



The Changing Face of Colorectal Cancer: What You Should Know and What You Can Do About It

UCSD Hot Topics in Medicine

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HEALTH SCIENCES

Disclosures

Consultant/Advisor for:

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*Companies developing non-invasive tests for colorectal cancer screening and surveillance

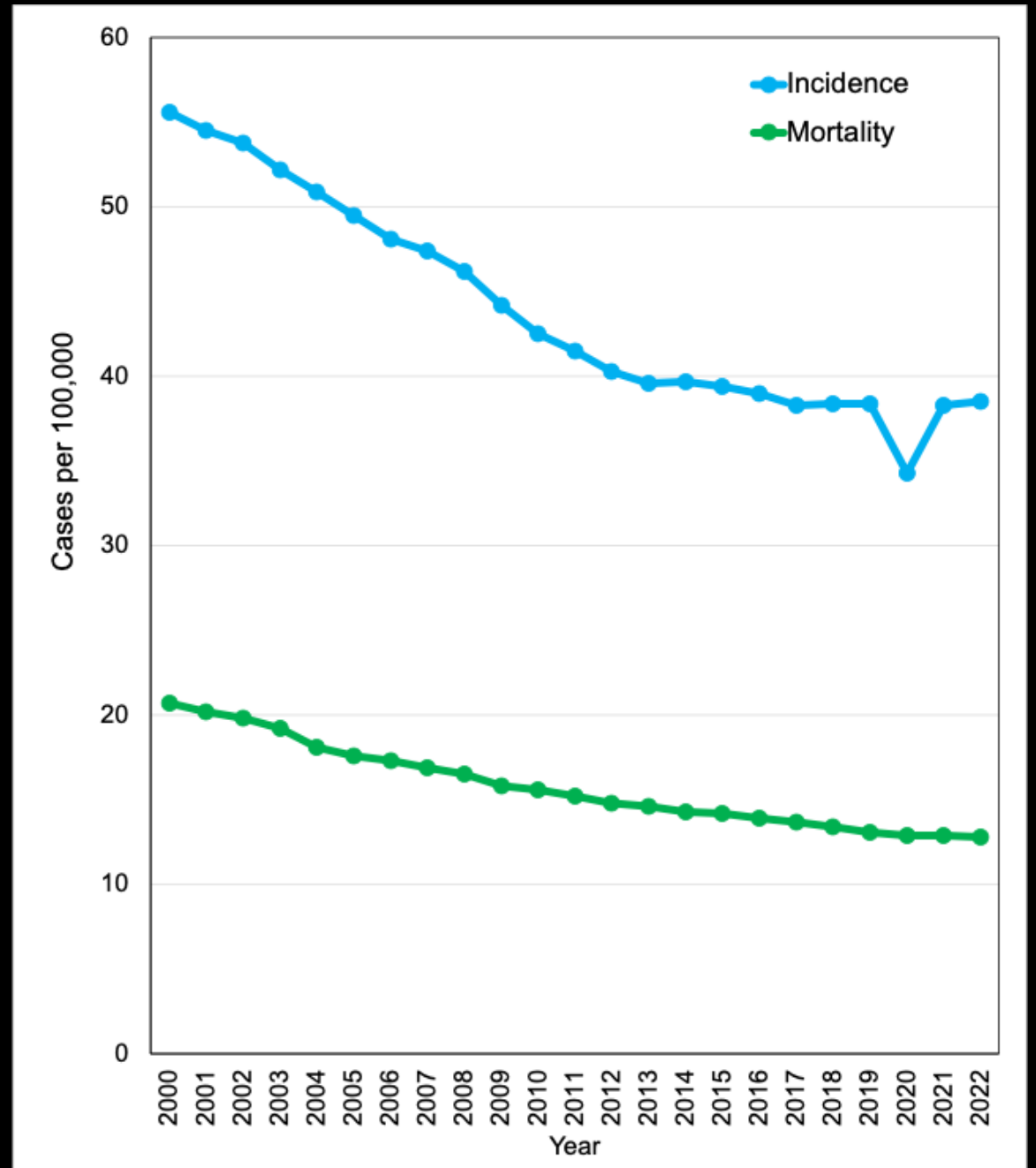
Agenda

- Trends in colorectal cancer epidemiology
- Novel evidence supporting screening
- 2026 American Cancer Society colorectal cancer screening guidelines
- Challenges and future directions

The CRC Success Story

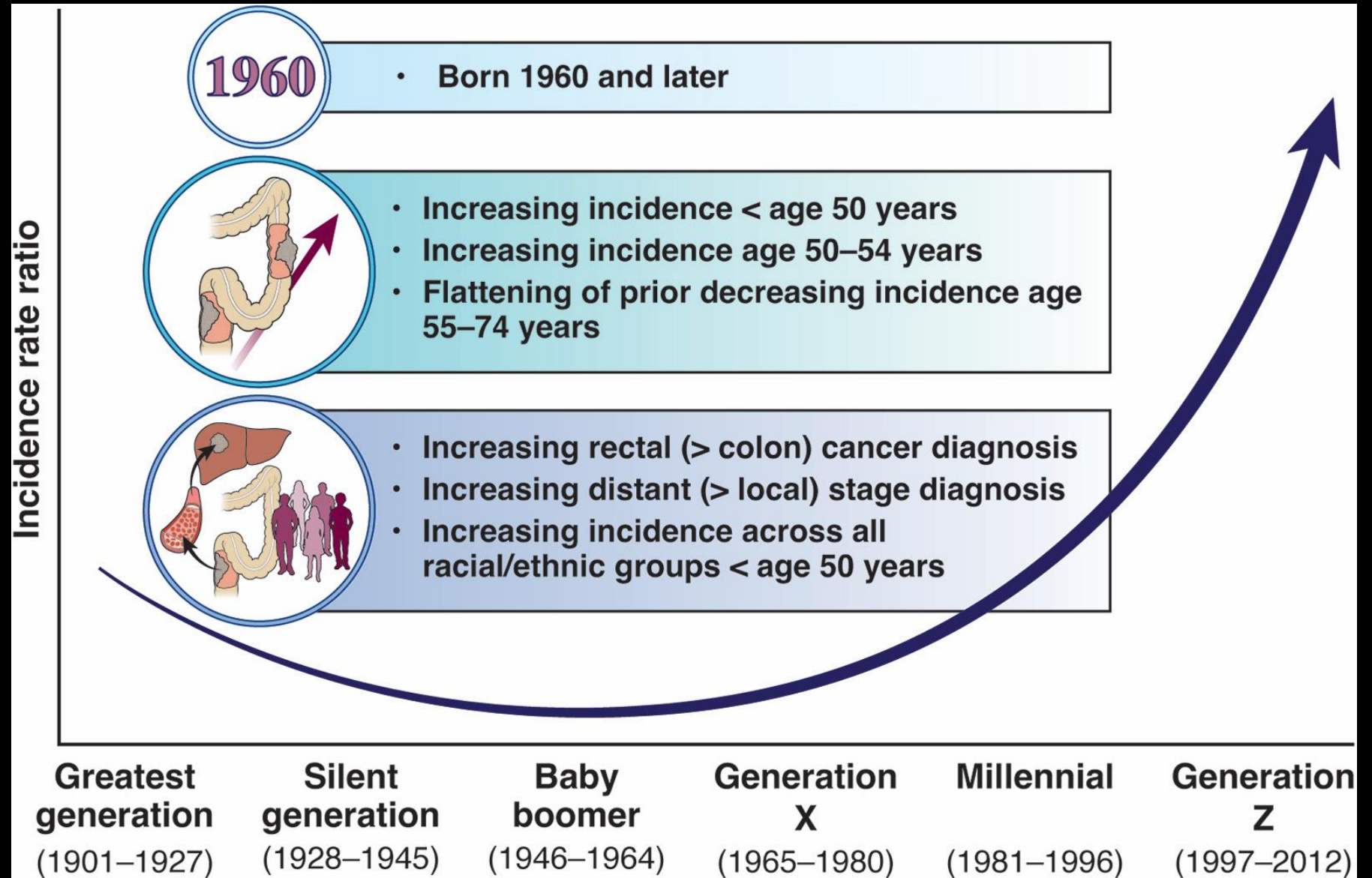
- For all groups combined, incidence and mortality have improved over time
 - Screening, risk factors, treatment
- Incomplete picture:
 - Recent annual percentage change not changing
 - For all ages:
 - #3 most common cancer: 158,850 cases
 - #2 cause of cancer death: 55,230 deaths
 - <age 50
 - #1 cause of cancer death

Surveillance Epidemiology End Results 21 2000-2022 delay-adjusted incidence and mortality. Includes appendix.
SEER*Explorer accessed 1/9/26.



Generational trends in CRC: established and emerging

Birth Cohort Colorectal Cancer

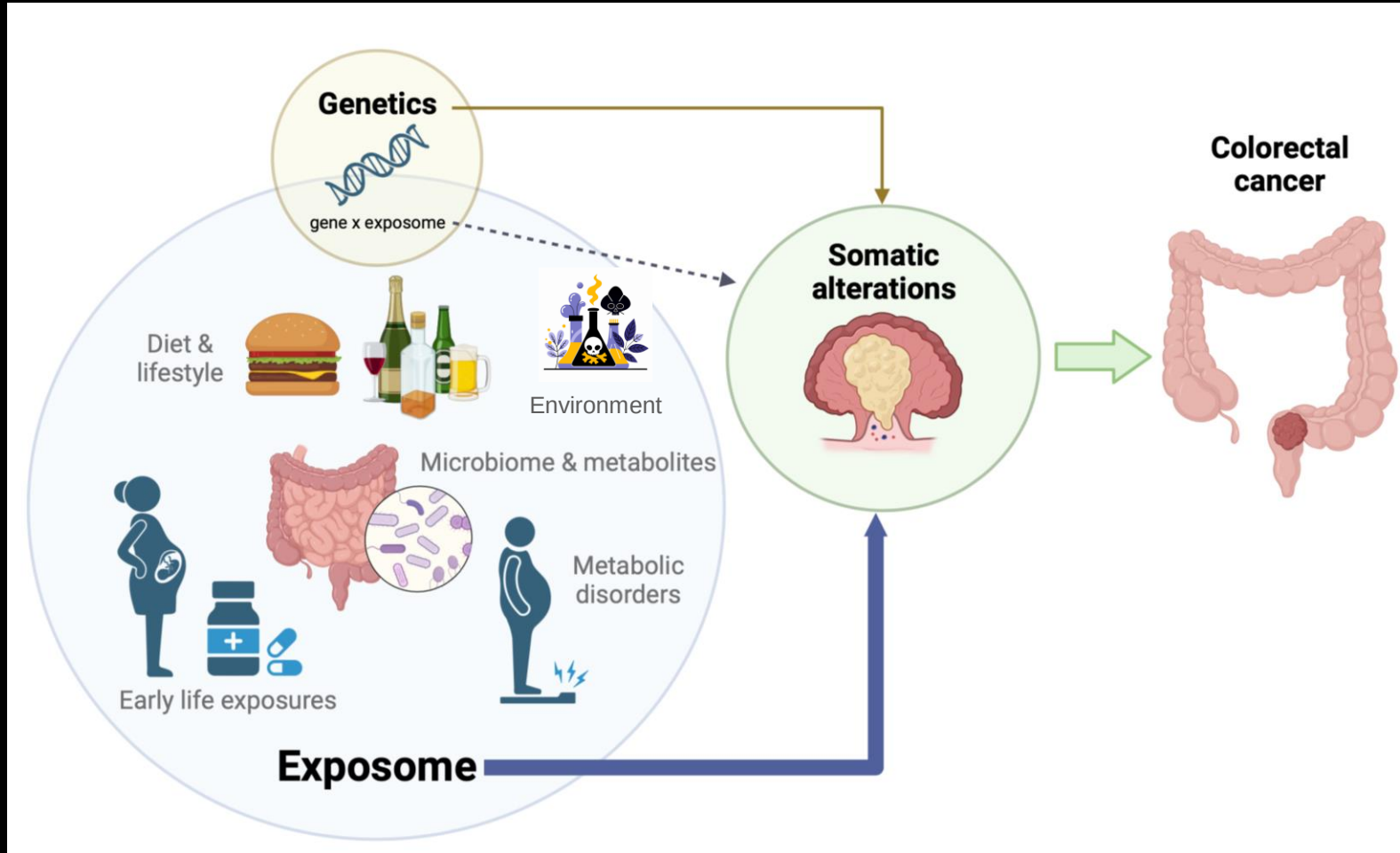


Birth cohort patterns are an important clue



Factors driving increasing incidence are becoming more prevalent or concentrated with successive generations

The exposome is the driver, but vastly understudied



Usual Suspects and Unique Exposures Linked with Early CRC

- Obesity
- Hyperlipidemia
- Smoking
- Alcohol
- Sugar-sweetened beverages
- Ultra-processed food
- In utero: sulfonamides, Bendectin, obesity
- Picloram

Environmental factors largely ignored

What can we do now to address changing epidemiology?

- Support innovative, disruptive translational research
 - Cohort, case-control studies leveraging ability to characterize the exposome
- Individuals age ≥ 45 age eligible for screening
 - ↑ Urgency to get people up to date and ensure complete follow-up
- Individuals under age 45 and ≥ 45 unscreened
 - Close the clinical loop on potential red-flag signs and symptoms of CRC

Screening – Recent Evidence

- Randomized trials: incidence and mortality
- Prospective observational studies of new tests

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)

“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/>

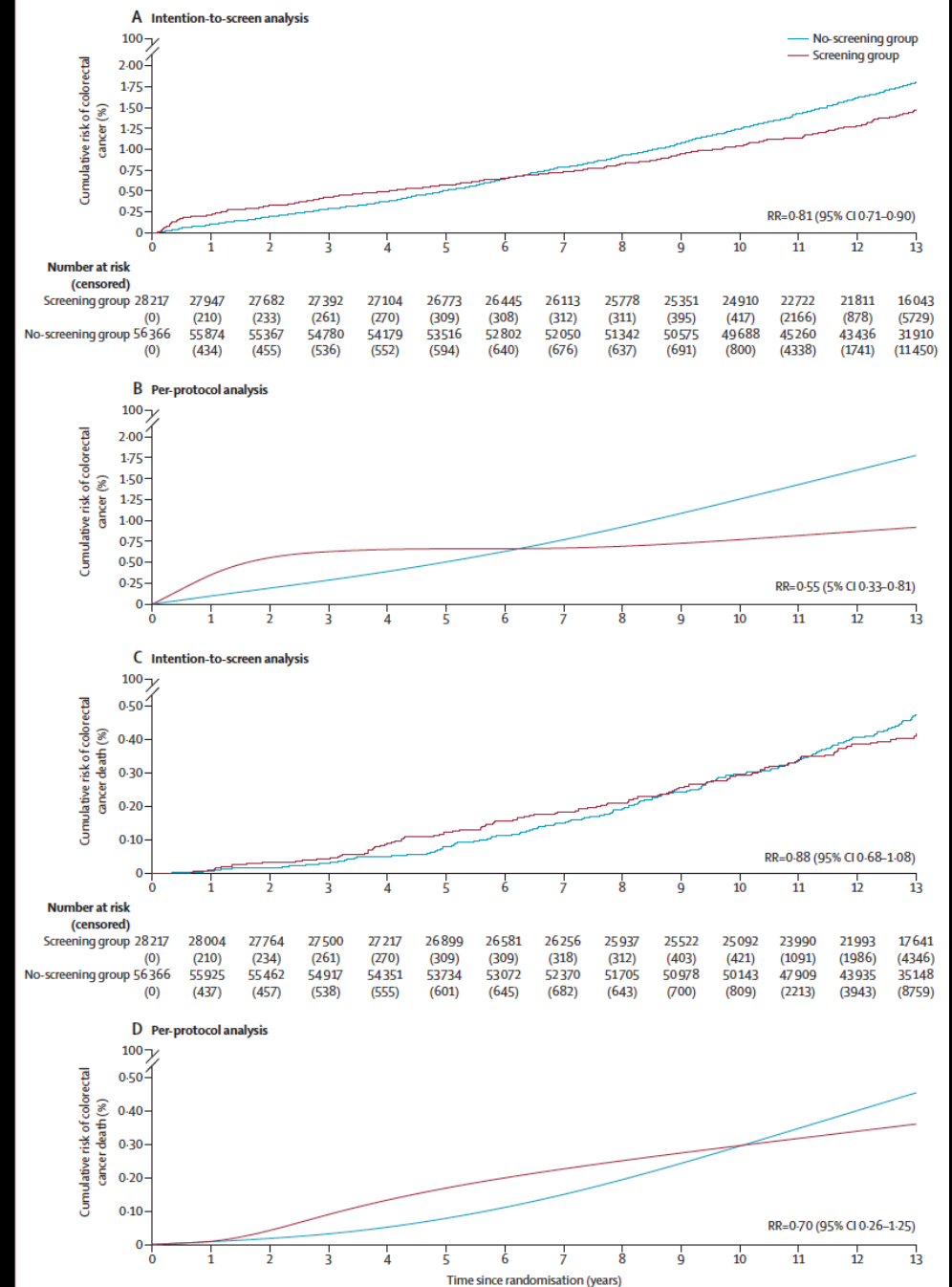
<https://www.cnn.com/2022/10/09/health/colonoscopy-cancer-death-study>

<https://www.medpagetoday.com/hematologyoncology/coloncancer/105724>

<https://www.healthline.com/health-news/regular-colorectal-cancer-screenings-should-begin-at-age-50-suggests-acp>

RCT: Colonoscopy vs. No Invitation

- ~85,000 age 55-64 in Norway, Sweden, and Poland
- Median follow-up 13 years
- 19% relative reduction CRC incidence
- No reduction in mortality
- Per protocol:
 - 45% reduction for incidence
 - Non-significant 30% reduction for mortality



RCT: Colonoscopy vs. FIT

- ~57,000 age 50-69 in Spain
- Median follow-up 10 years
- No difference in incidence or mortality
- Per protocol:
 - 33% reduction for incidence
 - 83% reduction for mortality

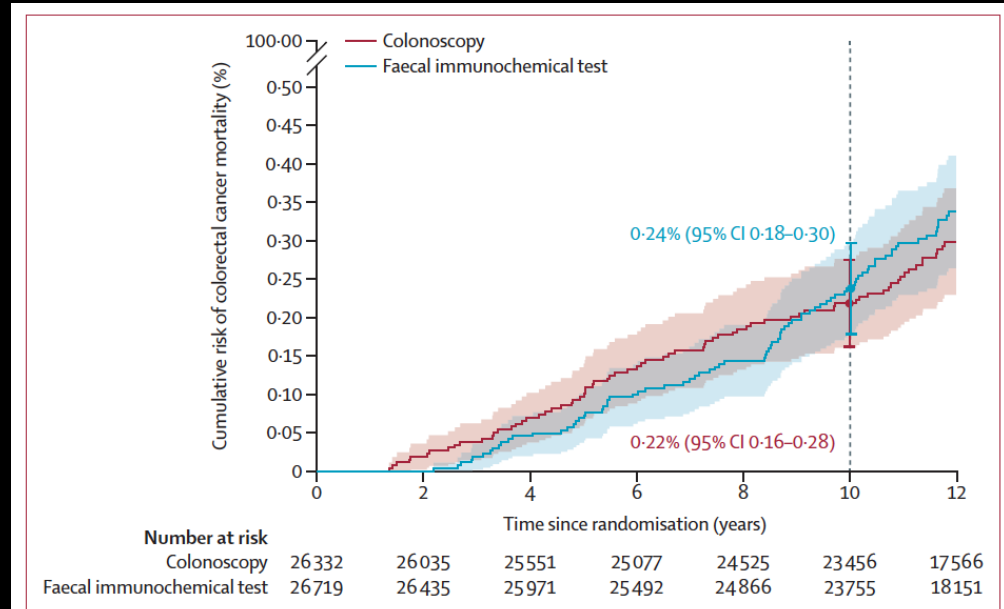


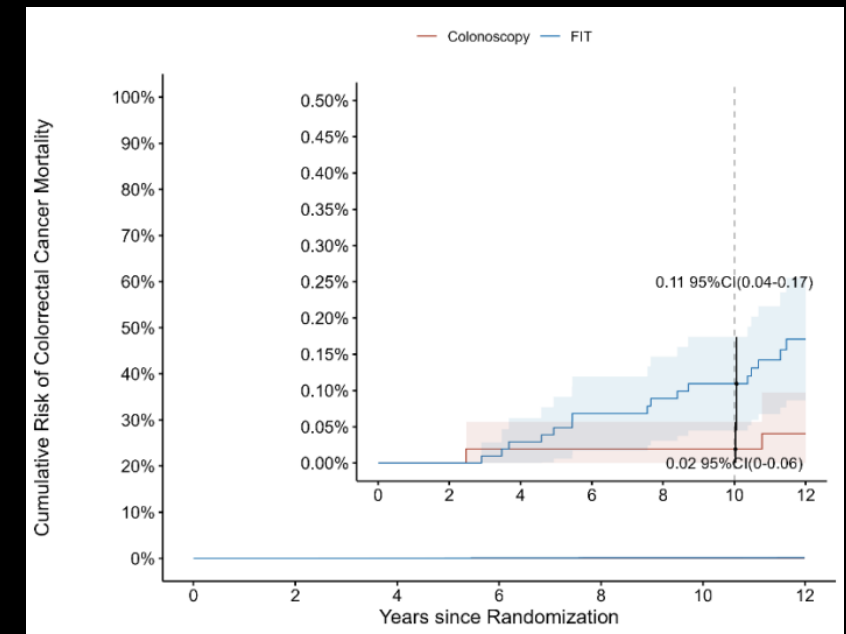
Figure 2: Cumulative risk of colorectal cancer mortality at 10 years in the intention-to-screen analysis population
Shaded areas indicate 95% CIs.

Effect of invitation to colonoscopy versus faecal immunochemical test screening on colorectal cancer mortality (COLONPREV): a pragmatic, randomised, controlled, non-inferiority trial

Antoni Castells*, Enrique Quintero*, Luis Bujanda, Susana Castán-Cameo, Joaquín Cubiella, José Díaz-Tasende, Ángel Lanas, Akiko Ono, Miquel Serra-Burriel, Eladio Frías-Arrocha, Cristina Hernández, Rodrigo Jover, Montserrat Andreu, Fernando Carballo, Juan Diego Morillas, Dolores Salas, Raquel Almazán, Inmaculada Alonso-Abreu, Jesús M Banales, Vicent Hernández, Isabel Portillo, Mercedes Vanaclocha-Espí, Mariola de la Vega, on behalf of the COLONPREV study investigators†

Summary

Background Colonoscopy and the faecal immunochemical test are accepted strategies for colorectal cancer screening. *Lancet* 2025; 405: 1231-39

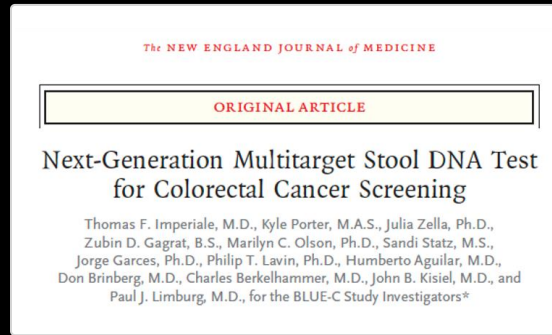


Colonoscopy RCT results in context

- Invitation to colonoscopy:
 - Reduced incidence compared to no invitation
 - Similar incidence compared to FIT invitation
 - Similar mortality compared to FIT invitation or no invitation
 - Incidence reduction on par with other tests
- Participation in colonoscopy
 - Reduced incidence and mortality compared to FIT or no invitation
- Population level --> longer follow-up to understand colonoscopy effects
- Individual level --> colonoscopy better than no screening and FIT

Test Strategy (n trials)	Incidence	Mortality
Colonoscopy vs. no screen (n=1)	↓ 19%	No Dif.
Sigmoidoscopy vs. no screen (n=4)	↓ 21-24%	↓ 20-25%
Guaiac FOBT vs. no screen (n=4)	↓ 20%	↓ 18%
Colonoscopy vs. FIT (n=1)	No Dif.	No Dif.

Recent Evidence: FDA approved non-invasive tests



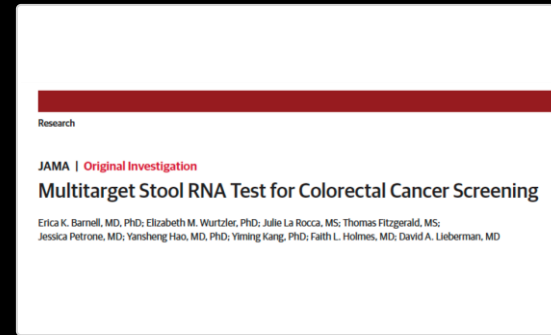
STOOL

sDNA–FIT 2.0

Cologuard Plus | Exact Sciences

Methylated DNA markers

LASS4 • LRRC4 • PPP2R5C
ZDHHC1 reference marker + FIT



STOOL

sRNA–FIT

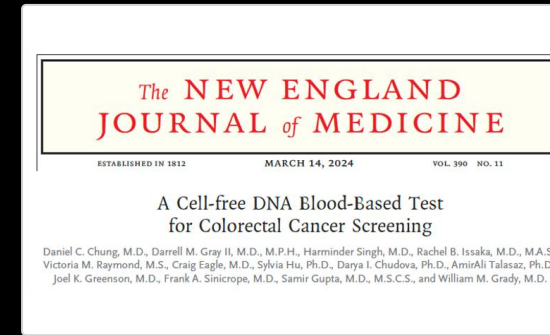
ColoSense | Geneoscopy

Eight RNA markers + FIT

GAPDH • ACY1 • AREG •
TNFRSF10B
CDH1 • EGLN2 • KRAS •
SMAD4

OC-Sensor FIT

Tobacco-smoking history



BLOOD

cfDNA Shield

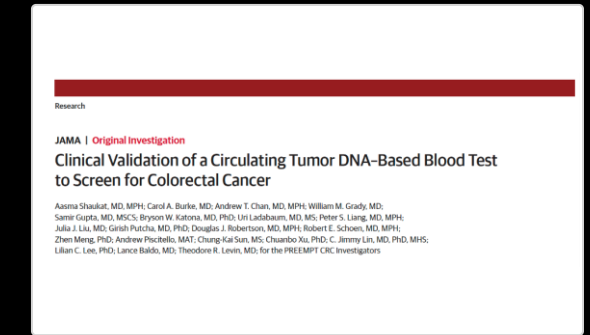
Shield | Guardant Health

cfDNA methylation

DNA methylation patterns

Aberrant fragmentation patterns

Somatic pathogenic variants: APC +
KRAS



BLOOD

cfDNA SimpleScreen

SimpleScreen | Freenome

cfDNA methylation

DNA methylation patterns

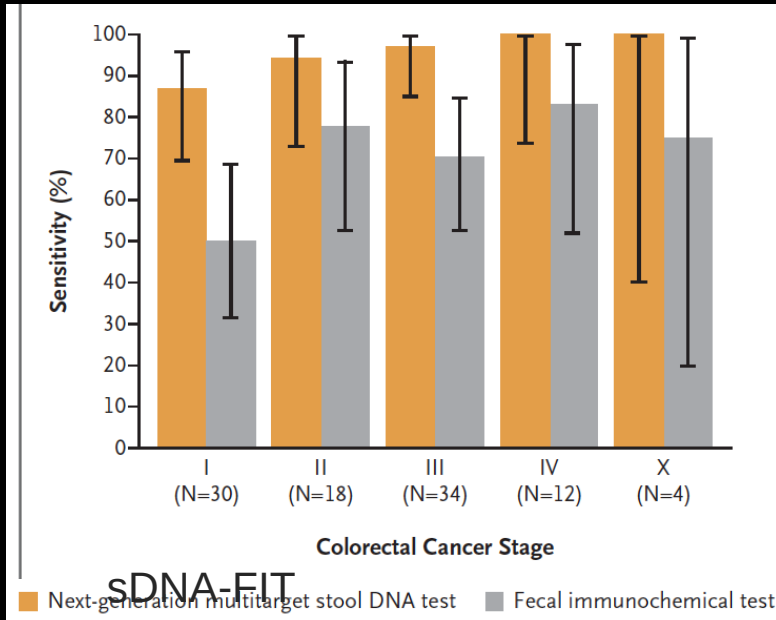
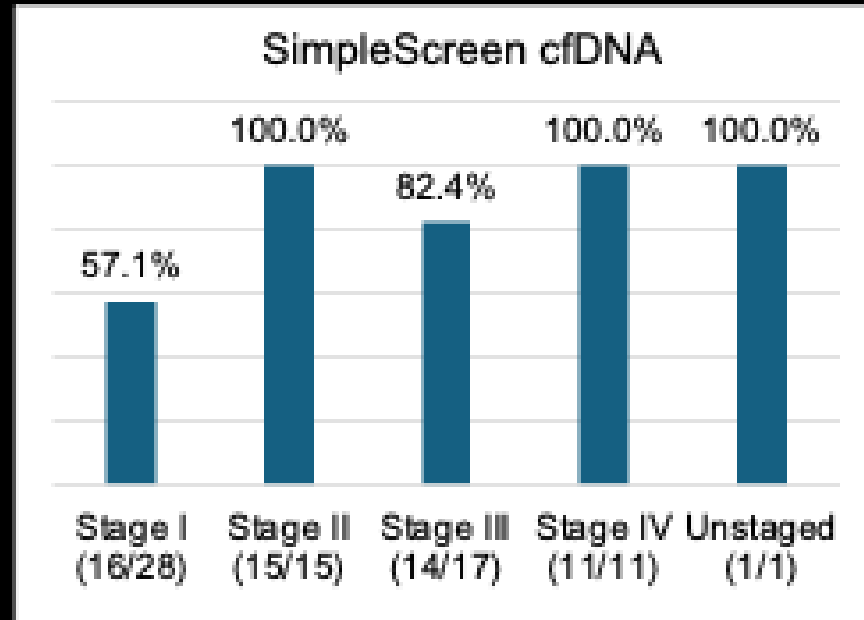
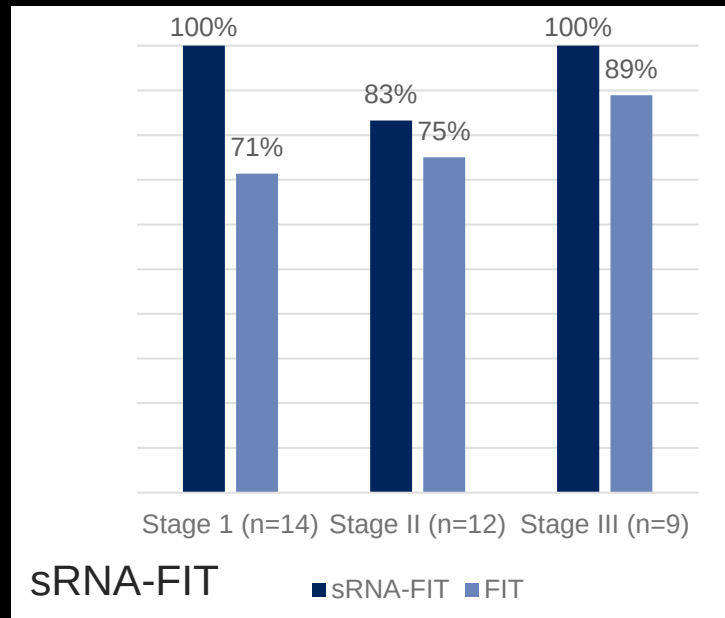
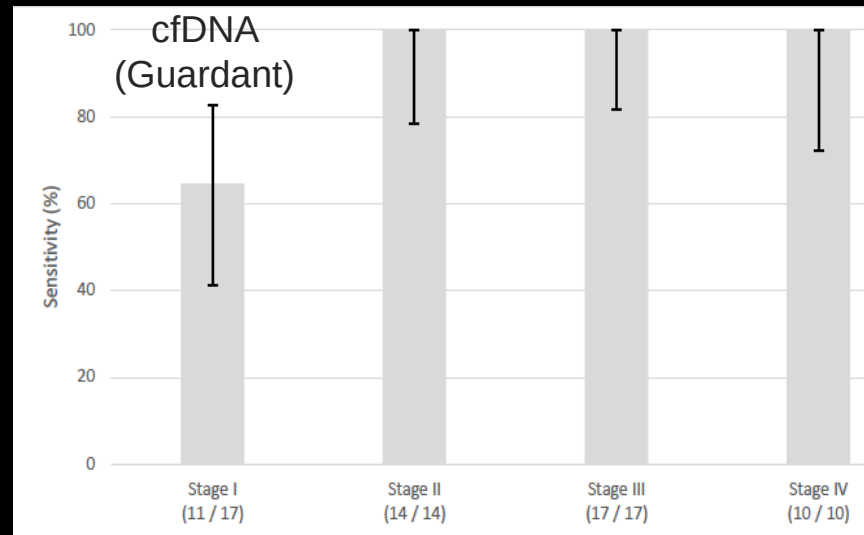
Sensitivity for CRC



- All emerging tests have better CRC sensitivity than FIT and guaiac FOBT
- Novel fecal tests approaching colonoscopy

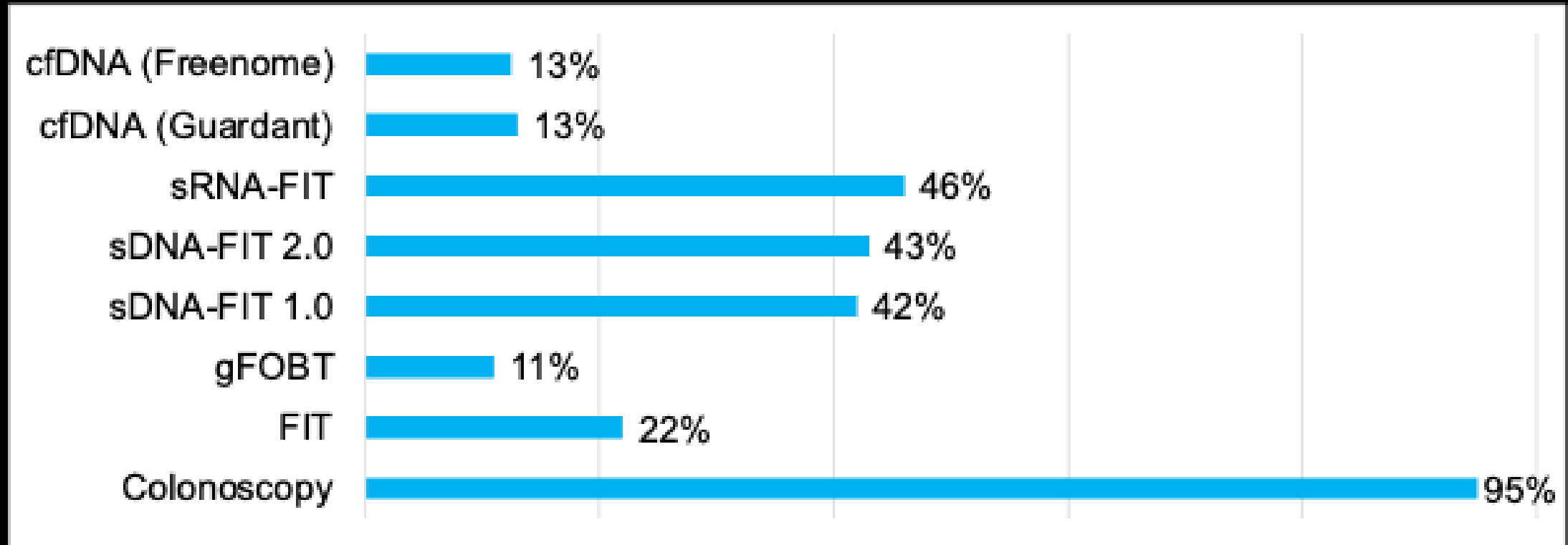
Knudsen A JAMA 2021; Knudsen AHRQ Publication No. 20-05271-EF-2 2021; Imperiale T NEJM 2014; Imperiale T NEJM 2024; Chung D NEJM 2024; Barnell E JAMA 2023

Stage-Specific Sensitivity for CRC



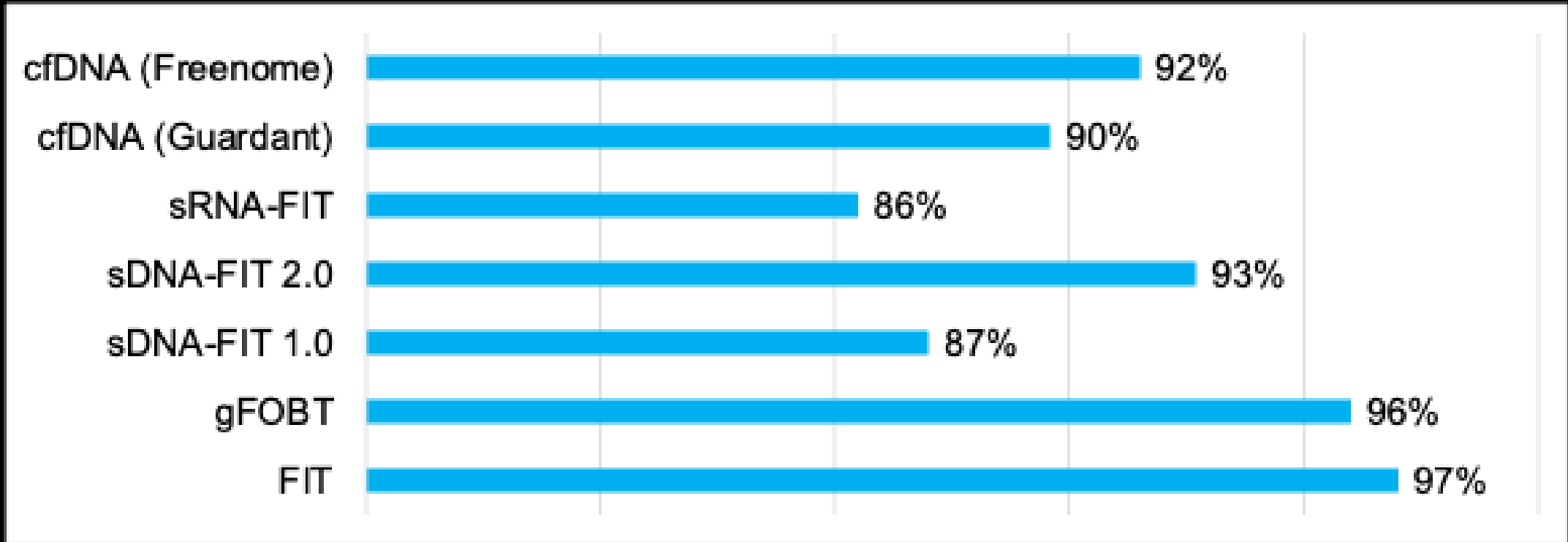
- Low sample size
- Novel stool tests:
 - Stage 1 sensitivity high and appears better than FIT
- Blood based tests:
 - Stage 1 sensitivity lower

Sensitivity for Advanced Polyps



- All emerging tests have lower sensitivity for advanced polyps compared to colonoscopy
- Emerging stool tests have higher sensitivity than FIT
- cfDNA has lower sensitivity for advanced polyps compared to FIT, sDNA-FIT 1.0, and emerging fecal tests

Specificity in those without advanced neoplasia

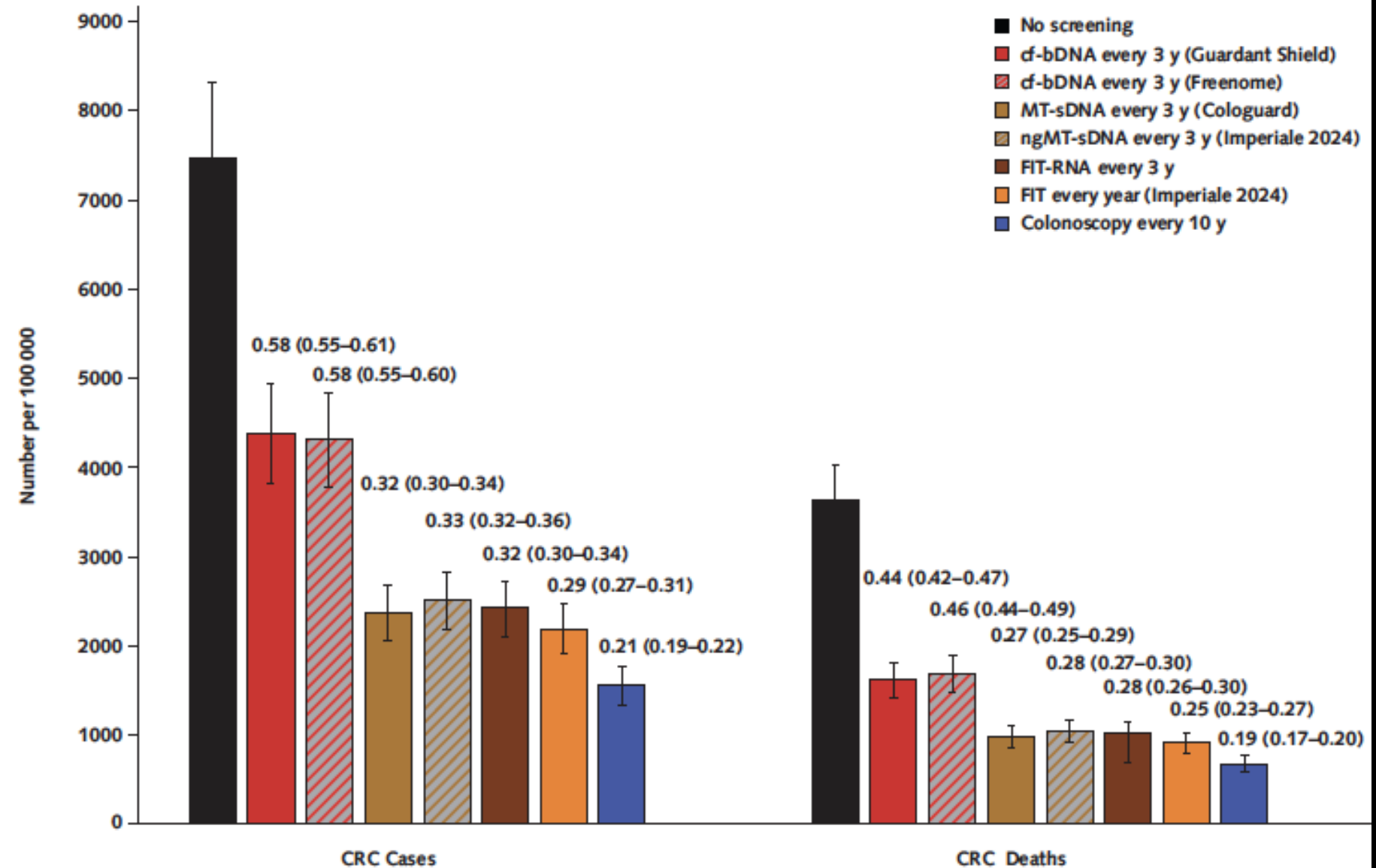


- Defined by proportion of patients with non advanced adenomas, non-neoplastic findings, or negative colonoscopy who have a negative test
- Specificity remains better for FIT compared to emerging tests
 - Specificity declines with age for all novel tests but not for FIT

Comparative Effectiveness

- Modelling study
- Gradient of predicted risk reduction
colonoscopy > fecal tests > blood tests

Figure 1. Clinical outcomes with emerging and established CRC screening strategies.



ORIGINAL RESEARCH

Annals of Internal Medicine

Projected Impact and Cost-Effectiveness of Novel Molecular Blood-Based or Stool-Based Screening Tests for Colorectal Cancer

Uri Ladabaum, MD, MS; Ajitha Mannaikthara, PhD; Robert E. Schoen, MD, MPH; Jason A. Dominitz, MD, MHS; and David Lieberman, MD

Blood-based tests: unintended consequences

- Lower projected impact on incidence and mortality
- Ideal impact:
 - Increase participation among people who would not otherwise be screened
- Unintended consequence:
 - Induce people who would have been otherwise screened with colonoscopy or fecal tests to complete screening with a blood test

Percent change in proportion of CRC deaths based on:

1) Proportion of unscreened who get screened with cfDNA vs.

2) Proportion of people who substitute FIT or Colonoscopy with cfDNA

	0% addition	10% addition	20% addition
0% substitution	No change	-8.9 (-9.4 to -8.3)	-18 (-19 to -17)
10% substitution	5.4 (5.1 to 5.8)	-3.5 (-4.3 to -2.6)	-12 (-14 to -11)
30% substitution	16.3 (15.1 to 17.5)	7.4 (5.9 to 9.0)	-1.5 (-3.4 to -0.6)

Addition = absolute fraction of population among 40% unscreened for whom cfDNA was added

Substitution = absolute fraction of population among 60% currently screened for whom another test was replaced with cfDNA

Outcome = Percentage change in 1949 CRC deaths per 100,000 occurring pre-cfDNA introduction (current state)

2026 American Cancer Society Guidelines

Recommended Age: ≥ 45 years for individuals with average risk

Preferred Options

Direct Visual Exams

- Colonoscopy every 10 years
- Sigmoidoscopy every 5 years
- CT colonography every 5 years

High-Sensitivity Stool Tests

- FIT annually
- Guaiac FOBT annually
- Multi-target DNA-FIT every 3 years (Cologuard)
- Multi-target RNA-FIT every 3 years (Colosense)

Non-Preferred but Acceptable

- For those who decline or do not complete a preferred test

Blood-based tests

- Cell-free DNA every 3 years (Shield or SimpleScreen)

Colorectal cancer screening: An update to the American Cancer Society guideline, 2026

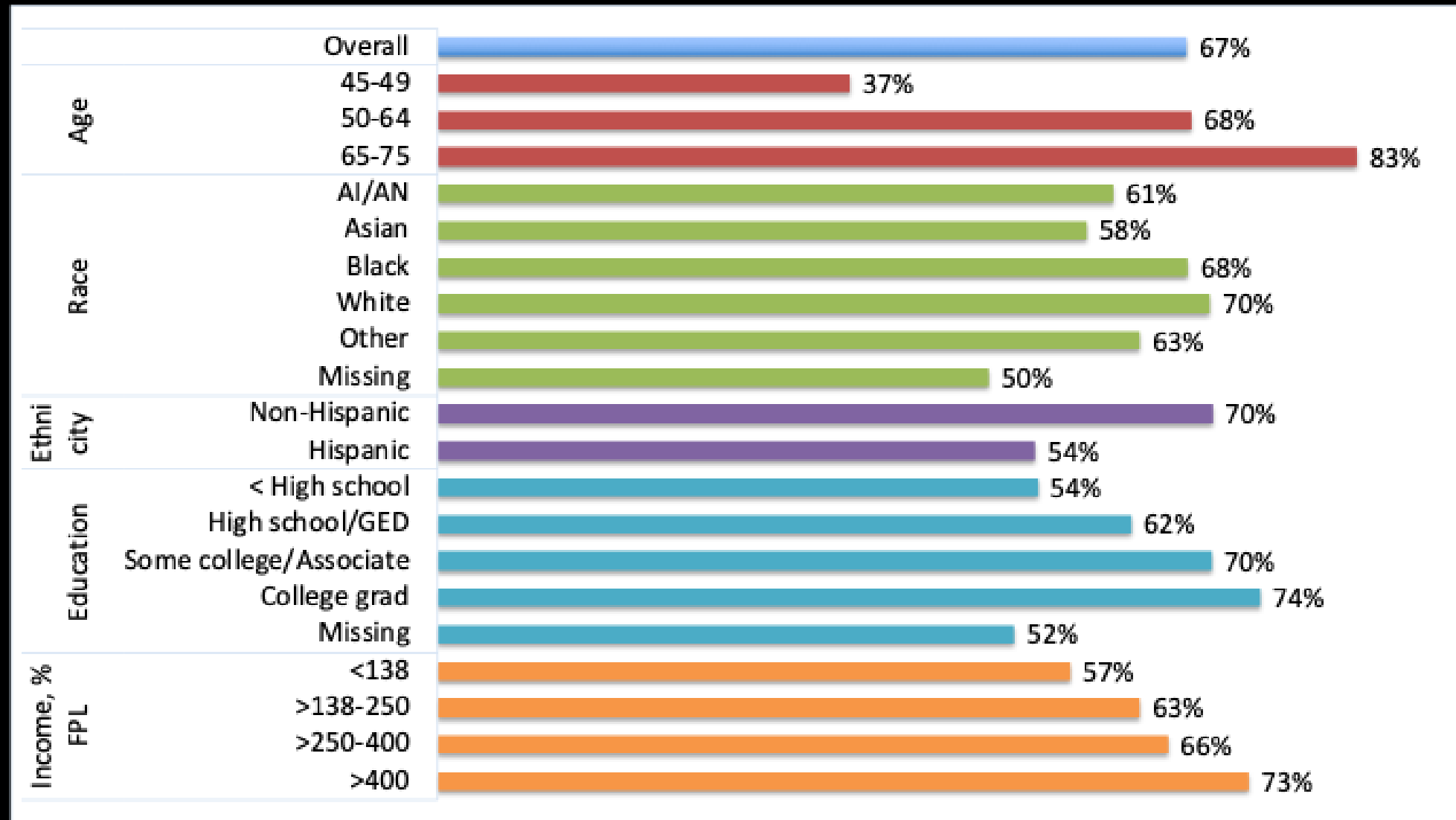
CA Cancer J Clin. 2026;e70083.
<https://doi.org/10.3322/caac.70083>

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Challenges and future directions

- Participation
- Abnormal test follow up
- Symptoms suggestive of CRC

Uptake is suboptimal, and varies greatly across the population

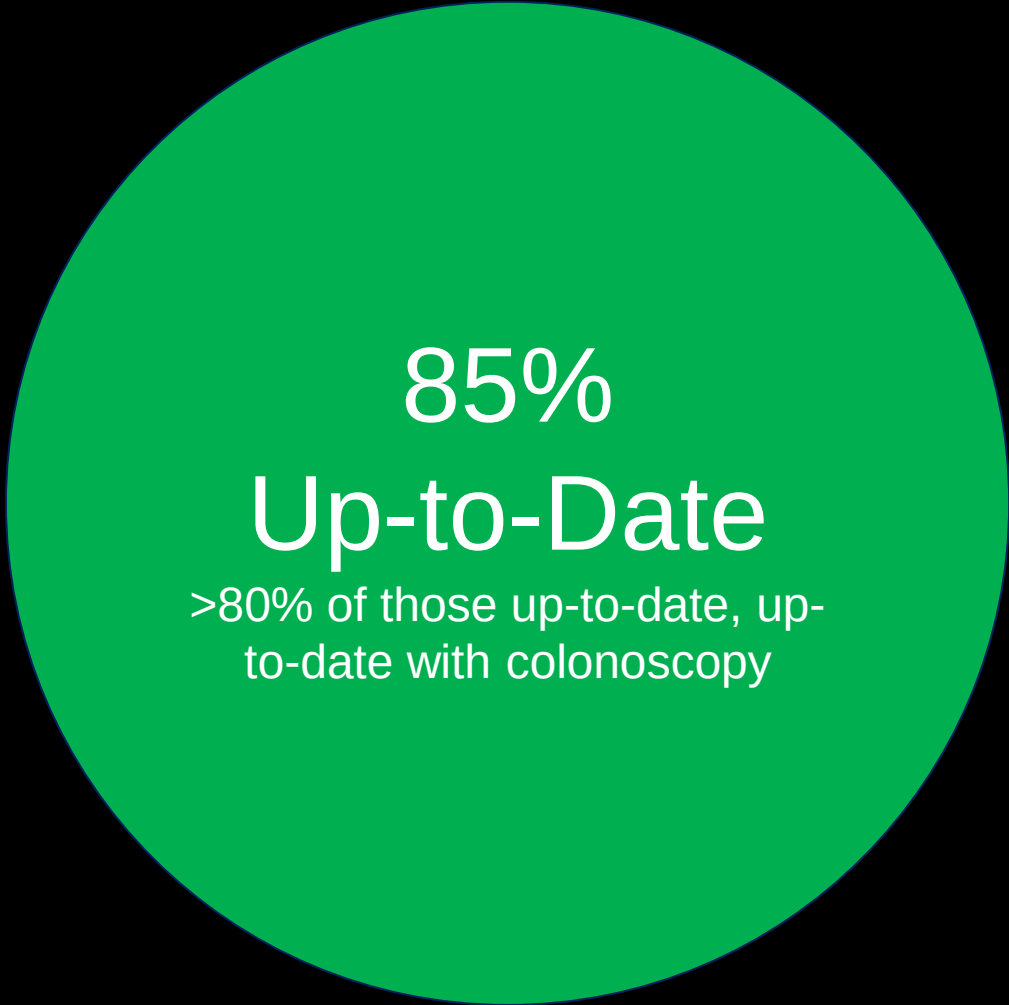


Opportunities for addressing screening rates

- Multiple evidence-based interventions exist
 - Test choice
 - E.g. colonoscopy and at least one non-invasive (e.g. FIT or sDNA-FIT)
 - Mailed FIT outreach
 - Mailed invitation, including a FIT kit, +/- reminders
 - 22% absolute increase in screening participation over usual care

Optimal Example: UCSD

- In Clinic
 - Test choice
 - Reminders
- Outreach
 - Mailed FIT outreach prior to 2026
 - Mailed Bulk Cologuard outreach 2026
 - Automated MyChart and phone call reminders up to 4x/yr
- Challenges
 - Substitution of less effective tests for more effective tests as options expand
 - Abnormal non-invasive test follow-up
 - San Diego County screening 58%, Federally Qualified Health Center 48%



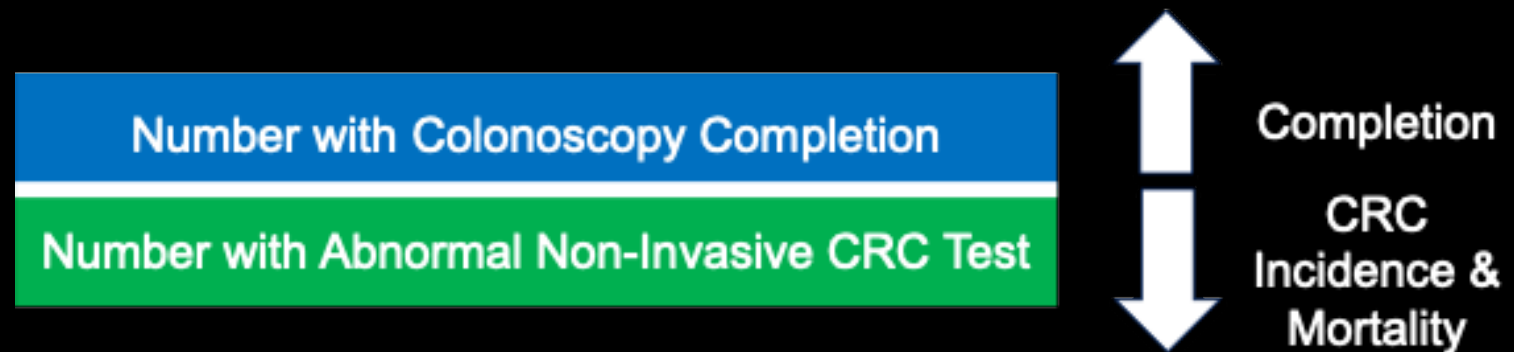
85%
Up-to-Date
>80% of those up-to-date, up-to-date with colonoscopy

Follow up of abnormal tests is suboptimal

- Lack of colonoscopy completion after abnormal FIT associated with 2.5 fold increased risk for CRC death
 - 1 in 20 have cancer
 - 1 in 4 have a large polyp
- Goal is 80%
- Colonoscopy completion after abnormal FIT varies 18%-69% nationally
 - Cologuard f/u nationally 62%
 - cfDNA (Shield) f/u 56%

Opportunities for addressing non-invasive test follow up

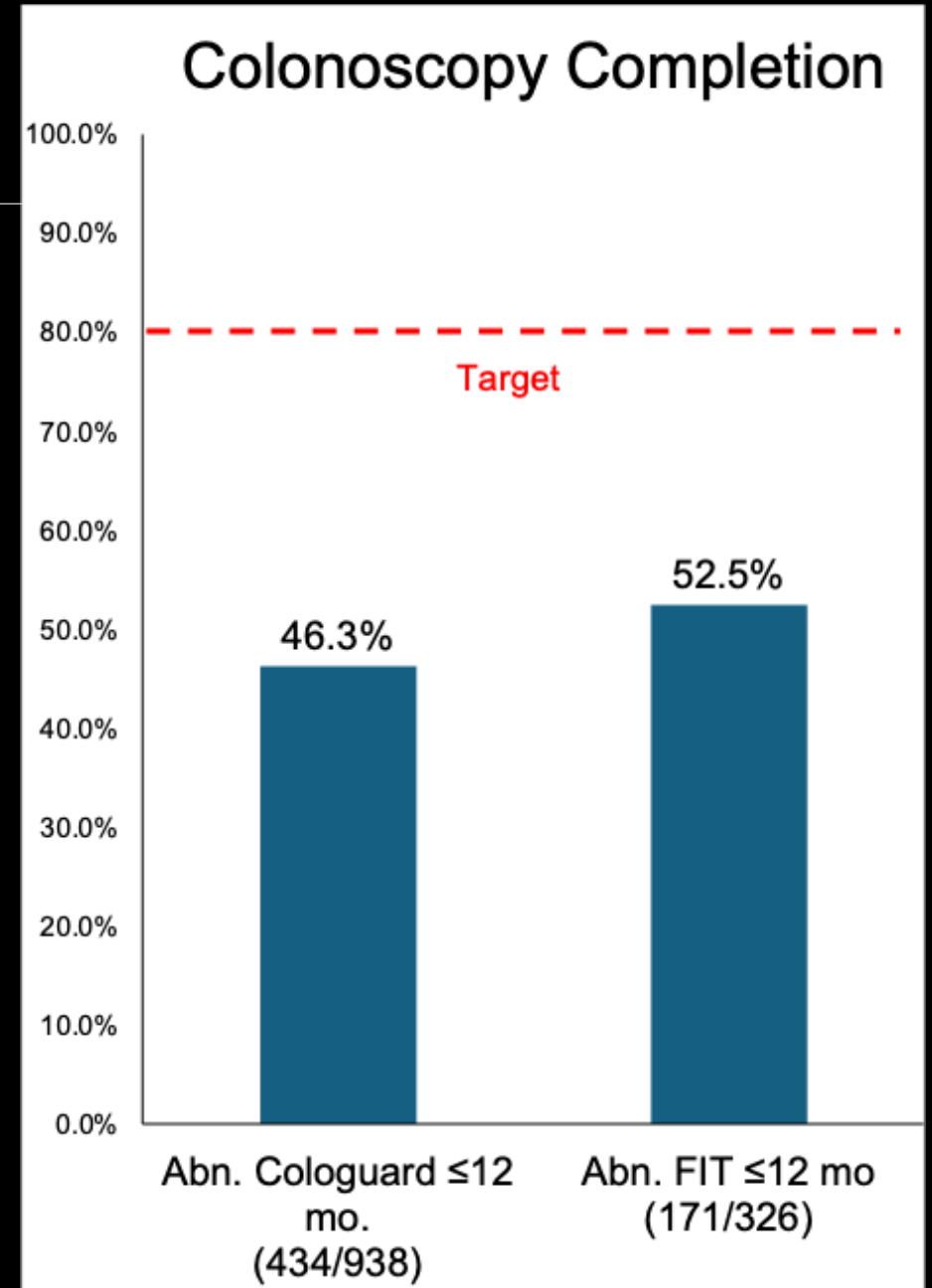
- Patient-level: navigation
- Provider-level: reminders and performance feedback
- System-level: automated referrals; pre-colonoscopy calls; patient registries; problem list/coding
- Dissemination of new HEDIS (Healthcare Effectiveness Data and Information Set) quality metric



Inadomi J Arch Int Med 2012; Dougherty MK. JAMA Int Med 2018; Issaka RB Prev Med 2018; Gupta S; CA Cancer J Clin 2020; Somsouk JNCI 2020; Coronado CEBP 2022; Raich CEBP 2022; Green BB J Am B Fam Med 2014; Selby Ann Int Med 2017; Selby Clin Transl Gastro 2019; O'Leary M Preventive Medicine Reports; Shareef, Gupta J Primary Care Com Health 2024; Burns Am J Gastro 2024; https://www.ncqa.org/blog/hedis-my-2027-whats-new-whats-changed-whats-retired/?utm_campaign=qualitymatters-newsletter&utm_medium=email&utm_source=sf&utm_content=_general____04-08-2026

UCSD approach and results

- Abnormal FIT/Cologuard registry
- Patient and clinician outreach by GI team
- Ample colonoscopy capacity
- Opportunity:
 - Innovative strategies for promoting appropriate use of non-invasive tests and optimal follow-up



Timely diagnosis

- Common red flag signs and symptoms associated with CRC have been established
- Delays in diagnosis common
 - Mean 6.4 (1.8-13.7), median 4 (2.0-8.7) months Demb JAMA Network Open 2024
- Need: Strategies for “needle in haystack” problem
 - Symptoms highly prevalent but positive predictive value low

Figure 2. Pooled Proportions of Presenting Signs and Symptoms for Early-Onset Colorectal Cancer

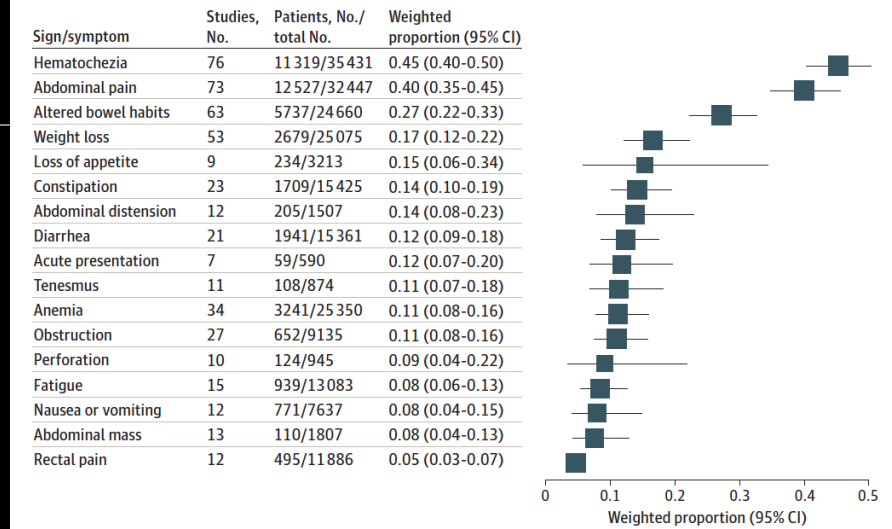
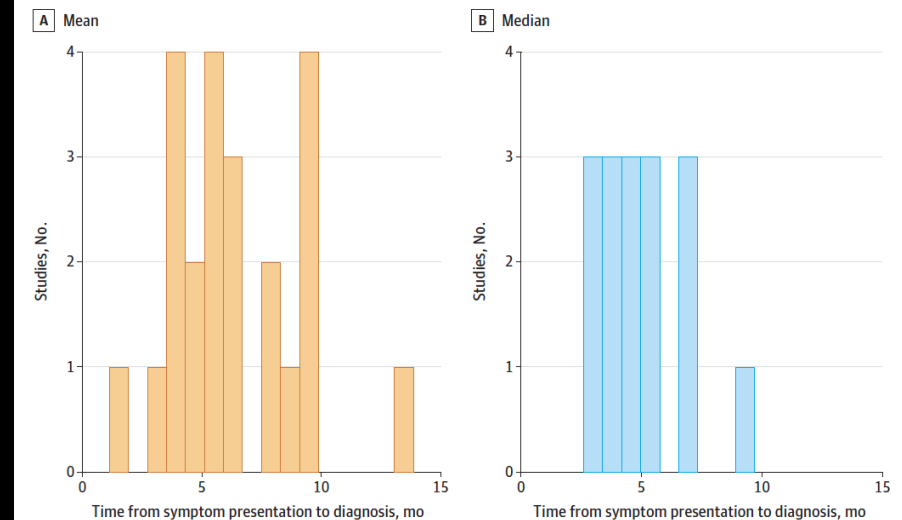
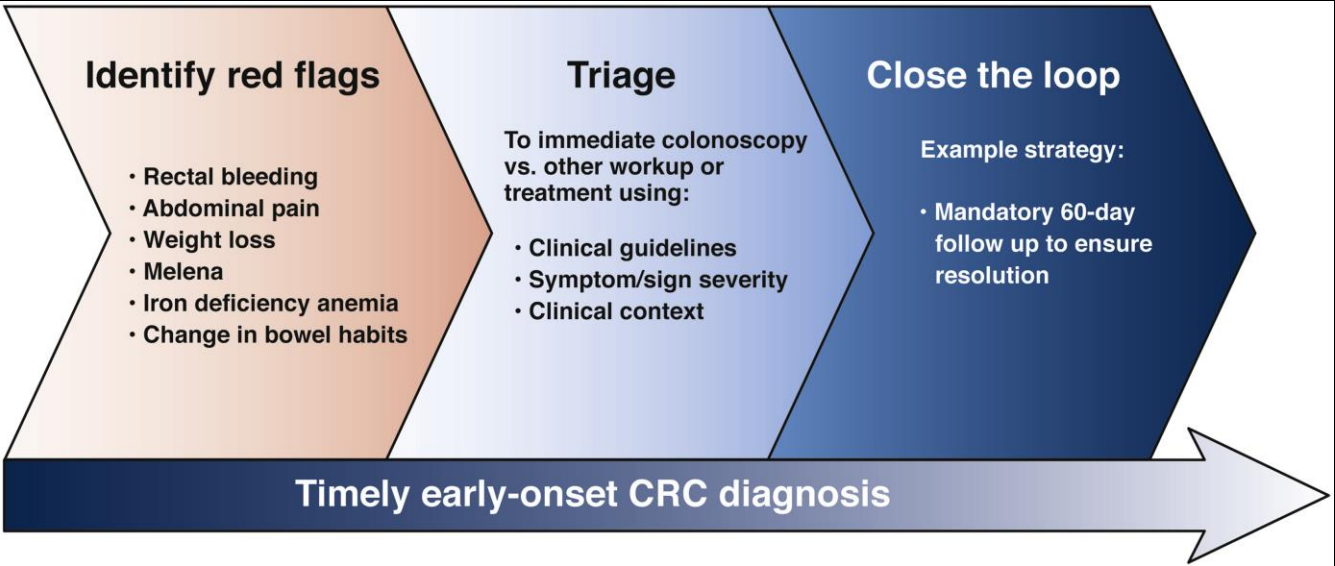


Figure 4. Histogram of Study Frequencies of Time From Symptom Onset to Diagnosis, by Measurement Type

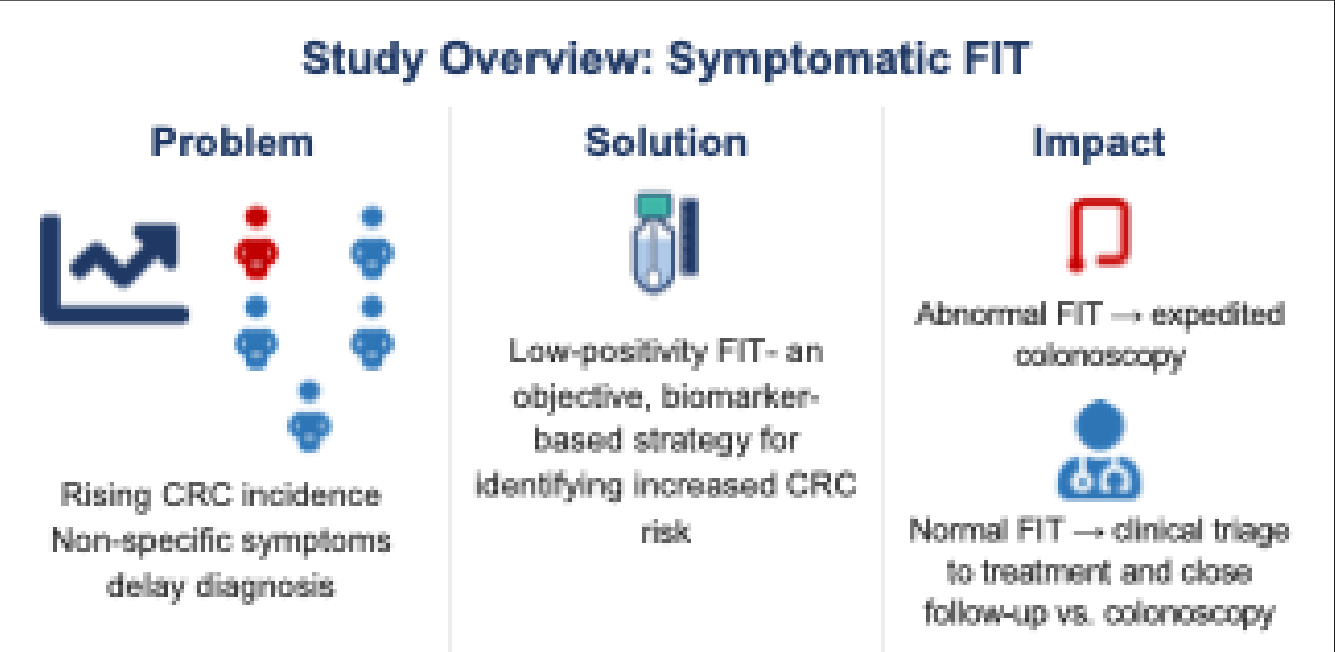


Solutions

Optimize Practice



Research



Scorecard: where are we and where do we need to go?

Current State

- Epidemiology of CRC is changing
 - ↑ Early and middle age onset
- RCTs: Similar FIT and colonoscopy outcomes on intent to screen but different per protocol
- Multiple established and emerging tests without RCTs
- Highly variable sensitivity
- Abnormal test follow up suboptimal

Future State

- Discover etiologic drivers
- High rates of screening participation
- High awareness/diagnostic resolution of symptoms
- Results of ongoing studies with longer follow up
- Comparative studies of participation, including of replacement of established tests by emerging tests
- Novel interventional trials
- Quality metric that promotes tracking and follow up

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 - Curebound Cancer Health Equity Grant
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 - Folasade May (UCLA), Sonia Kupfer (U Chicago), Caitlin Murphy (U Chicago)
- Population Health and SureNet Teams
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 - Robert El-Kareh, Jennifer Holland, Gaby Karbarz, Tracy Magee, Jinyao Qu, Gabriel Rosario, Thomas Savides, Jennifer Sweetser, Ming Tai-Seale, Sean Villafranca, Amanda Walker
 - Step Family Foundation: Concierge for All
- Timely Diagnosis Concepts
 - Joshua Demb
- Symptomatic FIT Study
 - Kaitlyn Lew, Aaron Boussina, Leisa Sutton, Katheryn Rodriguez, Isaac Ceseña, Allison Lynch, Amar Mandvi, Megha Shankar

End
