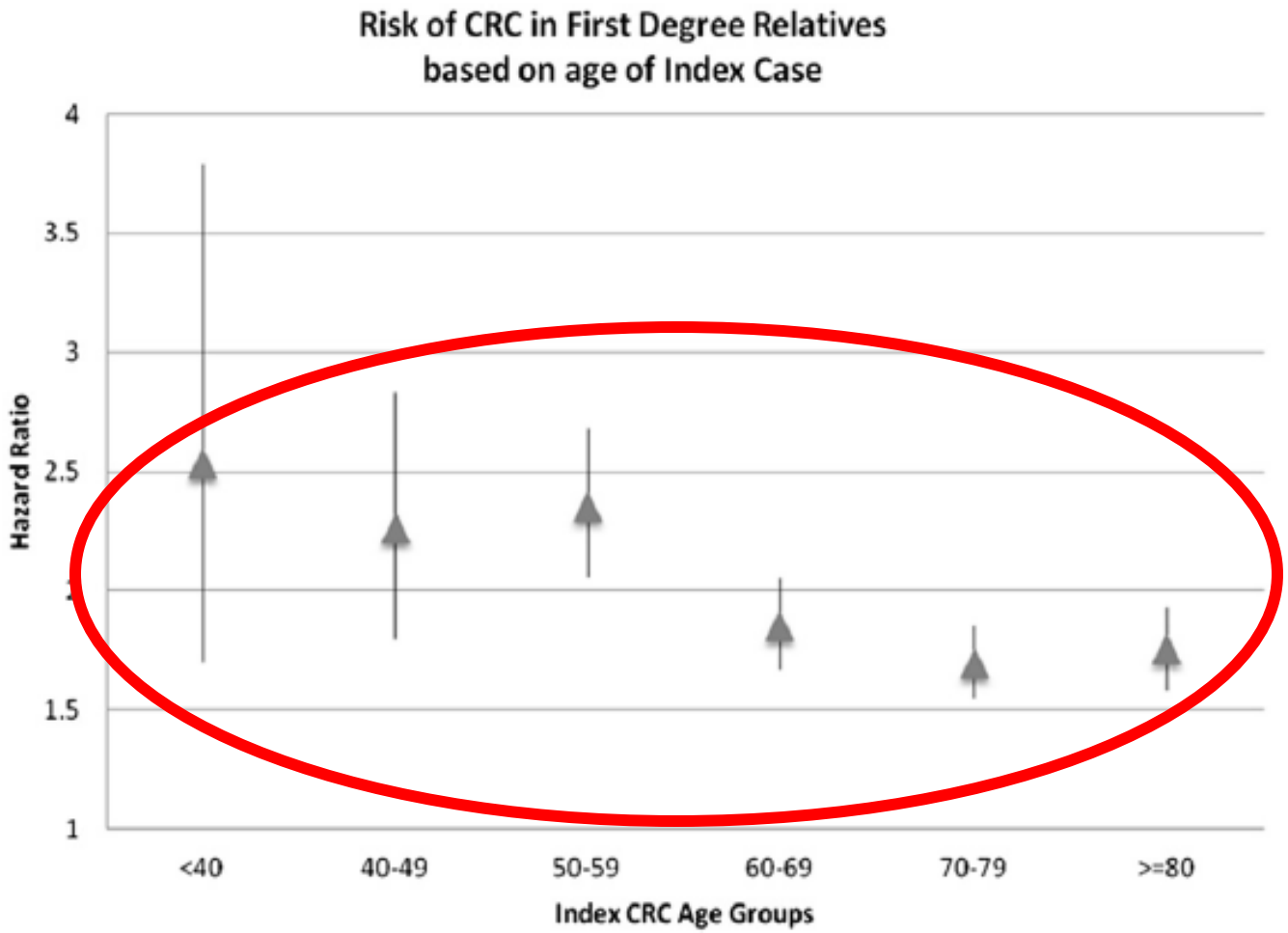


Figure 1. Cumulative Incidence of Colorectal Cancer According to Age and the Presence or Absence of a Family History of the Disease.

Fuchs, N Engl J Med. 1994;331:1669-1674



Supplementary Figure 1. Risk for CRC in relatives stratified by age of index case displayed on line plot.

Samadder, Clin Gastroenterol Hepatol. 2015;13:2305-2311

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Second- and third-degree relatives with CRC at any age	Colonoscopy beginning at age 45 y[zz]	Repeat every 10 y or if positive, repeat per colonoscopy findings
First-degree relative with confirmed advanced adenoma(s) (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology, TSA), or advanced SSPs (≥1 cm, any dysplasia) at any age [aaa,eee,fff]	Colonoscopy beginning at age 40 y or at age of onset of adenoma in relative, whichever is first	Repeat every 5–10 y[bbb,ccc] or if positive, repeat per colonoscopy findings

Table 3. Selected Familial Relative Risk (FRR) Estimates for Probands With 0 or 1 Affected First-Degree Relatives (FDRs) and Various Combinations of Affected Second-Degree Relatives (SDRs) and Third-Degree Relatives (TDRs)

No. of affected FDRs	No. of affected SDRs	No. of affected TDRs	No. of probands	FRR (95% CI)
0	0	0	1,470,367	0.83 (0.81–0.86)
0	0	≥3	44,662	1.08 (0.97–1.20)
0	1	2	20,321	1.33 (1.13–1.55)
0	1	≥3	13,858	1.21 (0.98–1.48)
0	2	≥3	4061	1.48 (0.98–2.16)
0	≥3	≥3	2120	1.02 (0.41–2.09)
1	0	0	41,369	1.76 (1.63–1.89)
1	0	2	5560	1.90 (1.59–2.25)
1	0	≥3	3255	2.01 (1.61–2.47)
1	1	0	8836	1.88 (1.59–2.20)
1	1	2	1882	2.50 (1.87–3.28)
1	1	≥3	1357	3.28 (2.44–4.31)
1	2	0	1669	2.37 (1.58–3.43)
1	2	1	1006	1.98 (1.15–3.17)
1	2	2	523	2.70 (1.44–4.62)
1	2	≥3	578	2.38 (1.19–4.26)
1	≥3	0	453	2.79 (1.12–5.76)
1	≥3	2	206	5.32 (2.14–10.96)
1	≥3	≥3	322	5.20 (2.24–10.24)

Taylor, Gastroenterology 2010;138:877-885

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First-degree relative with confirmed advanced adenoma(s) (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology, TSA), or advanced SSPs (≥1 cm, any dysplasia) at any age [aaa,eee,fff]	Colonoscopy beginning at age 40 y or at age of onset of adenoma in relative, whichever is first	Repeat every 5–10 y[bbb,ccc] or if positive, repeat per colonoscopy findings

Table 2. Risk of Advanced Adenomas Among Siblings of Patients With Advanced Adenomas

	Exposed siblings, n (%) (n = 200)	Unexposed siblings, n (%) (n = 400)	mOR (95% CI)[a]	*P* value
No adenomas	120 (60.0)	324 (81.0)	1	—
All adenomas	78 (39.0)	76 (19.0)	3.29 (2.16–5.03)	<.001
Advanced adenomas	23 (11.5)	10 (2.5)	6.05 (2.74–13.36)	<.001
Adenomas ≥10 mm[b]	21 (10.5)	7 (1.8)	8.59 (3.44–21.45)	<.001
>25% villous features[b]	11 (5.5)	5 (1.3)	6.28 (2.02–19.53)	.001
High-grade dysplasia[b]	4 (2.0)	1 (0.3)	19.98 (2.03–197)	.010
Cancer	2 (1.0)	0 (0.0)	—	—
Multiple adenomas[c]	13 (6.5)	9 (2.3)	5.16 (2.02–13.19)	.001
Distal adenomas[d]	34 (17)	31(7.8)	3.83 (2.1–6.96)	<.001
Proximal adenomas[e]	27 (13.5)	30(7.5)	2.5 (1.36–4.6)	.003
Synchronous adenomas[f]	17 (8.5)	15 (3.8)	3.94 (1.79–8.65)	.001

Ng, Gastroenterology 2016;150:608–616

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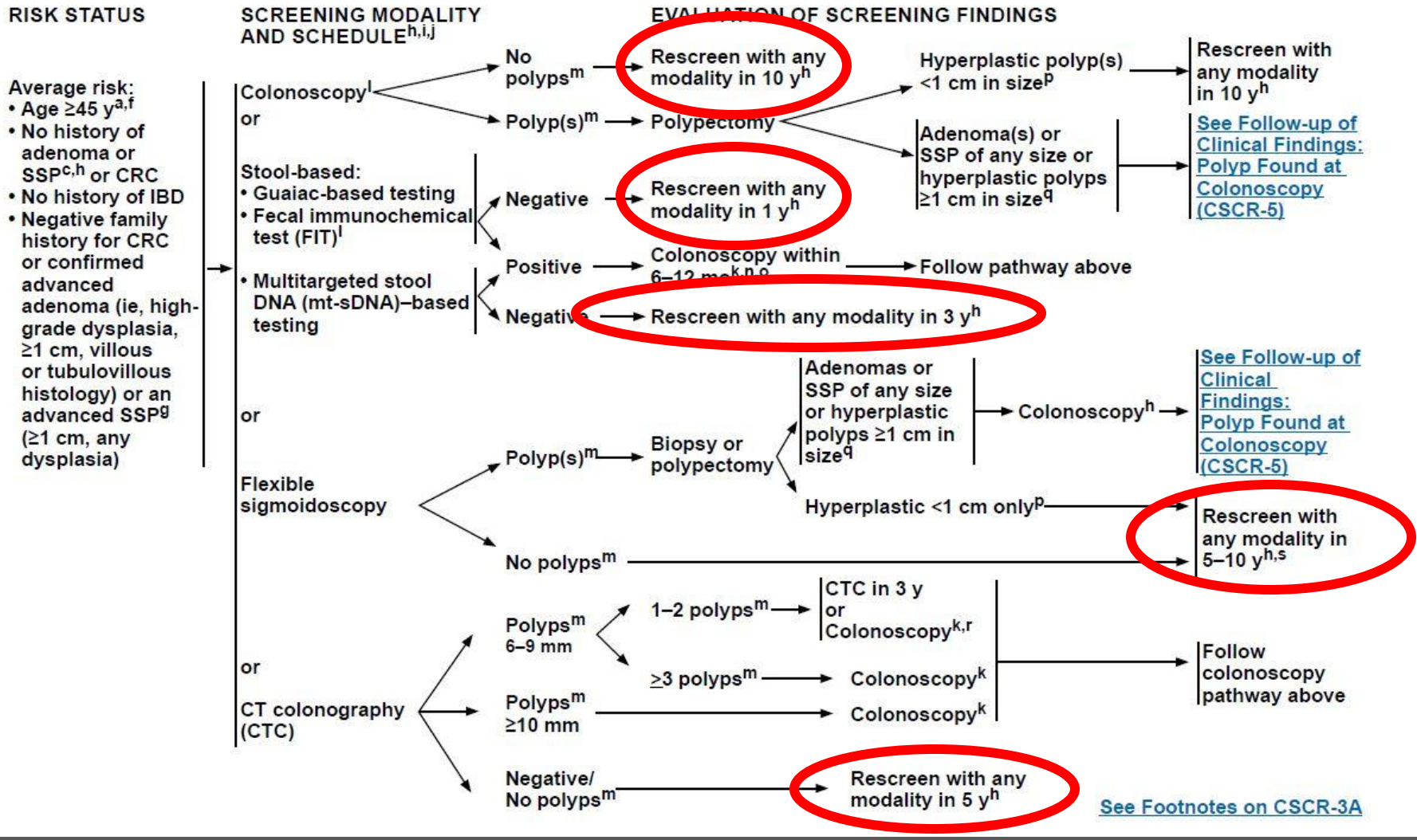
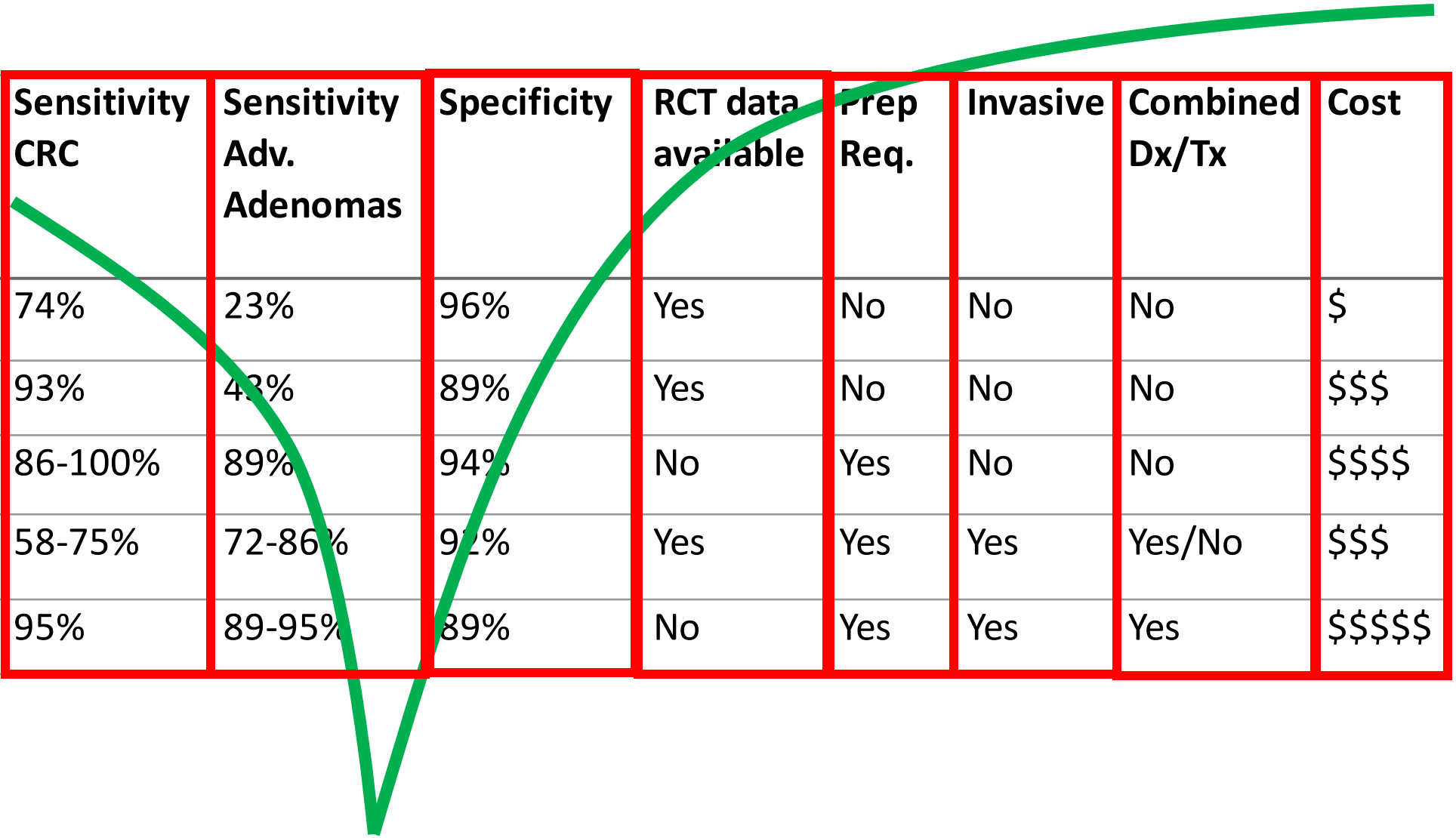
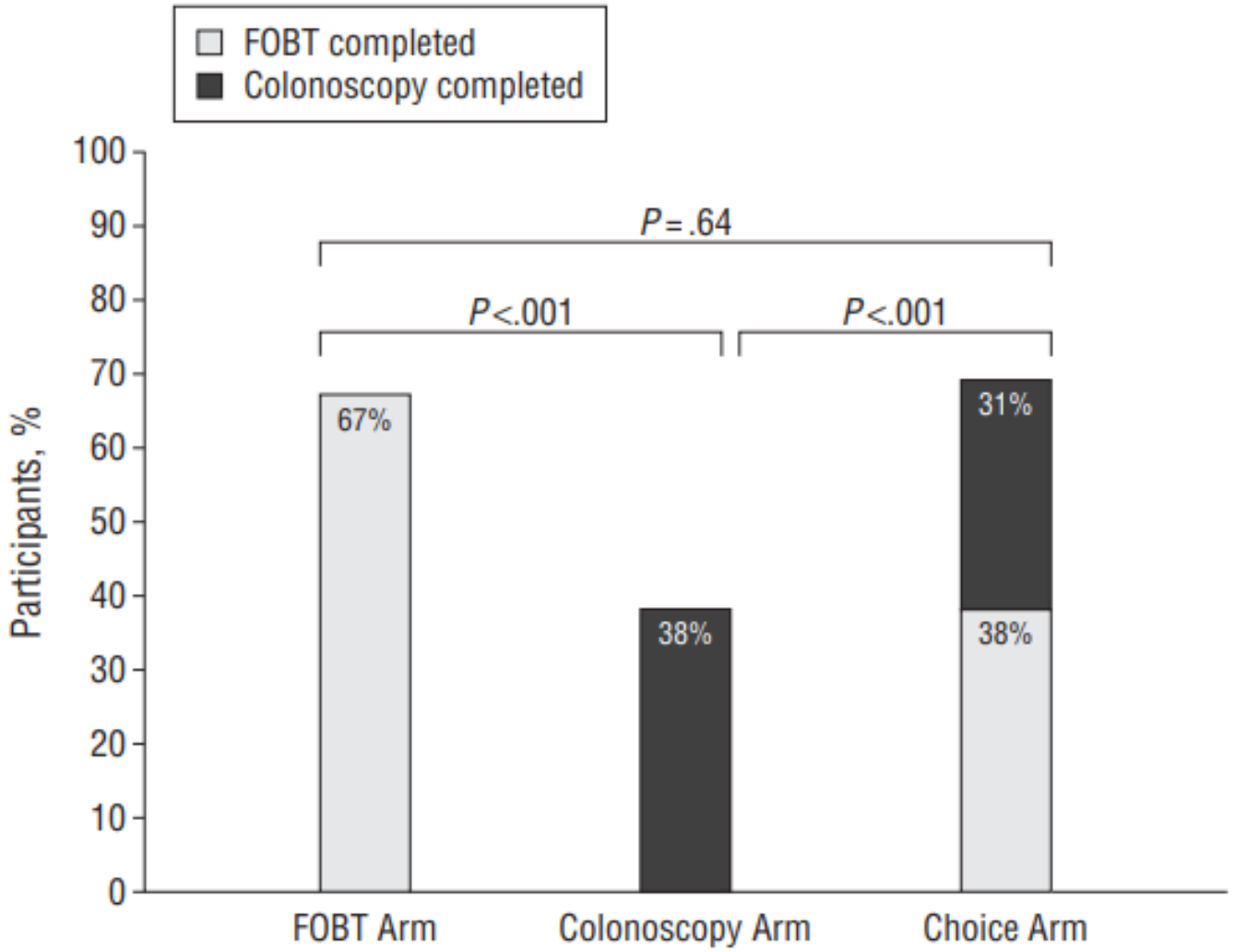


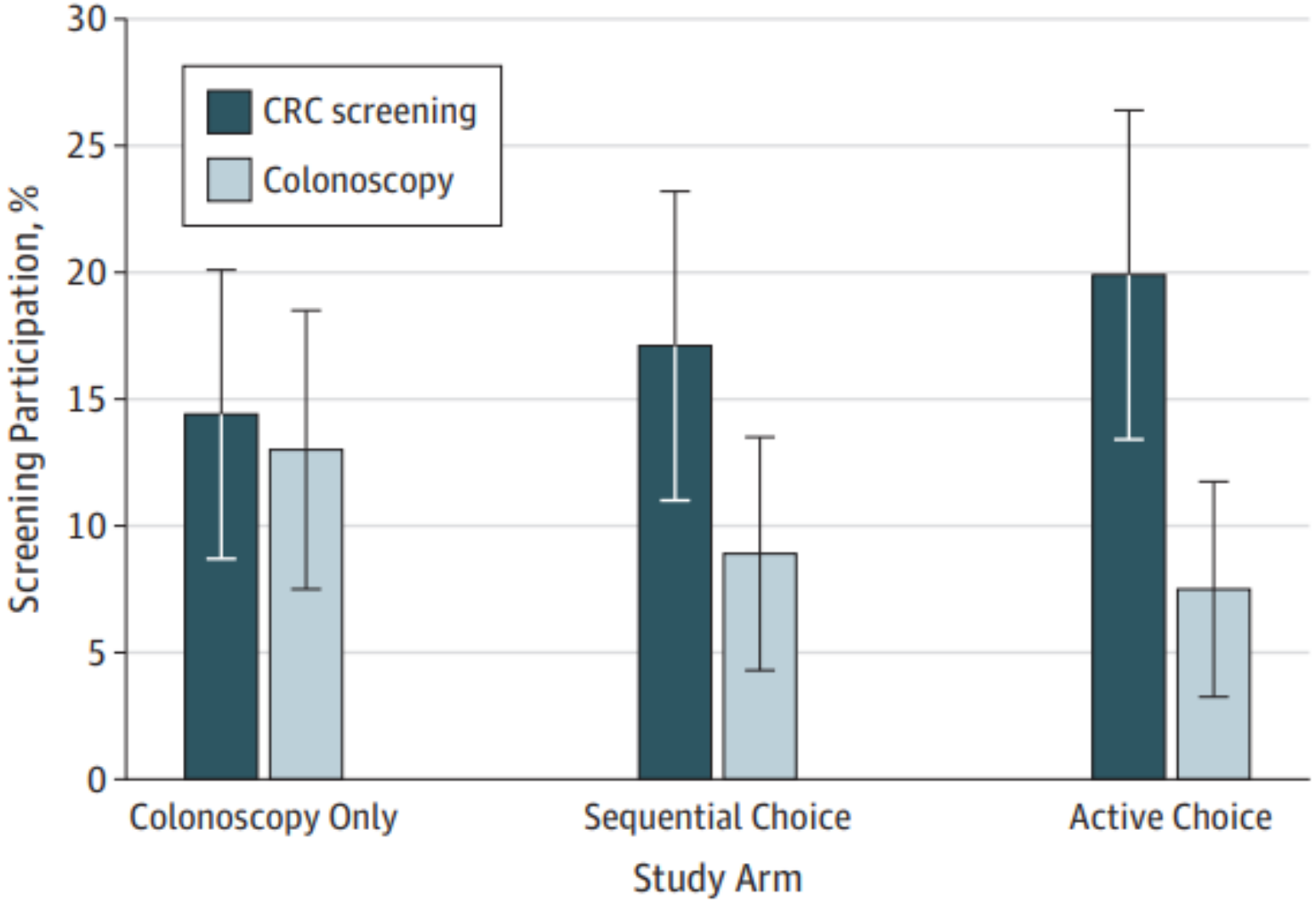
Screening modality	Sensitivity CRC	Sensitivity Adv. Adenomas	Specificity	RCT data available	Prep Req.	Invasive	Combined Dx/Tx	Cost
FIT	74%	23%	96%	Yes	No	No	No	$
mt-sDNA	93%	42%	89%	Yes	No	No	No	$$$
CTC	86-100%	89%	94%	No	Yes	No	No	$$$$
Sigmoidoscopy	58-75%	72-86%	92%	Yes	Yes	Yes	Yes/No	$$$
Colonoscopy	95%	89-95%	89%	No	Yes	Yes	Yes	$$$$$



Pickhardt, Radiology 2011;259:393-405. Lin, JAMA 2021;325:1978-1998. Whitlock, Ann Intern Med 2008;149:638-658. Zauber, Ann Intern Med 2008;149:659-669.



Inadomi, Arch Intern Med. 2012;172(7):575-582



Mehta, JAMA Network Open. 2019;2(8):e1910305.

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Table 5. Colorectal Cancer Screening (%), Adults 45 Years and Older, US, 2018

	Stool test*	Colonoscopy†	Up to date‡	
	≥50 years	≥50 years	≥50 years	50-75 years
Overall	11	61	66	67
Gender				
Males	12	62	67	67
Females	10	60	64	66
Age (years)				
50-64	10	56	61	62
50-54	9	42	48	–
55-64	10	63	68	–
65+	12	66	71	77
75+	10	60	63	–
Race/ethnicity				
White	10	63	68	69
Black	12	60	65	66
Hispanic	15	52	59	59
American Indian/Alaska Native	12	53	59	56
Asian	15	47	55	58

https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/colorectal-cancer-facts-and-figures/colorectal-cancer-facts-and-figures-2020-2022.pdf

Table 5. Colorectal Cancer Screening (%), Adults 45 Years and Older, US, 2018

	Stool test*	Colonoscopy†	Up to date‡	
	≥50 years	≥50 years	≥50 years	50-75 years
Education				
Less than high school	11	46	52	53
High school diploma	10	57	62	63
Some college	11	62	68	68
College graduate	11	68	73	73
Income level				
<100% FPL	12	49	55	57
100 to <200% FPL	12	48	55	57
≥200% FPL	11	65	70	70
Insurance status				
Uninsured	5	26	30	30
Private	9	60	65	65
Medicare or Medicare & Medicaid	14	61	67	73
Private & Medicare	11	71	74	80
Medicaid or Other state plan	14	44	53	54

https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/colorectal-cancer-facts-and-figures/colorectal-cancer-facts-and-figures-2020-2022.pdf

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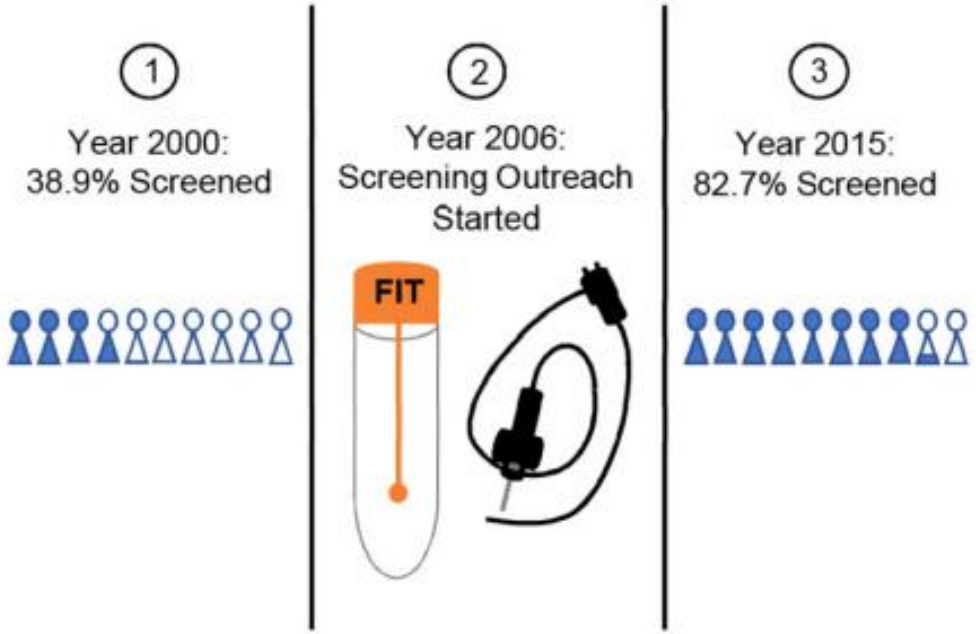
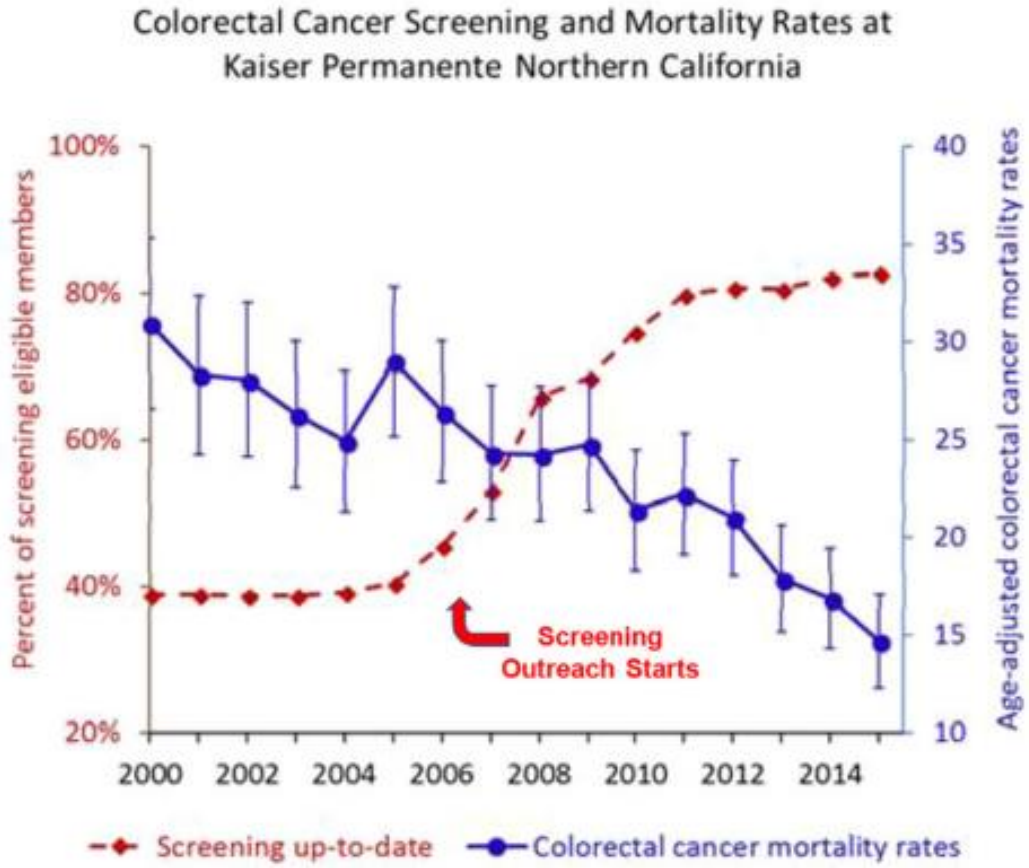
SCREENING MODALITY AND SCHEDULE

- Screening of average-risk individuals reduces CRC incidence by detecting and removing pre-cancerous polyps, and CRC mortality by detecting cancer at an early, curable stage.
- CRC screening should be performed as part of a population-based program that includes a systematic method for 1) identifying those who are eligible for and wish to undergo screening; 2) risk stratification and administration of the screening tests at agreed upon intervals; 3) shared decision-making with patients regarding the choice of screening method; 4) standardized reporting of the results; and 5) follow-up of those with a positive test. The program should also include a systematic method for the arranging of repeat screening and surveillance.
- Organized screening programs that provide direct outreach to patients and clinic-focused interventions have been shown to increase CRC screening rates, reduce mortality, and minimize disparities by race/ethnicity.[1] Examples of evidence-based interventions to increase CRC screening rates include mailed stool test outreach, patient navigation, patient education and reminders, and clinician-directed feedback and alerts.[2]
- Screening rates improve when programs offer different options of screening tests to ensure that testing characteristics are aligned with patient preference.[3]





Levin, Gastroenterology 2018;155:1383-1391.

What recent changes have been made to the NCCN CRC Screening Guidelines?

- Age for initiation of average-risk screening lowered from 50 to 45 for all combinations of race and sex
- No other changes were made to the recommended average risk screening modalities or strategies
- Age for initiation of screening for those with affected first-degree family members with CRC or adv. adenomas/SSPs maintained at 40
- Age for initiation of screening for those with second- and third-degree family members with CRC lowered from 50 to 45

Caveats of NCCN CRC Screening Guidelines

- Patients presenting with symptoms suggestive of possible CRC such as iron deficiency and rectal bleeding should be evaluated with colonoscopy in a timely fashion.
- We continue to endorse colonoscopy every 10 years, FIT every year, multitargeted stool DNA combined with FIT every 3 years, flexible sigmoidoscopy every 5-10 years and CT colonography every 5 years.
- CRC screening should be performed as part of a systematic, population-based program to achieve the best results and insure equitable outcomes.