Colorectal Cancer Screening

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NO DISCLOSURES

Learning Objectives

- Recognize differences between available CRC screening modalities

- Understand screening guidelines for average risk and high risk individuals

- Identify risk factors associated with CRC

- Be aware of the increasing incidence of CRC in young adults

# Colorectal Cancer is the 2nd Leading Cause of Cancer Deaths

Estimated New Cases

			Males	Females			
Prostate	164,690	19%		Breast	268,120	30%
Lung & bronchus	121,680	14%		Lung & bronchus	112,350	13%
Colon & rectum	75,610	9%		Colon & rectum	64,640	7%
Urinary bladder	62,380	7%		Uterine corpus	63,230	7%
Melanoma of the skin	55,150	6%		Thyroid	40,900	5%
Kidney & renal pelvis	42,680	5%		Melanoma of the skin	36,120	4%
Non-Hodgkin lymphoma	41,730	5%		Non-Hodgkin lymphoma	32,950	4%
Oral cavity & pharynx	37,160	4%		Pancreas	26,240	3%
Leukemia	35,030	4%		Leukemia	25,270	3%
Liver & intrahepatic bile duct	30,610	4%		Kidney & renal pelvis	22,660	3%
All Sites	**856,370**	**100%**		**All Sites**	**878,980**	**100%**

Estimated Deaths

			Males	Females			
Lung & bronchus	83,550	26%		Lung & bronchus	70,500	25%
Prostate	29,430	9%		Breast	40,920	14%
Colon & rectum	27,390	8%		Colon & rectum	23,240	8%
Pancreas	23,020	7%		Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%		Ovary	14,070	5%
Leukemia	14,270	4%		Uterine corpus	11,350	4%
Esophagus	12,850	4%		Leukemia	10,100	4%
Urinary bladder	12,520	4%		Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%		Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%		Brain & other nervous system	7,340	3%
All Sites	**323,630**	**100%**		**All Sites**	**286,010**	**100%**

Siegel et al CA: A Cancer Journal for Clinicians 2018

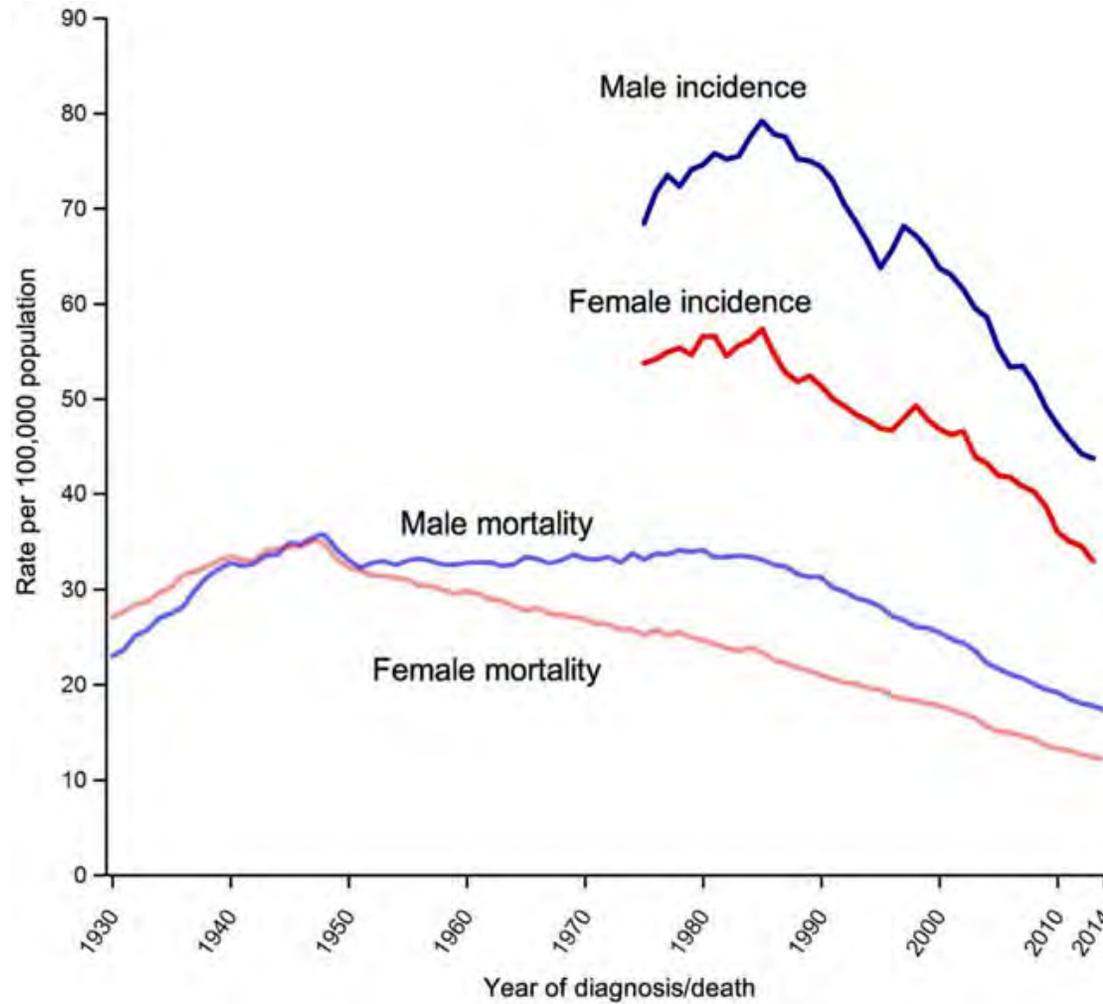# Percentage of Adults Up to Date with Screening in United Sates, 2000–2015
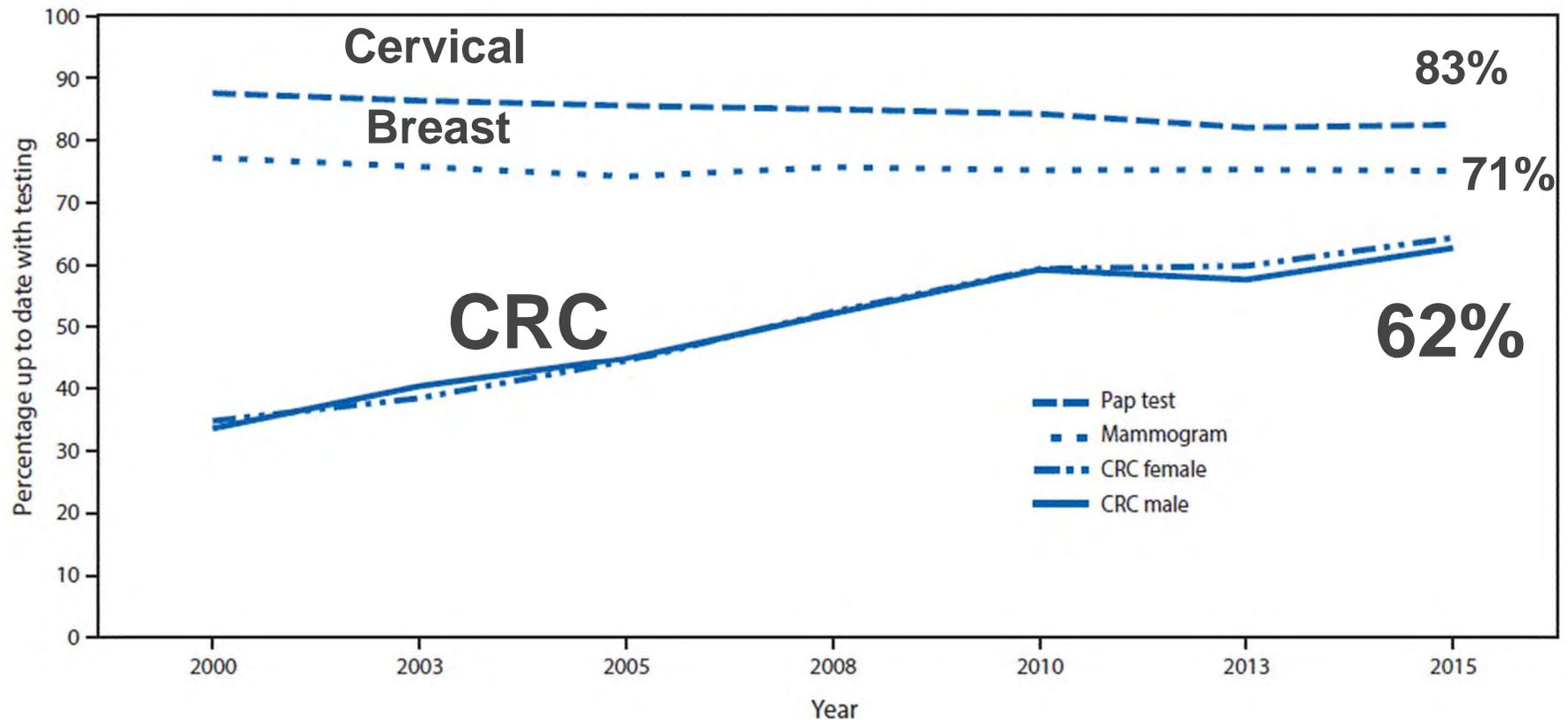
White A, Thompson TD, White MC, et al. Cancer Screening Test Use --United States
MMWR 2017;66:201–206

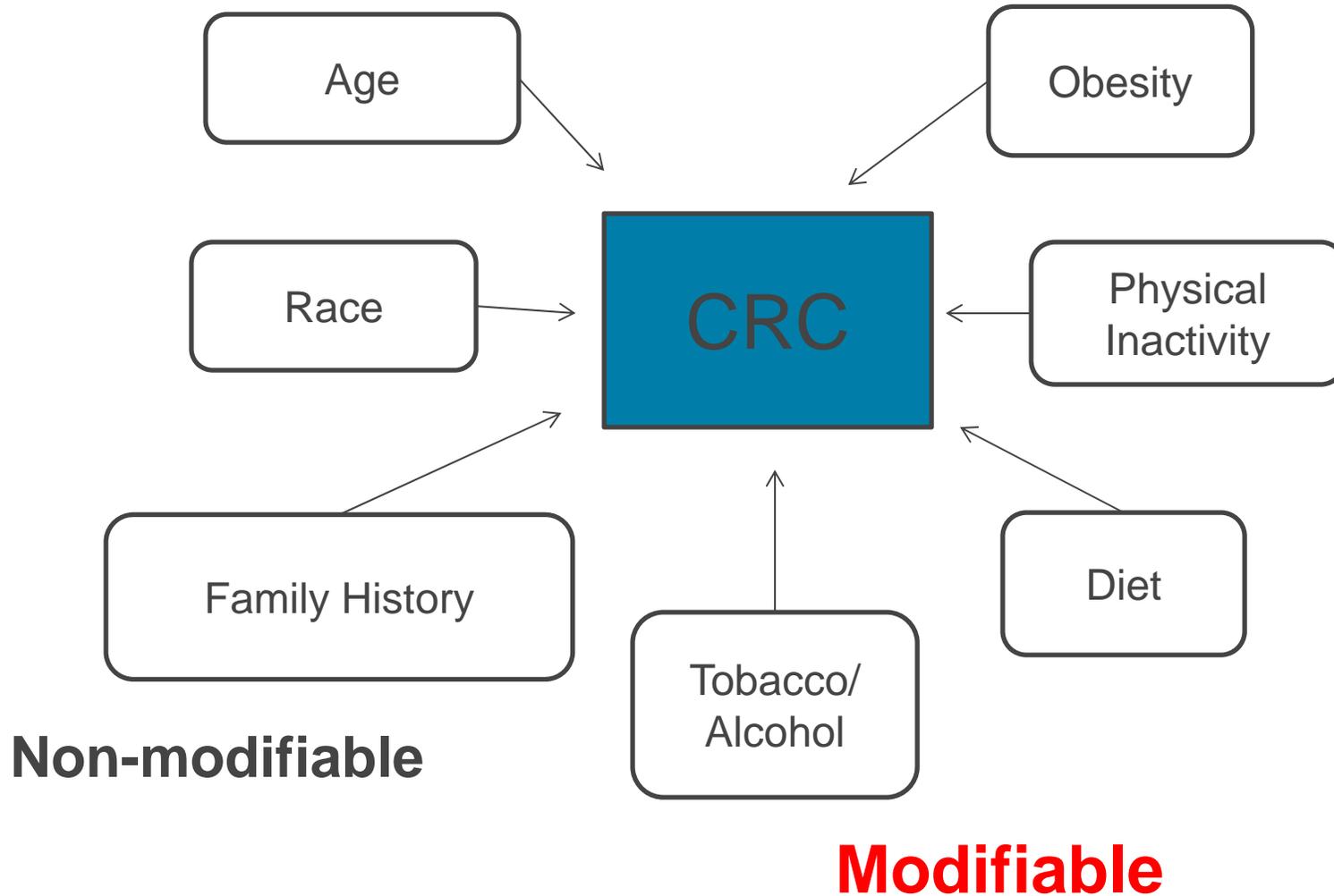# Percentage of Adults Up to Date with CRC Screening by State, 2016
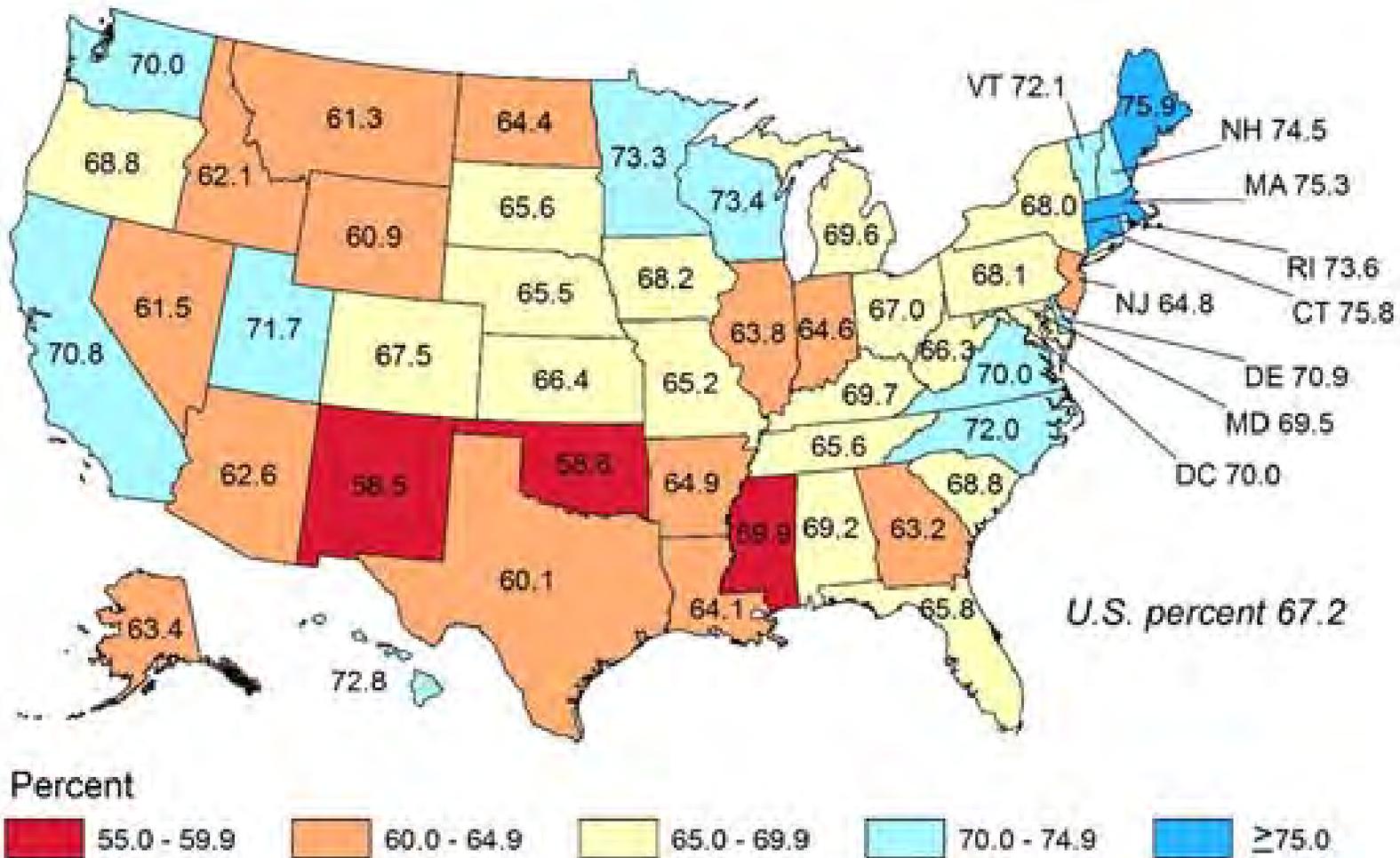
Joseph DA, King JB, Richards TB, Thomas CC, Richardson LC. Use of colorectal cancer screening tests by state. *Preventing Chronic Disease* 2018;15:170535.

CRC Incidence and Mortality are Declining

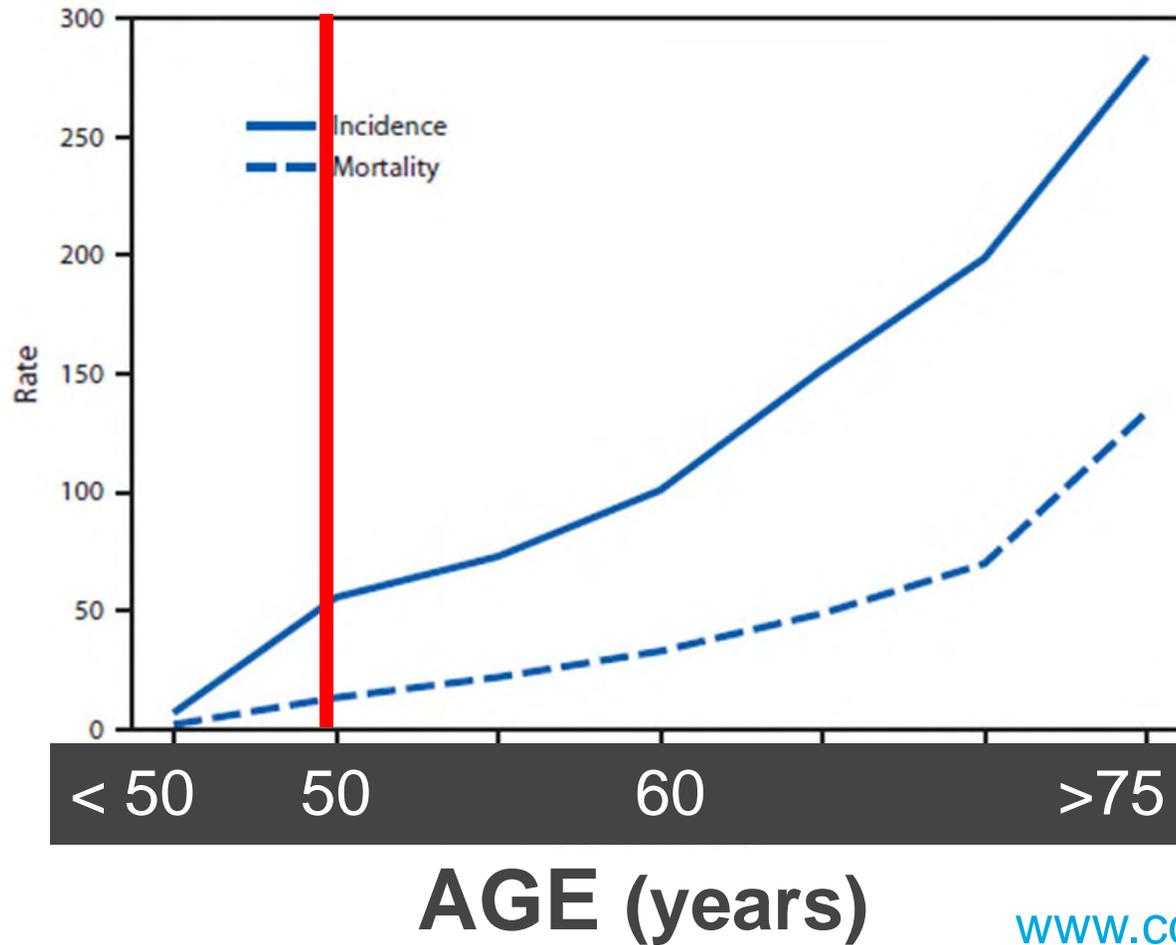*Siegel, R et al. Ca Cancer J Clin2017;67:177–193*

Major Risk Factors For Colorectal Cancer

Age

Obesity

Race

CRC

Physical Inactivity

Family History

Tobacco/ Alcohol

Diet

Non-modifiable

Modifiable

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Advancing Age is Greatest Risk Factor for Development of CRC and Colon Polyps

CRC

www.cdc.gov

Screening Guidelines Vary, Race is a Risk Factor

Society	Age to Start	Exceptions
USPSTF	50	None
MSTF	50	45 for blacks*
ACP	50	40 for blacks*
ACS	45*	None

Patients need to discuss coverage with their insurer, and age to start for some patients may be dictated by insurance coverage

Qaseem A, et al. Ann Intern Med. 2012
Rex et al., Am J Gastro 2017
Wolf AMD, et al. CA: Cancer J Clin. 2018
JAMA. USPSTF Recommendations. 2016

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Blacks Have the Highest CRC Incidence & Death Rates

Table 3. Sex-Based Incidence and Mortality Rate Ratios per 100,000 (Adjusted to the 2000 US Standard Population) for Selected Gastrointestinal Cancers for 2010–2014, With Comparing Blacks to Non-Hispanic Whites

Variable	All races	Asian/ Pacific Islander	American Indian/ Alaskan	Hispanic	Black	NHW	Absolute difference (black − NHW)	Black to NHW rate ratio[a]
CRC								
Incidence								
Male	46.0	40.2	45.5	41.5	56.4	45.9	+10.5	1.23
Female	35.1	28.8	37.5	29.9	43.2	35.3	+7.9	1.22
Mortality								
Male	17.7	12.4	14.0	15.8	25.3	17.3	+8.0	1.46
Female	12.4	8.8	10.0	9.7	16.5	12.3	+4.2	1.34

Asktorab H, et al. Gastro 2017 153: 910-923

Multi-Society Task Force Ranking of Screening options for Average Risk Patients

Tier 1	
Colonoscopy every 10 years	
Annual fecal immunochemical test	
Tier 2	
CT colonography every 5 years	
FIT–fecal DNA every 3 years	
Flexible sigmoidoscopy every 10 years (or every 5 years)	
Tier 3	
Capsule colonoscopy every 5 years	
Available tests not currently recommended	
Septin 9	

Rex et al., Am J Gastro 2017

Multiple Available Screening Options

	Colonoscopy	Flexible Sigmoidoscopy	CT Colonography	FIT-DNA (Cologuard)	Fecal Occult Blood Test (FOBT)	
Type					Guaiac FOBT	FIT - iFOBT
Average Cost*	$950	$520	$315	$502	$22	
Sensitivity (True Positive)	High (>95%)	Moderate to High (>95% in distal colon)	High (>90%)	High (92%)	Low (33%)	Moderate (75%)
Specificity (True Negative)	High	High	High	High	Moderate	Moderate
USPSTF Recommended Frequency	10 years	5 years	5 years	3 years	1 year	
CDPHP Coverage¹^	✓	✓	Prior Authorization	Prior Authorization	✓	
Advantages	• Gold standard • Most sensitive • Biopsy and polypectomy can be performed during the procedure • Used as a diagnostic test when a person has symptoms • Used as a follow-up test when the results of another test are unclear or abnormal	• Minimal discomfort • Biopsy and polypectomy can be performed during the procedure	• Minimally invasive • No sedation needed	• No colon cleansing • Samples collected at home • No sedation needed	• No colon cleansing • Samples collected at home • No sedation needed	• No colon cleansing • Samples collected at home • No sedation needed • **Requires 1 sample** • **Does not require dietary restrictions**
Limitations	• Unable to detect some small polyps or cancers • Bowel cleansing required • Dietary restrictions • Sedation necessary • Small risk of bleeding or tearing	• Only allows view of rectum and lower colon • Bowel cleansing • Small risk of bleeding or tearing	• Bowel cleansing required • Unable to detect some polyps • Exposure to ionizing radiation	• High cost • Low sensitivity to adenomas	• Requires 3 samples • Requires dietary restrictions • Unable to detect some polyps and cancers	• Unable to detect some polyps and cancers

*Average cost to plan per commercial claim.
¹ Coverage may vary depending on plan restrictions.

Annual FIT: Advantages

- Non-invasive. Single stool sample. No diet restrictions
- No bowel purge or sedation required.
- Affordable ($22)
- Mortality benefit of gFOBT demonstrated in large RCTs
  - gFOBT shown to reduces CRC mortality by 9-22%
  - FIT more sensitive (75-80%) than gFOBT for CRC

Sensitivity of FIT for CRC

Table 1. Sensitivity and Specificity of FIT for Colorectal Cancer in an Average-Risk Population

Study, year	FIT brand	FIT samples	Cut-off value, µg/g	Cohort size	CRC, n	Reference standard[a]	Sensitivity	Specificity
Allison et al,[20] 1996	HemeSelect[b]	3	100	7493	35	2-year f/u	0.69	0.94
Itoh,[26] 1996	OC-Hemodia[b]	1	10	27,860	89	2-year f/u	0.87	0.95
Nakama et al,[31] 1996	Monohaem	1	20	3365	12	2-year f/u	0.83	0.96
Nakama et al,[32] 1999	Monohaem	1	20	4611	18	Colonoscopy	0.56	0.97
Cheng et al,[22] 2002	OC-Light	1	10	7411	16	Colonoscopy	0.88	0.91
Sohn et al,[36] 2005	OC-Hemodia[b]	1	20	3794	12	Colonoscopy	0.25	0.99
Morikawa et al,[30] 2005	Magstream HemSp	1	67	21,805	79	Colonoscopy	0.66	0.95
Launoy et al,[27] 2005	Magstream HemSp	2	67	7421	28	2-year f/u	0.86	0.94
Nakazato et al,[34] 2006	OC-Hemodia[b]	2	16	3090	19	Colonoscopy	0.53	0.87
Allison et al,[19] 2007	FlexSure OBT	3	300	5356	14	2-year f/u	0.86	0.97
Levi et al,[29] 2007	OC-Micro	3	15	80	3	Colonoscopy	0.67	0.83
Park et al,[33] 2010	OC-Micro	1	20	770	13	Colonoscopy	0.77	0.94
Parra-Blanco et al,[35] 2010	OC-Light	1	10	1756	14	2-year f/u	1.00	0.93
Levi et al,[28] 2011	OC-Micro	3	14	1204	6	2-year f/u	1.00	0.88
Chiang et al,[23] 2011	OC-Light	1	10	2796	28	Colonoscopy	0.96	0.87
de Wijkerslooth et al,[25] 2012	OC-Sensor	1	20	1256	8	Colonoscopy	0.75	0.95
Chiu et al,[24] 2013	OC-Light	1	10	8822	13	Colonoscopy	0.85	0.92
Brenner and Tao,[21] 2013	OC-Sensor	1	6.1	2235	15	Colonoscopy	0.73	0.96
Brenner and Tao,[21] 2013	Ridascreen[b]	1	24.5	2235	15	Colonoscopy	0.60	0.95
Imperiale et al,[37] 2014	OC-FIT CHEK	1	20	9899	65	Colonoscopy	0.74	0.96
Hernandez et al,[38] 2014	OC-Sensor	1	20	779	5	Colonoscopy	1.00	0.94

Robertson et al, *Gastro* 2017

Lowering Threshold for Positive FIT Increases Sensitivity for CRC

Table. Comparison of Brand-Specific Test Characteristics at Various Thresholds*

Test, by Threshold	Studies, n	Patients With CRC, n	Sensitivity (95% CI)	CRC Specificity (95% CI)
10 μg/g				
OC-Sensor	6	56	0.88 (0.76–0.94)	0.91 (0.89–0.93)
OC-Light	5	99	0.90 (0.72–0.97)	0.91 (0.83–0.95)
OC-Hemodia	1	27	0.89 (0.71–0.98)	0.94 (0.93–0.95)
FOB Gold	1	25	0.96 (0.80–1.00)	0.88 (0.87–0.89)
>10–<20 μg/g				
OC-Sensor	4	34	0.81 (0.55–0.94)	0.93 (0.91–0.93)
OC-Hemodia	1	19	0.53 (0.29–0.76)	0.87 (0.86–0.89)
FOB Gold	1	29	0.97 (0.82–1.00)	0.94 (0.93–0.95)
20 μg/g				
OC-Sensor	11	163	0.77 (0.66–0.85)	0.94 (0.91–0.96)
OC-Hemodia	1	12	0.25 (0.06–0.57)	0.96 (0.96–0.97)
FOB Gold	1	25	0.92 (0.74–1.00)	0.95 (0.94–0.96)
Magstream 1000/Hem SP	1	79	0.66 (0.54–0.76)	0.95 (0.95–0.95)

Imperiale TF, et al. Am Intern Med. 2019 March 5

Sensitivity of FIT for Advanced Adenomas Remains Low Regardless of Threshold

Table. Comparison of Brand-Specific Test Characteristics at Various Thresholds*

Test, by Threshold	Advanced Adenomas		
	Patients With Advanced Adenomas, *n*	Sensitivity (95% CI)	Specificity (95% CI)
10 μg/g			
OC-Sensor	898	0.36 (0.30–0.39)	0.91 (0.90–0.92)
OC-Light	1027	0.43 (0.24–0.66)	0.91 (0.83–0.95)
OC-Hemodia	56	0.59 (0.45–0.72)	0.94 (0.93–0.95)
FOB Gold	286	0.49 (0.43–0.55)	0.88 (0.87–0.89)
>10–<20 μg/g			
OC-Sensor	702	0.29 (0.25–0.34)	0.93 (0.92–0.94)
OC-Hemodia	53	0.25 (0.14–0.38)	0.87 (0.86–0.89)
FOB Gold	354	0.37 (0.32–0.43)	0.97 (0.96–0.97)
20 μg/g			
OC-Sensor	2286	0.26 (0.20–0.32)	0.95 (0.92–0.96)
OC-Hemodia	67	0.06 (0.02–0.15)	0.96 (0.96–0.97)
FOB Gold	286	0.34 (0.28–0.40)	0.95 (0.94–0.96)
Magstream 1000/Hem SP	648	0.23 (0.19–0.26)	0.95 (0.95–0.95)

Imperiale TF, et al. Am Intern Med. 2019 March 5

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Annual FIT: Limitations

- Adherence
  - Requires annual testing
  - Positive test requires follow-up colonoscopy
- Sensitivity for advanced adenomas is low
- Ineffective at detecting serrated lesions
  - Lack surface blood vessels

FIT- Fecal DNA: Two Tests in One (*Cologuard*)

2 DNA Methylation Markers
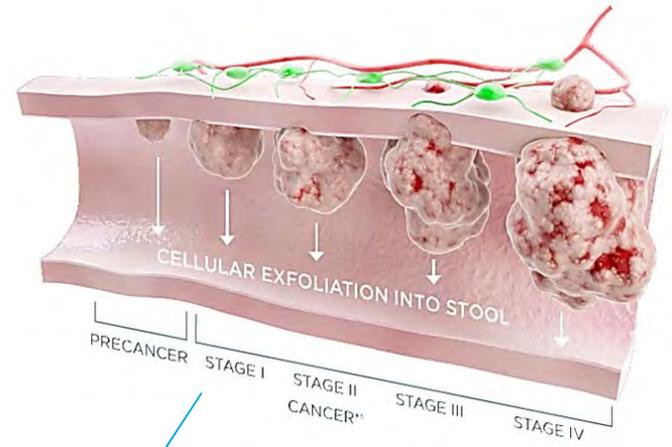*NDRG4 and BMP3*

7 DNA Mutation Markers
All KRAS

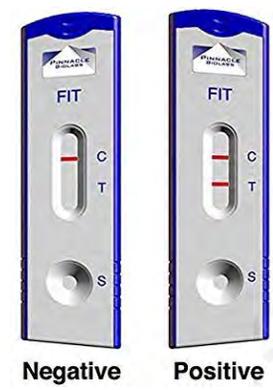**DNA Normalization Marker**
Beta Actin (Quantitative DNA)

Molecular Assay
(DNA)

Fecal Hemoglobin Marker

Hemoglobin Assay
(Protein)

One Result

CELLULAR EXFOLIATION INTO STOOL

PRECANCER STAGE I STAGE II STAGE III STAGE IV
CANCER

FIT

Negative   Positive

FIT-Fecal DNA (Cologuard) vs FIT

	Cologuard Performance	FIT† Performance	P-Value
Cancer	92.3% (83.0-97.5)	73.8% (61.5-84.0)	0.002
Advanced Adenoma	42.4% (38.9-46.0)	23.8% (20.8-27.0)	<0.001
Specificity*	86.6% (85.9-87.2)	94.9% (94.4-95.3)	<0.001
Specificity**	89.8% (88.9-90.7)	96.4% (95.8-96.9)	<0.001

Imperiale TF, et al. NEJM 2014; 370: 1287-1297.

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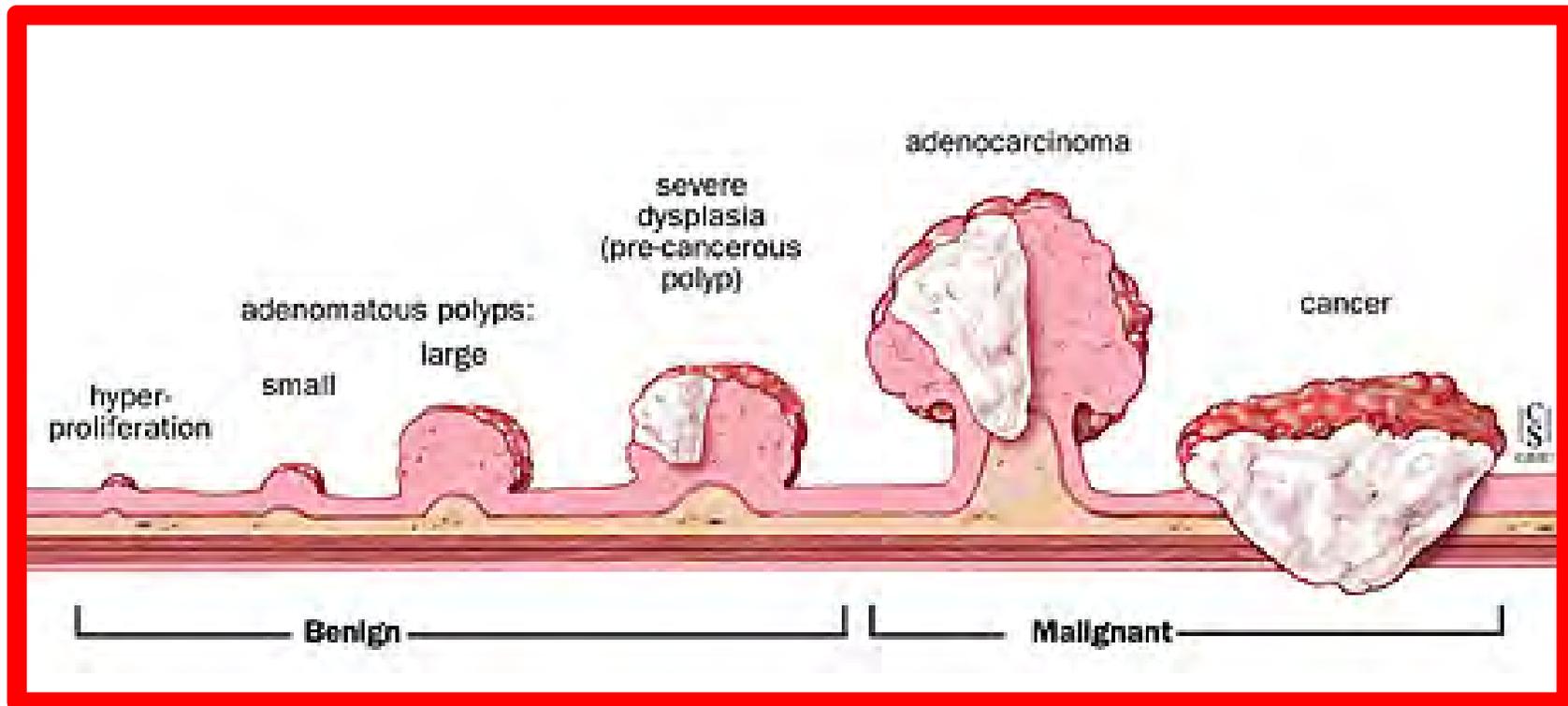# FIT- Fecal DNA (*Cologuard*): Advantages

- Non-invasive. Single stool sample. No diet restrictions.

- No bowel purge or sedation required.

- High sensitivity for CRC (92%)

- More sensitive than FIT for serrated lesions

  – 42%, SSP > 1 cm

- Adherence

  – Three year interval vs 1 year (FIT)

  – Navigation program reminders to encourage completion of the ordered test and reminder 3 yrs after negative test sent to MD and patient
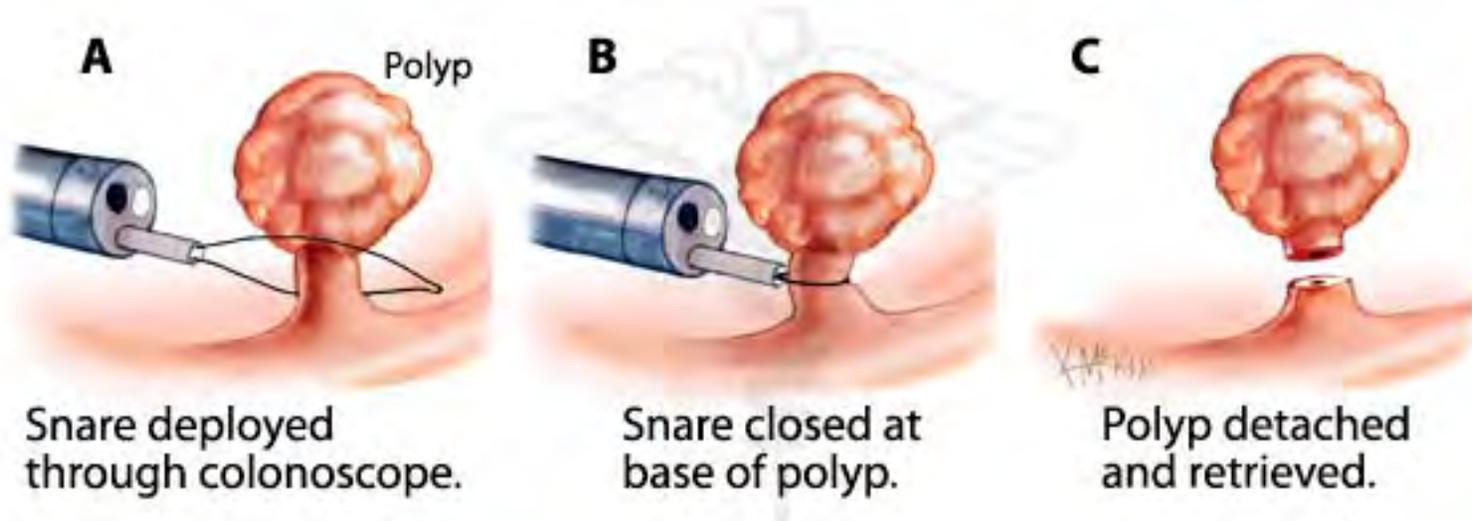
FIT- Fecal DNA (*Cologuard*): Limitations

- Costly compared to FIT ($500 vs $22)

- High false positive rate (12%)

  – False positive rate increases with age

  – Colonoscopy must follow any postive FIT-Fecal DNA but considered "diagnostic", greater financial burden to some patients

- Less sensitive than colonoscopy for CRC, adenomas, and serrated lesions

Colonoscopy is CRC Prevention Test Designed to Detect Pre-cancerous Polyps & Early CRC

Early

Endoscopy: Interrupting the Adenoma-Carcinoma Sequence

A — Polyp — Snare deployed through colonoscope.

B — Snare closed at base of polyp.

C — Polyp detached and retrieved.
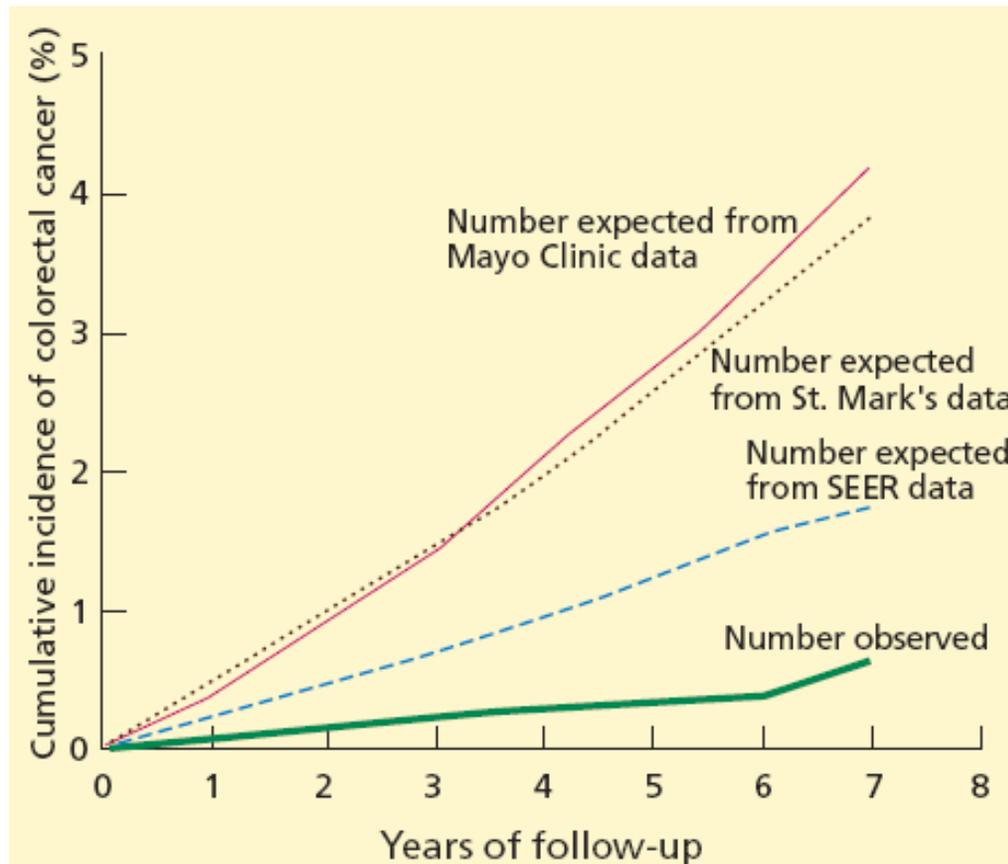
Removing Adenomatous Polyps Prevents CRC

FIGURE 1. Observed cumulative incidence of colorectal cancer in the National Polyp Study[6] compared with the expected incidence based on three reference groups.[7-9]

Winawer SJ, et al. NEJM 1993; 329: 1977-1981

Colonoscopy is a Highly Utilized Screening Test

- Gold standard for CRC screening
- Sensitivity of colonoscopy for CRC and colon polyps exceeds that of other available screening tests
- Diagnostic and therapeutic in single session
- Has sufficient sensitivity to be performed at a 10 year interval

Colonoscopy: Limitations

- Requires bowel purge and dietary modification
- Costly
- Procedure related risks
    - Sedation
    - Bleeding, perforation
- Small polyps or cancers can be missed

CRC Screening & Family History

Family History	Age to Start	Screening Modality	Interval
1st degree relative with CRC at age > 60	40	Average Risk Screening Options	Follow Average Risk Interval Recommendations
1st degree relative with **ADVANCED** adenoma age > 60	40	Average Risk Screening Options	Follow Average Risk Interval Recommendations

Rex, D et al. MSTF Recommendations . Gastro 2017. 153: 307-323.

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Can Average Risk Individuals Be Further Risk Stratified?

Appendix Table 2. Scoring Algorithm to Calculate Point Values for the Risk Score*

Categories, by Risk Factor	Reference Value (Wij)	Log-Odds Regression Coefficient (β)	Distance From Reference Group = $\beta \times$ (Wij − Wref)	Point Value = $\beta \times$ (Wij − Wref)/B†	Rounded Point Value
Family history of CRC					
0 first-degree relatives (reference)	0 (Wref)	–	0	0.00	0
≥1 first-degree relative	1	0.3259	0.3259	1.10	1
Waist circumference					
Small (reference)	0 (Wref)	–	0	0.00	0
Medium	1	0.3426	0.3426	1.16	1
Large	1	0.6313	0.6313	2.13	2
Sex					
Female (reference)	0 (Wref)	–	0	0.00	0
Male	1	0.5225	0.5225	1.77	2
Age					
<55 y (reference)	52.5 (Wref)	–	0	0.00	0
≥55–<60 y	57.5	0.0592	0.296	1.00	1
≥60–<65 y	62.5	0.0592	0.592	2.00	2
≥65–<70 y	67.5	0.0592	0.888	3.00	3
≥70 y	74.5	0.0592	1.3024	4.40	4
Cigarette smoking					
0 pack-years (reference)	0 (Wref)	–	0	0.00	0
0–<30 pack-years	1	0.725	0.725	2.45	2
≥30 pack-years	1	1.2042	1.2042	4.07	4

CRC = colorectal cancer.
* Based on a derivation set of 2993.
† Constant B is the number of regression units that reflect 1 point in the final point system. This value was chosen, on the basis of work by Sullivan and colleagues (33), to be the increase in risk for advanced neoplasia associated with a 5-y increase in age. The value was calculated by multiplying the regression coefficient for age (0.0592) by 5 (0.0592 × 5 = 0.296).

Colonoscopy is the Only Screening Strategy for High Risk Individuals

Artist rendition of colonoscopy doing a biopsy of a polyp.

CRC Screening & Family History

Family History	Age to Start	Screening Modality	Interval
1st degree relative with CRC at age < 60	40, or 10 yrs earlier	Colonoscopy	At least every 5 yrs
1st degree relative with **ADVANCED** adenoma age < 60	40, or 10 yrs earlier	Colonoscopy	At least every 5 yrs
Two or more 1st degree relatives with CRC at any age	40, or 10 yrs earlier	Colonoscopy	At least every 5 yrs
Two or more 1st degree relatives with **ADVANCED** adenoma at any age	40, or 10 yrs earlier	Colonoscopy	At least every 5 yrs

Guidelines Vary Regarding Age to Stop Screening

Guideline	Age 75-85	Over 85
U.S. Preventive Health Services Task Force	*Individualize**	**STOP**
U.S. Multi-Society Task Force on Colorectal Cancer (AGA, ACG, ASGE, ACS, ACR)	*Individualize*	*Individualize*

Stop in average risk patients with prior screening and no history of polyps

An Individualized Approach to Determine When to Stop CRC Screening

Saini et al, Am J Gastro 2018

Rising Incidence of CRC in Young Adults (age < 50)

- Currently 1 in 7 CRC cases in US are diagnosed in pts age < 50
  - Rising incidence of distal CRC
  - By 2030, 1 in 4 rectal cancers dx in pts age < 50

- At least 75% of CRC in young pts have no family history and no inherited syndrome

- Diagnosis is often delayed & CRC more likely to be diagnosed at more advanced stage

Cancer Epidemiol Biomarkers Prev 2009
Cancer 2016

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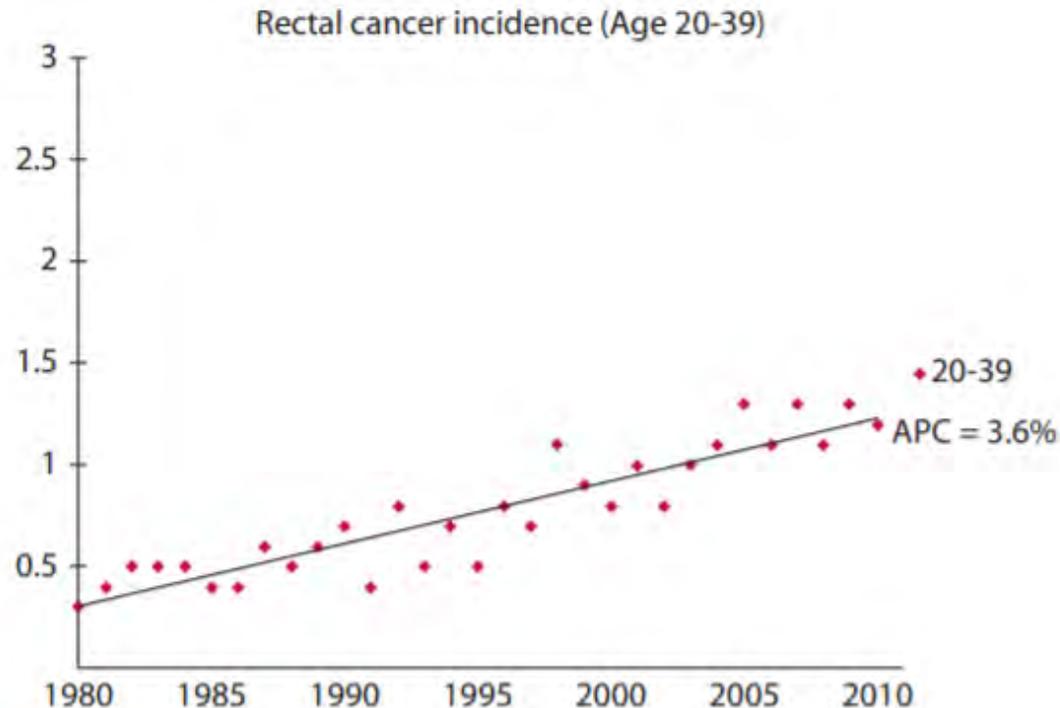# Rising Incidence of Rectal Cancer in Young Adults (Age 20-39)

Figure 2. Rectal cancer incidence (ages 20–39). Rectal cancer incidence, in patients aged 20 to 39, from 1980 to 2010, in cases per 100,000, using the SEER-9 database. The incidence quadruples and the annual percentage change (APC) is 3.6% ($p < 0.05$). SEER = Surveillance, Epidemiology, and End Results.

Tawadros P, et al. Dis Col Rectum 2015; 58: 474

Summary: CRC Screening

- Screening strategies, including colonoscopy and stool based testing, each have advantages and limitations.

- Stool based tests are approved for CRC screening in average risk individuals.

- All positive screening tests should be followed by a diagnostic colonoscopy.

- Awareness of rising incidence of CRC among young adults is needed to avoid delay to diagnosis.