

# 2023 SCSG LGI SYMPOSIUM







# Colorectal Cancer Screening: What's New, What's Tried and True?

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# Disclosures

- Consultant/Advisor for:** Geneoscopy; InterVenn; Universal Diagnostics; CellMax Life
- Grant/Research support:** National Institutes of Health, National Cancer Institute; Epigenomics; Freenome
- Employee of:** UC San Diego; Veterans Health Administration

All of these companies are developing tests for colorectal cancer screening and surveillance

# Case

- 48 year old man presents to establish primary care
  - PMHx: Hypertension, obesity
  - FMHx: No family history of colorectal cancer
  - Prior primary care physician had referred him at age 46 for colorectal cancer screening with colonoscopy which he did not complete
- Key questions:
  - What is his risk for CRC and how is it impacted by changing epidemiology?
  - What is the evidence base to support screening, and what test is best for this patient?



*“I try and do what my doctors tell me, but I’ve been busy with work and my young kids, and I heard I did not have to start until age 50.”*

# Outline

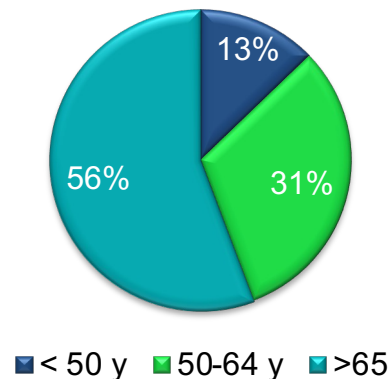
- Changing epidemiology
- Screening
  - Impact on incidence and mortality
  - Considerations for choosing a strategy
  - Age to initiate screening
  - 2021 US Preventive Services Task Force (USPSTF) guidelines
- Addressing the challenge of completion and follow up



# Colorectal Cancer Is a Major Public Health Problem

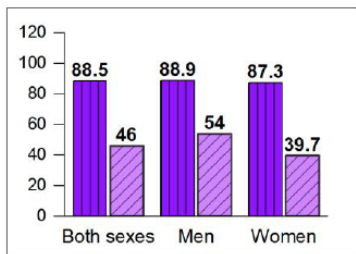
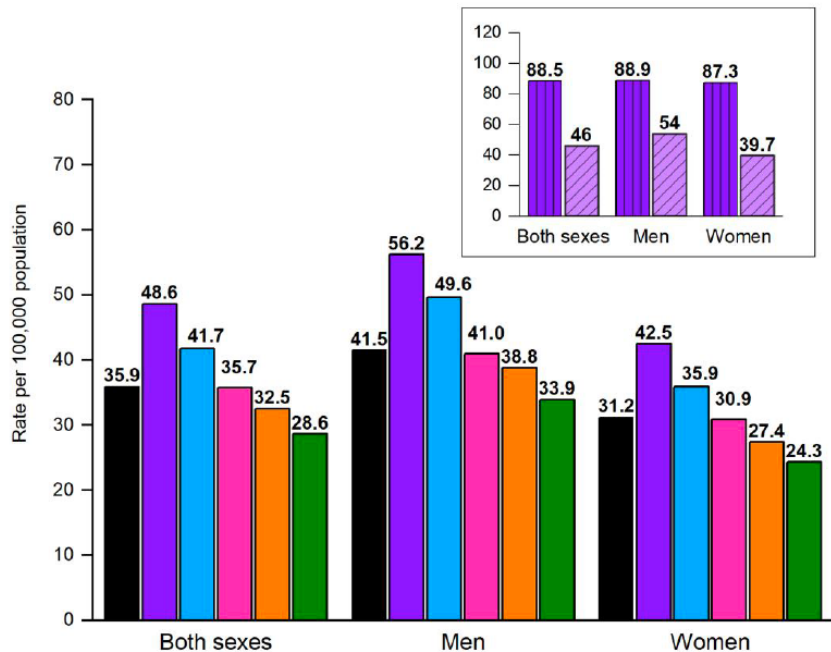
- 3<sup>rd</sup> most incident cancer for men and women
- 2<sup>nd</sup> leading cause of overall cancer death
  - ~153,000 cases annually
  - ~ 52,000 deaths annually
- Lifetime risk:
  - 4.1% for women
  - 4.4% for men

**Age distribution of CRC cases**

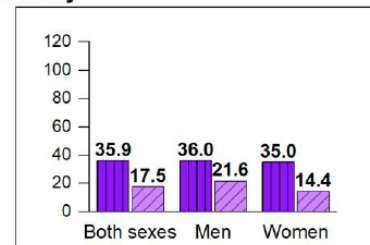
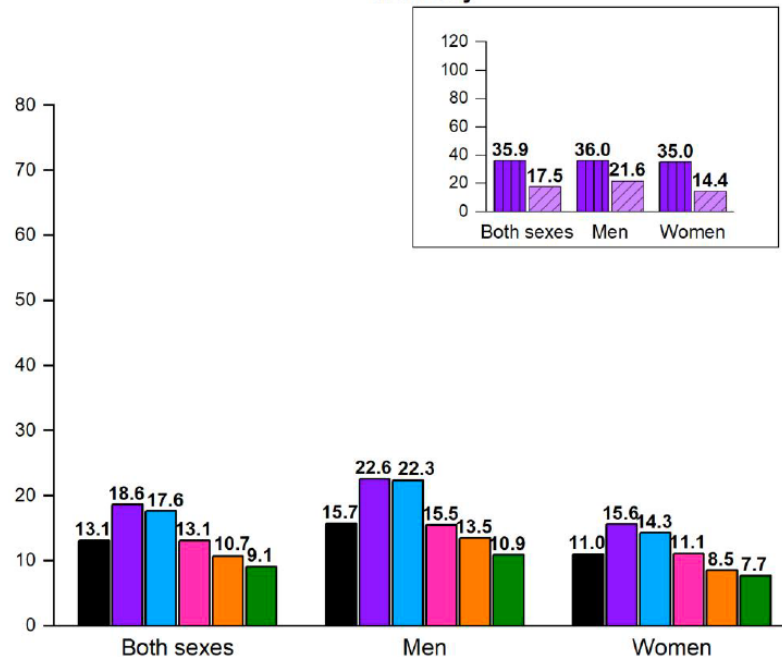


# Incidence and Mortality Vary by Race and Ethnicity

**Incidence**



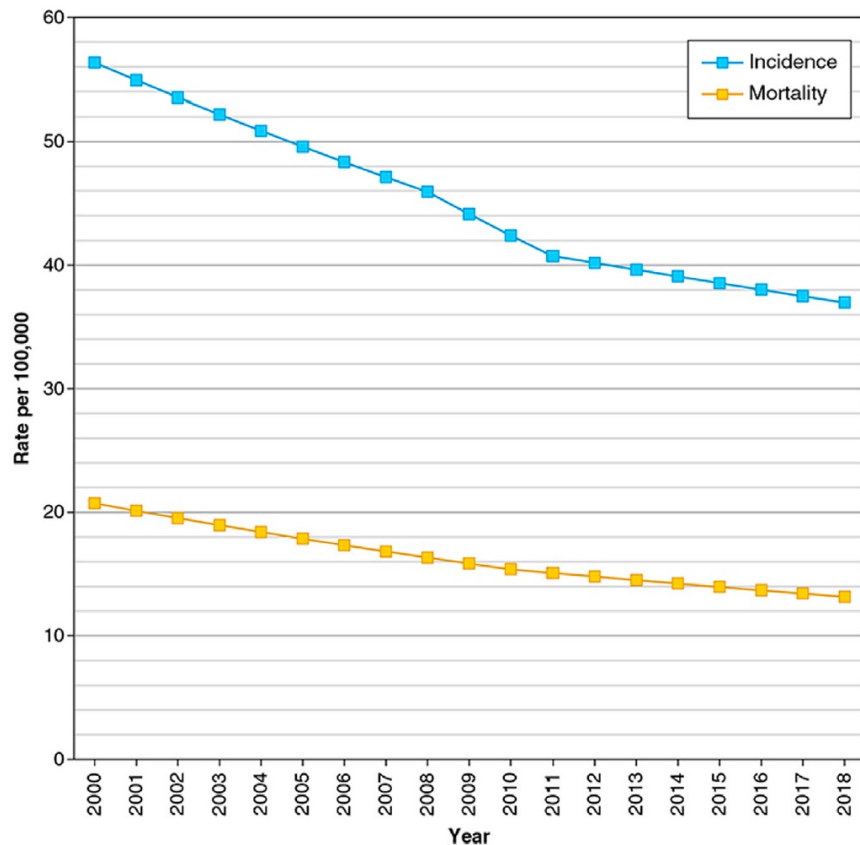
**Mortality**



All races and ethnicities
  AI/AN<sup>a</sup>
 NHB
  NHW
  Hispanic
  AAPI

AN<sup>a</sup>
 AI<sup>a</sup>

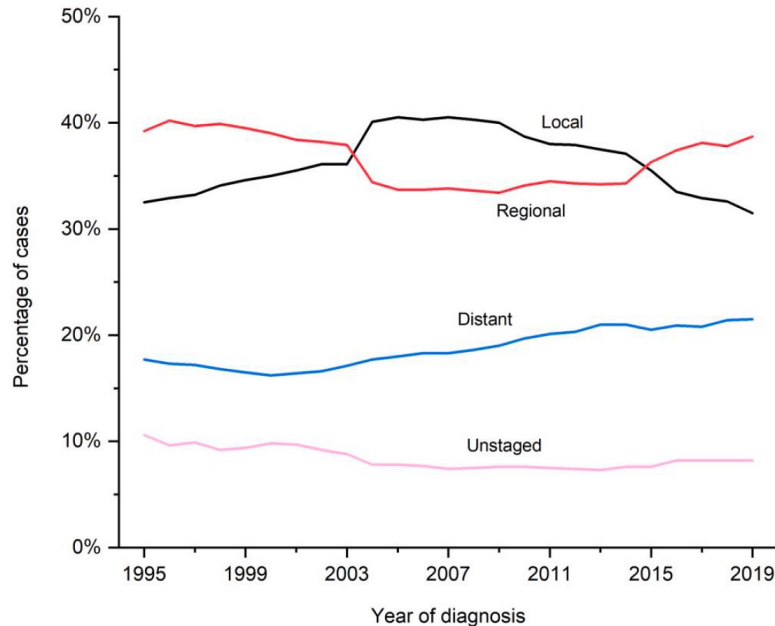
# For All Ages Combined, Incidence and Mortality Are Improving Over Time



Surveillance Epidemiology End  
Results 21 2000-2018 delay-adjusted  
incidence and mortality. Gupta S.  
Screening for colorectal cancers.  
*Hematol Oncol Clin N Am.* 2022.



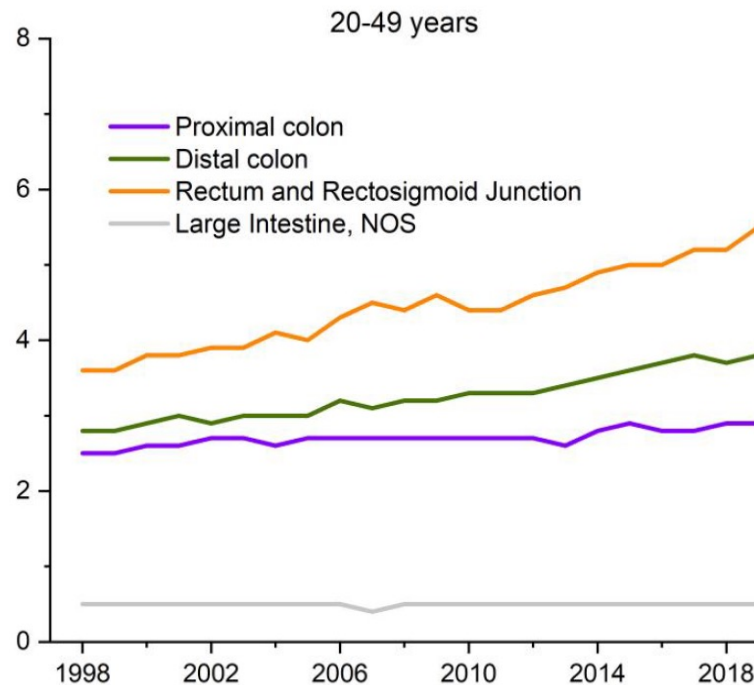
# But Advanced Stage Diagnosis Is Rising



**FIGURE 4** Trends in colorectal cancer stage distribution (%), 1995–2019, United States. Excludes appendiceal cancer. *Source:* North American Association of Central Cancer Registries, 2022.

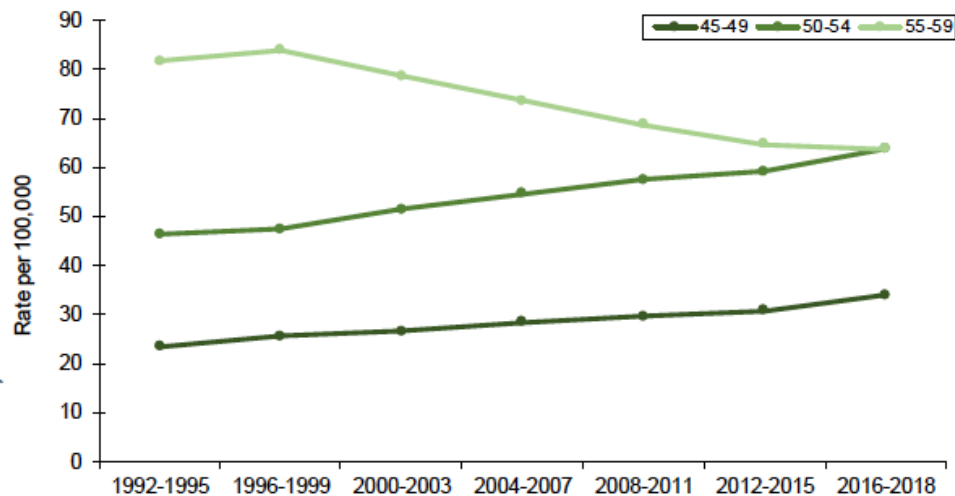
# Early Age Onset CRC Is Rising

- 3<sup>rd</sup> leading cause of cancer death under age 50
- Due to a birth cohort effect
  - Individuals born 1960 and later have increased CRC risk
  - Driving factors not well established
- 45 is the new 50
  - Current incidence among age 45 similar to prior risk among age 50



# And 50 Is the New 55

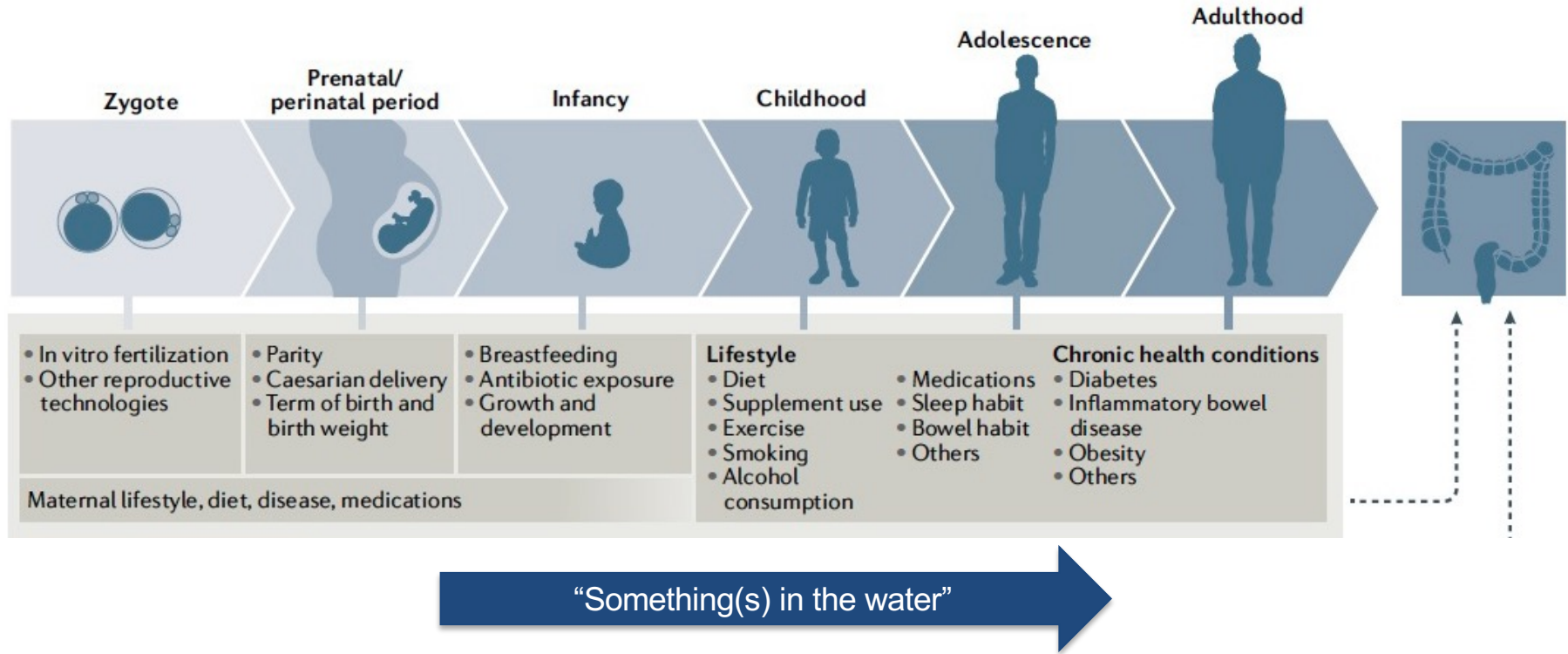
- Absolute number and rate of rectal and distal cancer for age 50-59 rising
  - Age 50-54 similar to historic 55-59 levels
- Factors driving early onset CRC are likely also driving later onset CRC
- Significant public health implications
  - Less likely screen up to date
  - Substantially higher risk



**Figure 1.** Age-specific incidence rates of CRC by 4-year intervals from Surveillance, Epidemiology, and End Results 13, 1992–2018.



# Potential Causes Should Be Examined Through Lens of a Birth Cohort Effect



# Causes May Include Usual Suspects and Unique Exposures

	Odds Ratio	95% CI
Obese BMI	1.54	1.01, 2.35
Hyperlipidemia	1.61	1.22, 2.13
Alcohol	1.71	1.62, 1.80
Smoking	1.35	0.81, 2.25
Sugar-sweetened beverages	2.18	1.10, 4.35
In utero exposures		
Long-acting sulfonamides	4.40	1.63, 11.88
Maternal obesity	2.51	1.05, 6.02
Bendectin (doxylamine; pyridoxine; dicyclomine)	3.38	1.69, 6.77

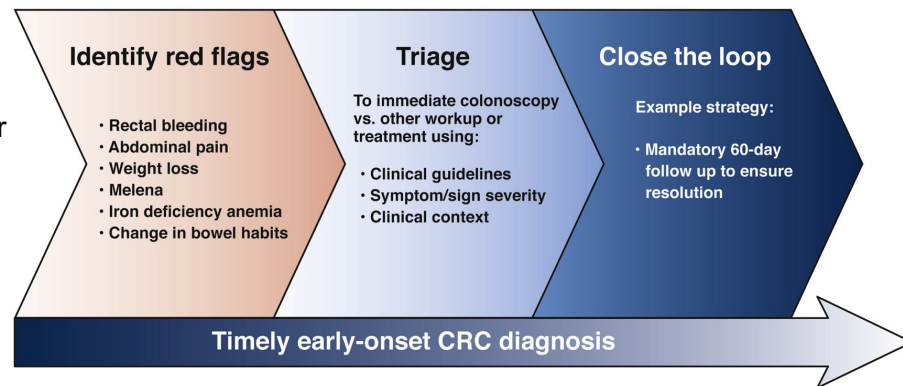
# Trends Have Major Implications for Clinical Practice

- **Individuals under age 45**

- Measure and act on family history
  - Among those with family history and CRC <age 50, if guidelines had been applied:
    - 82% could have been diagnosed earlier
    - 67% had CRC prevented
- Close the clinical loop on potential red-flag signs and symptoms of CRC

- **Individuals age  $\geq 45$  age eligible for screening**

- $\uparrow$  Urgency to get people up to date





A coastal scene featuring large, blue waves crashing in the foreground. In the background, a cliffside is densely packed with multi-story houses and buildings, some with balconies. A tall palm tree stands prominently on the cliff. The sky is clear and blue.

# Screening

# Currently Available US Preventive Services Task Force Recommended Options for Average Risk Screening

## Stool-based strategies



High-sensitivity  
FOBT



Fecal Immunochemical  
Test (FIT)



Stool DNA-FIT

## Direct-visualization techniques



CT Colonography



Flexible Sigmoidoscopy



Colonoscopy

Which of the following strategies have been shown by randomized trials to reduce incidence AND mortality? (Hint: >1 answer)

- a) Guaiac fecal occult blood testing
- b) FIT
- c) FIT-DNA
- d) CT Colonography
- e) Sigmoidoscopy
- f) Colonoscopy



# KHN Morning Briefing

Summaries of health policy coverage from major news organizations

## Study Casts Doubt On Effectiveness Of Colonoscopy As Cancer Screen

A 10-year clinical trial found that colonoscopies reduce colon cancer risk by only a fifth and did not significantly lower the chances of death. The results call into question the increased use of the procedure for screening purposes.

### **CNN: A Colonoscopy Study Has Some Wondering If They Should Have The Procedure. What You Should Know**

A new European study on colonoscopies – the largest of its kind – has complicated results, and it's left some people wondering whether they should have the procedure to screen for colon cancer. (Cohen, 10/10)

### **Stat: In Gold-Standard Trial, Colonoscopy Fails To Cut Rate Of Cancer Deaths**

For decades, gastroenterologists put colonoscopies on a pedestal. If everyone would get the screening just once a decade, clinicians believed it could practically make colorectal cancer “extinct,” said Michael Bretthauer, a gastroenterologist and researcher in Norway. But new results from a clinical trial that he led throw confidence in colonoscopy's dominance into doubt. (Chen, 10/9)

### **Bloomberg: Colonoscopy Screening Exams Fail To Prevent Cancer Deaths In Large Study**

Colonoscopy screening exams that are recommended for older US adults failed to reduce the risk of death from colon cancer in a 10-year study that questions the benefits of the common procedure. (John Milton, 10/9)

### **NBC News: Video: Colonoscopies Made No Difference In Death Rates, European Study Finds**

In one of the largest studies ever, researchers found colonoscopy screenings cut cancer risk by 18 percent and made no difference in death rates. (10/10)

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[Russian troops leave Kherson. Federal court strikes down Biden's student loan forgiveness. At least 4 dead after storm slams Florida.](#)

## New study examines the effectiveness of colonoscopies

By Brenda Goodman, CNN

Updated 3:57 PM EDT, Mon October 10, 2022

*“Now, a landmark study suggests the benefits of colonoscopies for cancer screening may be overestimated”*

[https://khn.org/morning-breakout/study-casts-doubt-on-effectiveness-of-colonoscopy-as-cancer-screen/;](https://khn.org/morning-breakout/study-casts-doubt-on-effectiveness-of-colonoscopy-as-cancer-screen/)

[https://www.cnn.com/2022/10/09/health/colonoscopy-cancer-death-study.](https://www.cnn.com/2022/10/09/health/colonoscopy-cancer-death-study)

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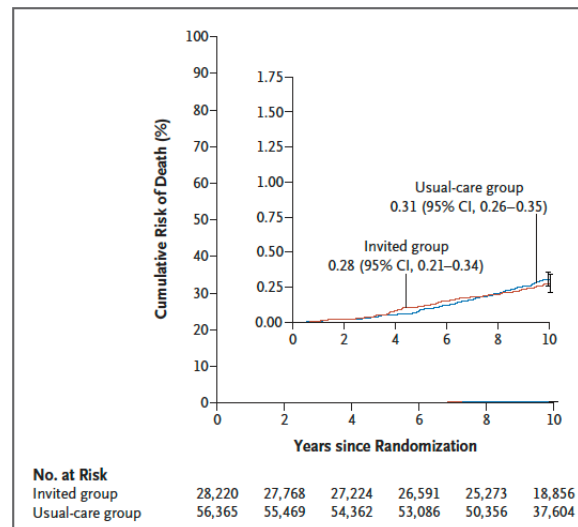
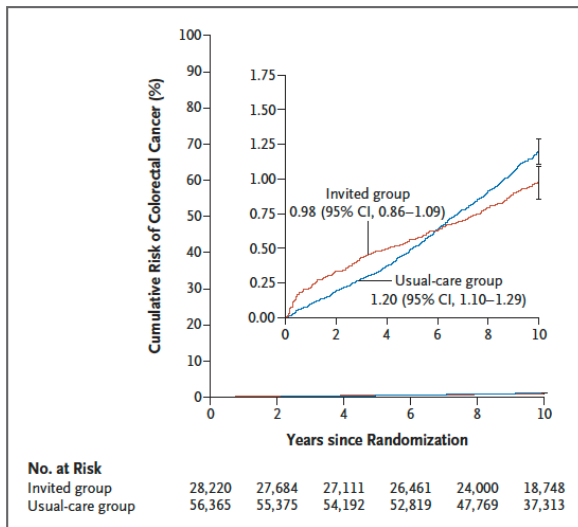
VOL. 387 NO. 17

Effect of Colonoscopy Screening on Risks of Colorectal Cancer  
and Related Death

M. Bretthauer, M. Laberg, P. Wieszchy, M. Kalager, L. Emilsson, K. Garborg, M. Rupinski, E. Dekker, M. Spaander, M. Bugajski, Ø. Holme, A.G. Zauber, N.D. Pilonis, A. Mroz, E.J. Kuipers, J. Shi, M.A. Hernán, H.-O. Adami, J. Regula, G. Hoff, and M.F. Kaminski, for the NordICC Study Group\*

## NordICC (Nordic-European Initiative on Colorectal Cancer) trial

<b>Setting</b>	<ul style="list-style-type: none"><li>Norway, Sweden, and Poland 2009-2014<ul style="list-style-type: none"><li>No usual care population CRC screening</li></ul></li></ul>
<b>Design</b>	<ul style="list-style-type: none"><li>RCT among 84,585 individuals age 55-64 years comparing:<ul style="list-style-type: none"><li>Colonoscopy invitation (n=28,220)</li><li>No invitation (n=56,365)</li></ul></li></ul>
<b>Follow-up</b>	<ul style="list-style-type: none"><li>Interim analysis through 10 years</li></ul>
<b>Primary outcomes</b>	<ul style="list-style-type: none"><li>Incident and fatal CRC</li><li>Intent-to-screen analysis<ul style="list-style-type: none"><li>Screening participation: 42%</li></ul></li></ul>



CRC Incidence Risk Ratio (CI)	CRC Mortality Risk Ratio (CI)
0.82 (0.70 to 0.93 )	0.90 (0.64–1.16)

Figure S3: 10-year cumulative colorectal cancer incidence in adjusted per-protocol analyses

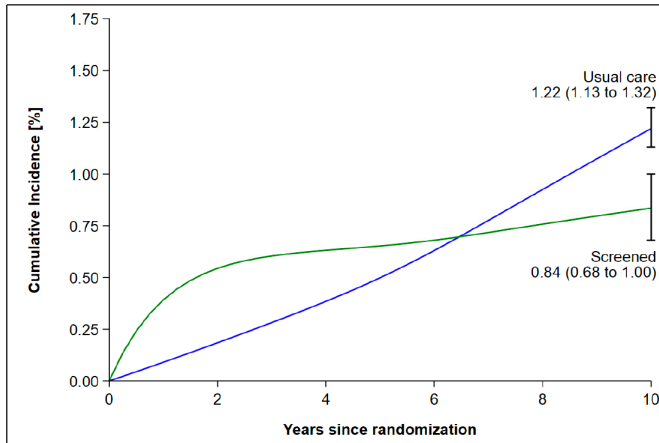
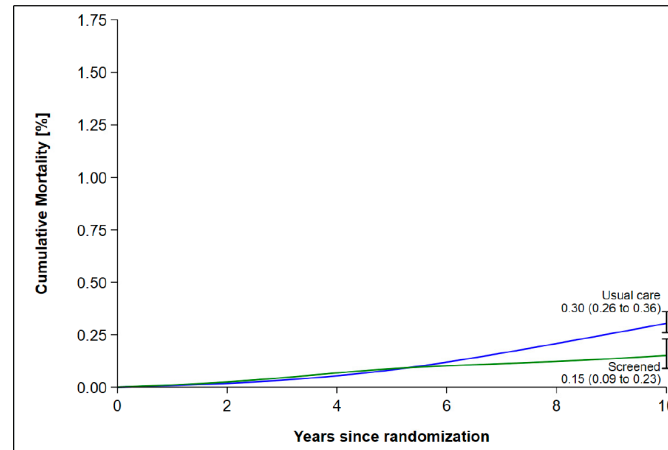


Figure S4: 10-year cumulative colorectal cancer mortality in adjusted per-protocol analyses.

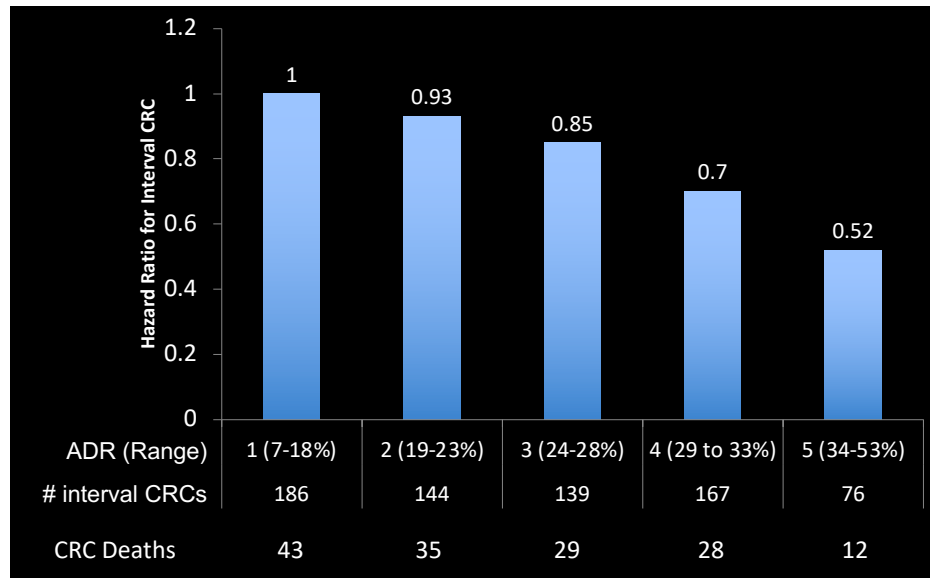


	CRC Incidence Risk Ratio (CI)	CRC Mortality Risk Ratio (CI)
<b>Intent-to-Screen</b>	0.82 (0.70–0.93 )	0.90 (0.64–1.16)
<b>Per-protocol</b>	0.69 (0.55–0.83)	0.50 (0.27–0.77)



# Explaining the Disappointing Results

- Bias
  - Stage shift to earlier CRC was not seen
    - “Worried unwell” may have elected for screening instead of “worried well”
- Validity
  - Low rate of participation
  - Insufficient follow up time
  - Endoscopist performance
    - 29% below adenoma detection rate benchmark of 25%
    - Variable performance also in US



# Conclusions From NordICC Study

- Authors
  - Benefit of colonoscopy may be more limited than previously hypothesized
- Alternative
  - Effectiveness of colonoscopy highly dependent on participation, quality, and time to realize the benefit

# Counterpoint: Increasing Evidence From Observational Studies That Colonoscopy Exposure Is Highly Protective

- Studies from US and Poland demonstrate persist and substantially lower risk for CRC incidence and mortality, including up to 12–17 years follow up
  - 80–85% relative reduction in CRC incidence and mortality

Figure 2. Adjusted Risk of Colorectal Cancer Incidence by Time Interval After a Negative Colonoscopy Result

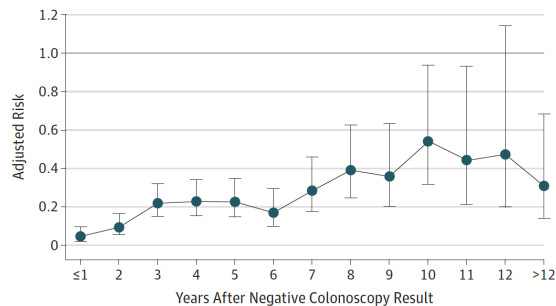


Figure 3. Adjusted Risk of Colorectal Cancer Mortality by Time Interval After a Negative Colonoscopy Result

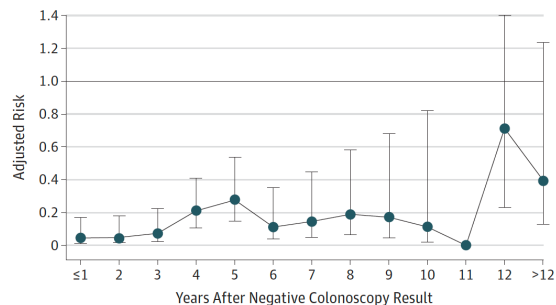
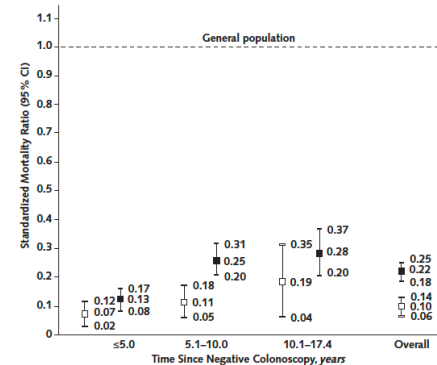
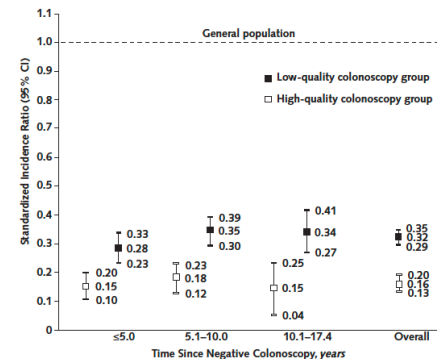


Figure 2. Standardized incidence ratios and standardized mortality ratios during follow-up after a single negative high-quality or low-quality screening colonoscopy.



A coastal scene featuring large, blue waves crashing in the foreground. In the background, a cliffside town with numerous houses and buildings is visible under a clear blue sky. The text "Comparisons of Strategies" is overlaid in white on the waves.

# Comparisons of Strategies



# Incidence and Mortality RCT Evidence: Intent-to-Screen

Test Strategy	Relative impact of screening vs no screening	
	Incidence	Mortality
<b>Guaiac FOBT</b>	↓ 20%	↓ 18%
<b>Sigmoidoscopy</b>	↓ 22%	↓ 28%
<b>Colonoscopy</b>	↓ 18%	

# Selecting a Test Today

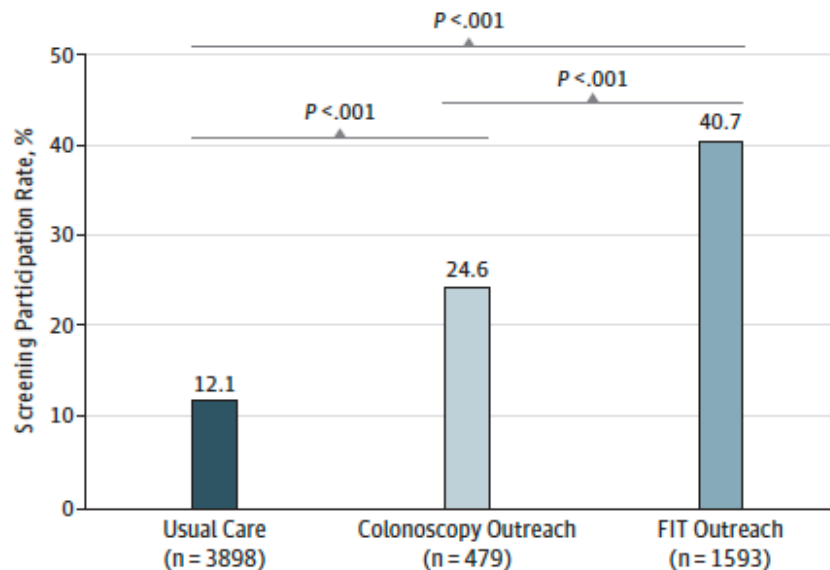
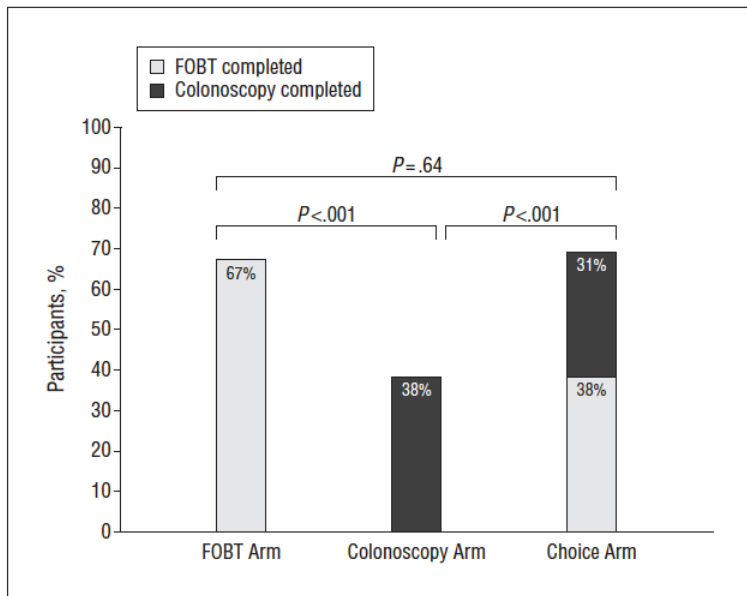
- Very limited head-to-head CRC incidence/mortality data comparing one strategy to another
- Base choice on:
  - Sensitivity/specificity
  - Observational data on incidence and mortality
  - Acceptability
  - Modelling

# Available Tests Vary by Sensitivity, Specificity, and Evidence on CRC Risk Reduction

Test	Sensitivity for Advanced Neoplasia	Sensitivity for CRC	Specificity	Impact on Incidence and Mortality vs. No Screening
<b>gFOBT</b> Hemoccult Sensa, Beckman Coulter	6 to 17%	50 to 75%	96 to 99%	<b>RCT evidence</b> of 20% relative incidence reduction, 18% relative mortality reduction.
<b>Sigmoidoscopy</b>	95%*	95%*	87%**	<b>RCT evidence</b> of 22% relative incidence reduction, 28% relative mortality reduction
<b>Colonoscopy</b>	95%	95%	86 to 89%**	<b>RCT evidence</b> of 18% relative incidence reduction. <b>Observational studies</b> suggest 69% relative incidence reduction, 68% relative mortality reduction.
<b>FIT</b> OC Sensor and OC-Light, Polymedco	25 to 27%	74 to 81%	95 to 96%	No RCT evidence. <b>Observational studies</b> suggest 21% relative incidence reduction, 59% relative mortality reduction.
<b>FIT-DNA</b> Cologuard, Exact Sciences	47%	93%	89%	No RCT or observational study evidence.

gFOBT, guaiac fecal occult blood test; FIT, fecal immunochemical test; sDNA-FIT, multi-target stool DNA FIT test; RCT, randomized controlled trial; CRC, colorectal cancer  
 \*within reach of the sigmoidoscope; \*\*false positives are defined by polyps biopsied or removed which were not adenomas; \*\*\*reported sensitivity is for polyps > 1cm  
 Gupta S. Screening for colorectal Cancer. *Hem Onc Clin NA*. 2022.

# Acceptability: Participation Varies Substantially by Test Offered



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

ORIGINAL INVESTIGATION

## Adherence to Colorectal Cancer Screening

A Randomized Clinical Trial of Competing Strategies

John M. Inadomi, MD; Sandeep Vijan, MD, MS; Nancy K. Janz, PhD; Angela Fagerlin, PhD; Jennifer P. Thomas, BS; Yungui V. Lin, RN, MA; Roxana Muñoz; Chim Lau, BA; Ma Somsouk, MD, MAS; Najwa El-Nachef, MD; Rodney A. Hayward, MD

JAMA Internal Medicine Published online August 5, 2013 Original Investigation

## Comparative Effectiveness of Fecal Immunochemical Test Outreach, Colonoscopy Outreach, and Usual Care for Boosting Colorectal Cancer Screening Among the Underserved

A Randomized Clinical Trial

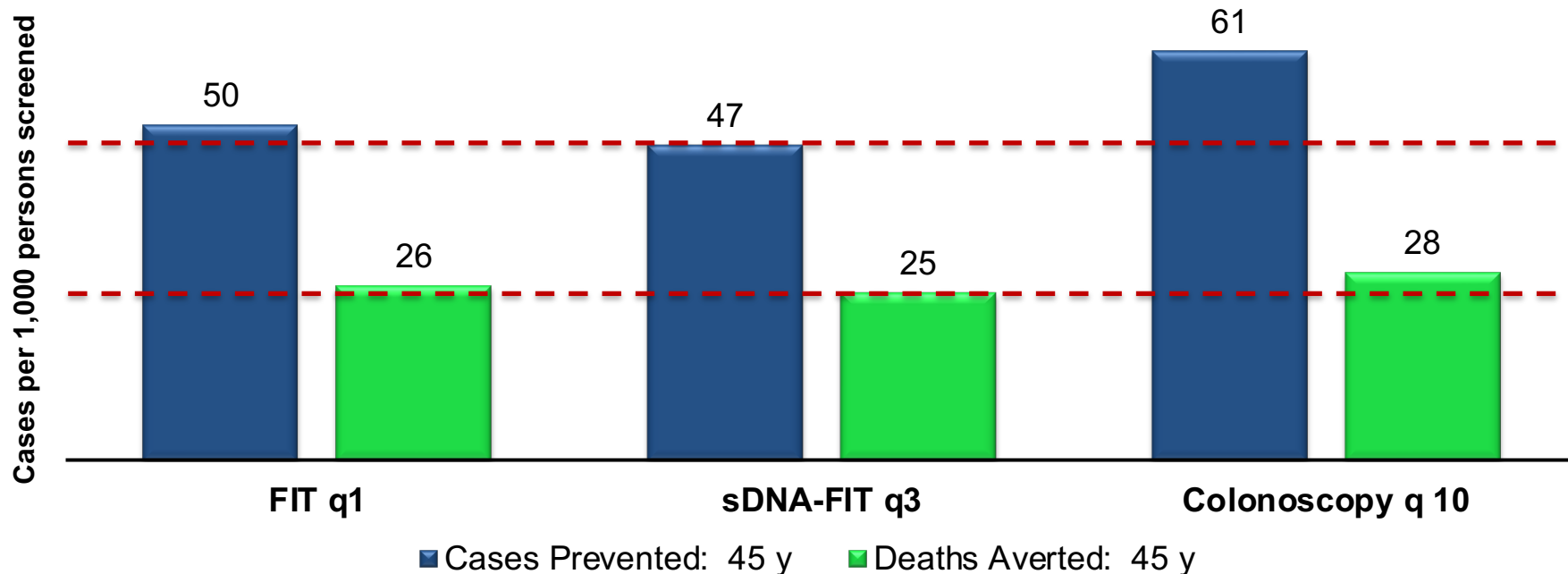
Samir Gupta, MD, MSc; Ethan A. Halm, MD; Don C. Rockey, MD; Marcia Hammons, BSN; Mark Koch, MD; Elizabeth Carter, MD; Luisa Valdez, MRCMA; Lysoa Tong, MS; Chai Alm, PhD; Michael Kashner, PhD; Keith Agreteright, MD; Jerrin Tiro, PhD; Zhou Gong, BA; Sandi Pruitt, PhD; Colette Sugg Skinner, PhD



# Modelling: US Preventive Services Task Force Approach

- Review of epidemiology and evidence
- 3 models simulating over 100 strategies
  - Varied test type, test frequency, age to start/stop
  - Assumed perfect adherence to participation and follow up
- Outcomes
  - CRC cases and deaths averted
  - Screening-related complications
- Key questions
  - How do the test strategies compare?
  - What is the incremental benefit of initiation at age 45 instead of 50?

# Modelling: CRC Cases Prevented and Deaths Averted by Screening Strategy Starting at Age 45, USPSTF 2021



- Assumed perfect participation
- USPSTF concluded # cases and deaths prevented similar across strategies

# 2021 USPSTF Recommendations

Age Group	Recommendation	Grade	Modalities
50 to 75	<p style="text-align: center;"><u>Screen</u></p> <ul style="list-style-type: none"><li>High certainty of substantial net benefit</li></ul>	A	<ul style="list-style-type: none"><li>Guaiac FOBT annually</li><li>Fecal immunochemical test (FIT) annually</li><li>FIT-DNA (Cologuard) q 1-3 yrs</li><li>Colonoscopy q 10 yrs</li><li>CT colonography q 5 yrs</li><li>Flexible sigmoidoscopy q 5yrs</li><li>Flex sig q 10 years plus annual FIT</li></ul>
45 to 49	<p style="text-align: center;"><u>Screen</u></p> <ul style="list-style-type: none"><li>Moderate certainty of moderate net benefit</li></ul>	B	
76 to 85	<p style="text-align: center;"><u>Selectively offer screening</u></p> <ul style="list-style-type: none"><li>Net benefit small, especially if previously up-to-date</li></ul>	C	

- No major changes in modalities recommended
- No preference for one test over the other
- Age 45 now endorsed by ACS, AGA, ASGE, ACG
- Screening is cost effective, including at age 45: FIT cost savings, colonoscopy is efficient

# On Horizon: Multiple Trials of Non-Invasive Tests Set to Report

Trial (Sponsor)	Specimen Source	Number of Subjects
Clinical Validation of An Optimized Multi-Target Stool DNA ( <b>Mt-sDNA 2.0</b> ) Test, for Colorectal Cancer Screening "BLUE-C". (Exact Sciences)	<b>Stool</b>	24,000
Clinical Validation of the ColonoSight Test: a Multi-target Stool RNA ( <b>Mt-sRNA</b> ) Assay for Colorectal Neoplasia Screening in Average-risk Individuals Aged >45 Years Old. (Geneoscopy)	<b>Stool</b>	10,000
Prevention of Colorectal Cancer Through <b>Multiomics</b> Blood Testing. (PREEMPT, Freenome)	<b>Blood</b>	25,000
Evaluation of the <b>ctDNA</b> LUNAR Test in an Average Patient Screening Episode (ECLIPSE, Guardant Health)	<b>Blood</b>	20,000



# Be Prepared to Consider Two Scenarios

- Stool-based test with performance better than current FIT-DNA
  - Imagine sensitivity 95% for CRC, 75% for advanced adenoma, specificity 90%
- Blood-based test with performance for CRC similar or better than FIT
- Impacts:
  - Opportunity to get the 30-40% of population not up-to-date screened
  - More patients with abnormal tests requiring timely colonoscopy
  - Some patients and primary providers may increasingly choose non-invasive options for screening over colonoscopy

# Screening Summary

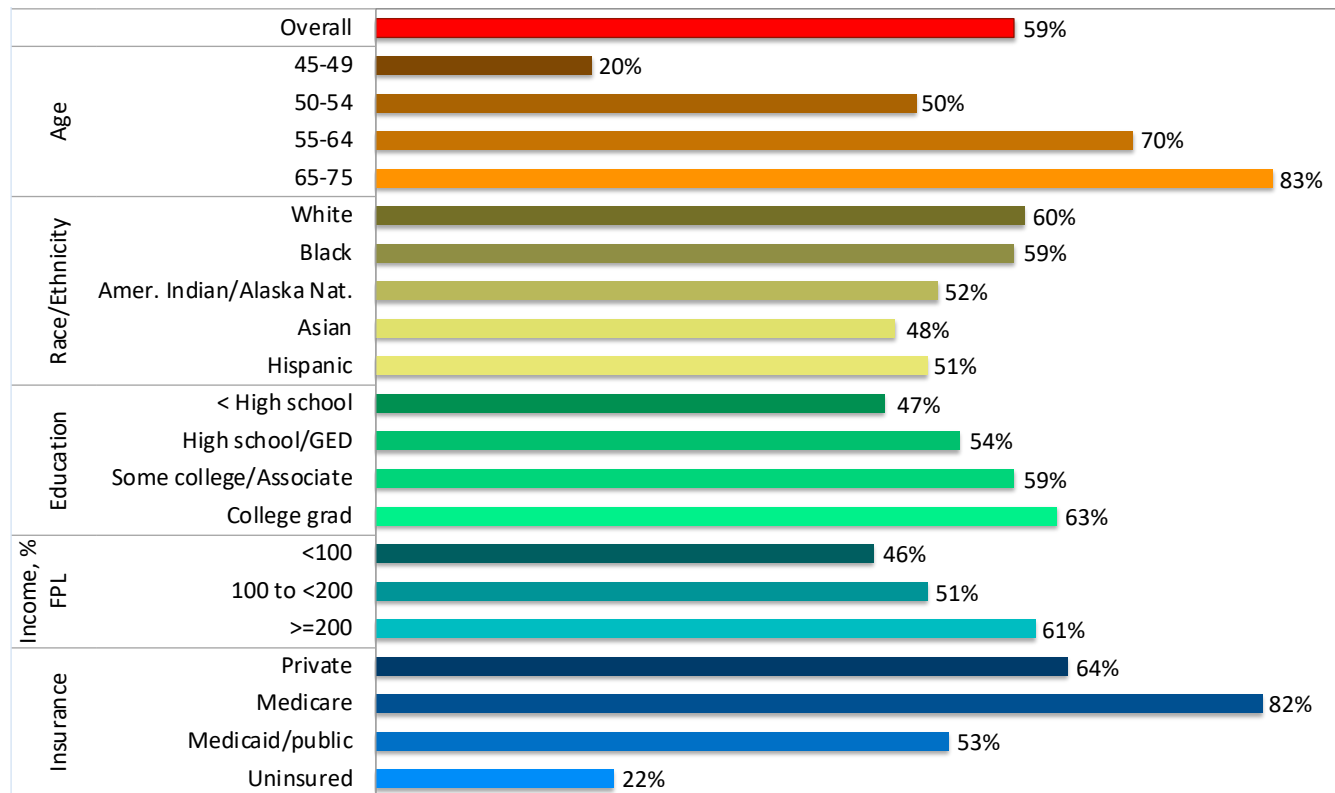
- Screening reduces incidence and mortality
- Multiple promising approaches to screening
- Key evidence gap:
  - Comparative effectiveness of modalities, including incremental benefit of colonoscopy
- In meantime: “Best test is the one that gets done, and done well!”
  - Dr. Sid Winawer, Memorial Sloan Kettering

A coastal scene with waves in the foreground and houses on a cliff in the background. The text is overlaid on the image.

# Challenge of Screening Participation and Follow Up

# Uptake Is Suboptimal, and Varies Greatly Across the Population

Up-to-Date with Screening, National Health Interview Survey, 2021





# Follow Up of Abnormal Tests Is Suboptimal

- Completion varies 18%–69% nationally, and ranges 18–57% at local community clinics
- Goal is 80%
- Lack of completion associated with 2.5 fold increased risk for CRC death
  - 1 in 20 have cancer
  - 1 in 4 have a large polyp

# Opportunities for Addressing Screening Rates

- Multiple evidence-based, population level interventions for promoting screening and follow up exist
  - Test choice
    - E.g. colonoscopy and at least one non-invasive test such as FIT or sDNA-FIT
  - Mailed FIT outreach
    - Mailed invitation, including a FIT kit, +/- reminders
    - 22% absolute increase in screening participation over usual care
  - For abnormal FIT follow up:
    - Patient-level: navigation
    - Provider-level: reminders and performance feedback
    - System-level: automated referrals; pre-colonoscopy calls, patient registries

# Back to Our Case

- 48 year old man presents to establish primary care
  - PMHx: Hypertension, obesity
  - FMHx: No family history of colorectal cancer
  - Prior primary care physician had referred him at age 46 for colorectal cancer screening with colonoscopy which he did not complete
- Approach:
  - Explain CRC incidence is rising and that screening can reduce incidence and mortality
  - Offer a choice of strategies based on preferences
    - Test sensitivity, specificity, effectiveness
    - Convenience and acceptability
  - Put in place systems to promote completion and follow-up



*“I try and do what my doctors tell me, but I’ve been busy with work and my young kids, and I thought I did not have to start until age 50.”*

# Take Home Points

CRC remains a major public health problem

45 is the new 50, and 50 is the new 55

Screening reduces incidence and mortality

Major national and local opportunities to improve screening and follow up





# Thank You!

Grant Support: NCI UG3 CA233314 01A1 (Martinez, Gupta, Castaneda, MPI), Cancer Center Support Grant CA023100-32; NCI U54 CA132379 CA132384 (Martinez; Madanat); American Cancer Society RSG-17-232-01-CPPB (Nodora); NCI R37 CA222866 (Gupta)

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