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Participating in the Webinar

All attendees will be muted and will remain in "Listen Only Mode"

Type your questions here so that the moderator can see them.
Not all questions will be answered but we will get to as many as possible.

A handout with the slides and room to take notes can be downloaded from your control panel.

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Week 22 – Thursday, June 1, 2023
Prior Authorization in GI: Tips from the ACG Prior Authorization Task Force
Faculty: Baharak Moshiree, MD, MSc, FACG, and Stephen T. Amann, MD, FACG
Moderators: Daniel J. Pambianco, MD, FACG, and Dayna S. Early, MD, FACG
At Noon and 8pm Eastern



Week 23 – Thursday, June 8, 2023
Leadership, Diversity, Ethical Care, and Equity
Faculty: Sonali Paul, MD, MS; Cassandra D. Fritz, MD; and Lauren D. Nephew, MD
Moderator: Sophie M. Balzora, MD, FACG
At Noon and 8pm Eastern

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Disclosures

Douglas J. Robertson, MD, MPH
Freenome: Advisory Board

T.R. Levin, MD, FACG
Freenome: Research Support

**All of the relevant financial relationships listed for these individuals have been mitigated*

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The Role of Non-Invasive Modalities in Colorectal Cancer Screening

Douglas J. Robertson, MD MPH
Chief, Gastroenterology White River Junction VA Medical Center
Professor Of Medicine
Geisel School of Medicine at Dartmouth &
The Dartmouth Institute

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Outline

- Does colorectal cancer screening work?
- Why consider strategies beyond colonoscopy?
- Non-invasive options
- Comparative effectiveness of most common strategies
- Colonoscopy vs FIT and FIT DNA
- FIT vs FIT DNA
- Future options including serology

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Screening Intuitively Make Sense When…

- Target disease is common in the assessed population
- Associated with high morbidity/mortality
- Has an identifiable and treatable preclinical phase

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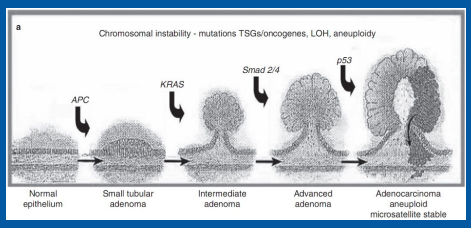
Colorectal cancer screening makes sense…

Estimated Deaths

	Males			Females	
Lung & bronchus	69,410	22%	Lung & bronchus	62,470	22%
Prostate	34,130	11%	Breast	43,600	15%
Colon & rectum	28,520	9%	Colon & rectum	24,460	8%
Pancreas	25,270	8%	Pancreas	22,950	8%
Liver & intrahepatic bile duct	20,300	6%	Ovary	22,950	5%
Leukemia	13,900	4%	Uterine corpus	12,940	4%
Esophagus	12,410	4%	Liver & intrahepatic bile duct	9,930	3%
Urinary bladder	12,260	4%	Leukemia	9,760	3%
Non-Hodgkin lymphoma	12,170	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,500	3%	Brain & other nervous system	8,100	3%
All Sites	**319,420**	**100%**	**All Sites**	**289,150**	**100%**

Stage	Distribution	5 year Survival
Localized	38	91
Regional	36	72
Distant	22	13



Siegel RL et al, CA Cancer J Clin. 2021; 71(1):7-33
Siegel RL et al, Cancer J Clin. 2017; 67:177-193
Ahnen DJ, Am J Gastroenterol 2011;106 :190-8

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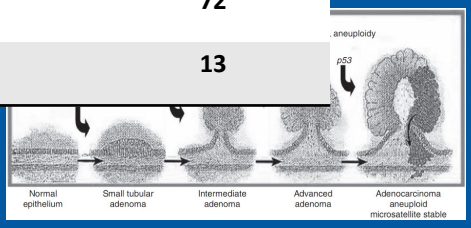

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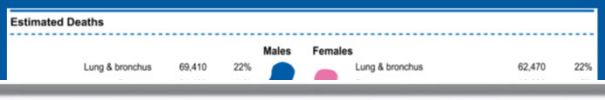
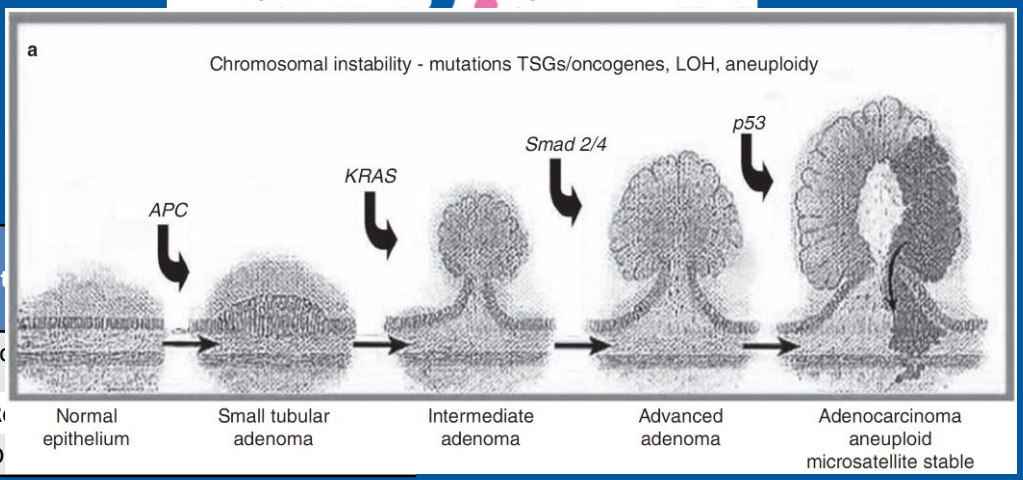
Colorectal cancer screening makes sense…





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Ahnen DJ, Am J Gastroenterol 2011;106 :190-8

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Reasons Why Colonoscopy Might Not Be The Best or Only Screening Test

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Reasons Why Colonoscopy Might Not Be The Best or Only Screening Test

- Risk/Benefit
- Polyps
- An imperfect 'gold standard'

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If 100 asymptomatic adults undergo screening colonoscopy how many can benefit?

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What is the lifetime risk of colorectal cancer?

Sex	% Diagnosis	% Death
Male	4.3 (1 in 23)	1.7 (1 in 59)
Female	3.9 (1 in 26)	1.6 (1 in 63)

http://www.cancer.org/cancer/cancerbasics/lifetime-probability-of-developing-or-dying-from-cancer (accessed on 3/4/2021)

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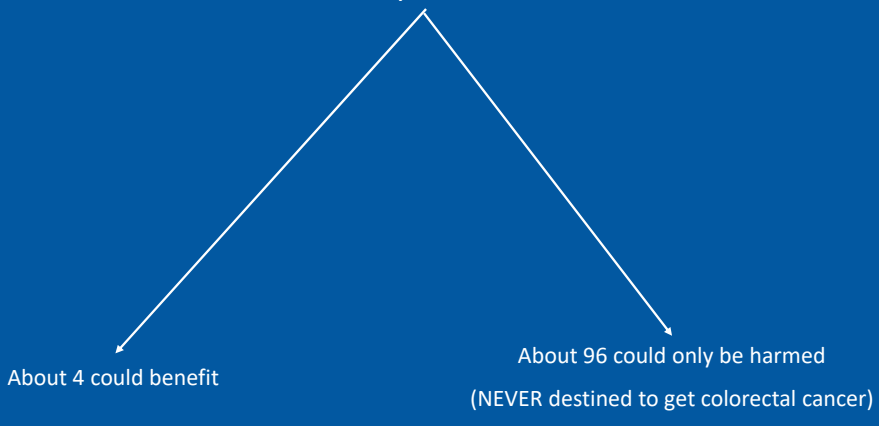
If 100 asymptomatic adults undergo screening colonoscopy how many can benefit?



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Reasons Why Colonoscopy Might Not Be The Best or Only Screening Test

- Risk/Benefit
- Polyps
- An imperfect 'gold standard'

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50% of the adult population has at least one adenoma!

- Randomized trial comparing chromocolonoscopy vs. white light endoscopy (N=660)
- Primary Outcome: Individuals with ≥1 adenoma

	≥ 1 adenoma	# adenomas per patient (mean)	# advanced adenomas per patient (mean)
Chromo	55.5%	1.3	.06
White Light	48.4%	1.1	.04

Kahi CJ et al, *Am J Gastroenterol* 2010; 105:1301–1307

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Reasons Why Colonoscopy Might Not Be The Best or Only Screening Test

- Risk/Benefit
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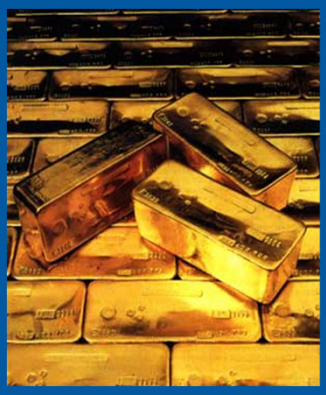

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Cancer After Colonoscopy In Those With Adenomas

- 'Pooling Project'
  - 8 large North American studies (N=9167)
  - Baseline colonoscopy with removal of ≥ 1 adenomas *and removal of all visualized lesions.*
  - Specified schedule of surveillance colonoscopies
    - Mean Follow up ~ 4 years
  - End-point data available on adenomas and colorectal cancers detected
    - Cancers Detected=58
    - Absolute Risk = 6/1000

Robertson DJ *et al Gut*. 2014 Jun;63(6):949-56

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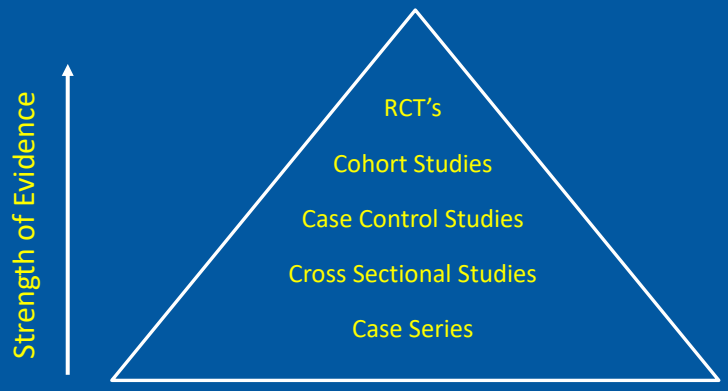
What is the strongest evidence for colorectal cancer screening?



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US based RCT's of CRC screening modalities

Site	Modality	Frequency	N	Follow-up (Years)	CRC Mortality Reduction
Mandel et al	Annual FOBT	Annual	46,551	13	33%
Schoen et al	Flexible Sig	Baseline & 3 or 5 years	154,900	11.2	26%

Mandel et al. *N Engl J Med* 1993:1365-71
Schoen et al. *J Natl Cancer Inst*. 2011:1310-22

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Colonoscopy & CRC Mortality-US Studies

Study	Population	Overall
Nishiara	Nurses & Physician Health Studies	0.32 (0.24, 0.45)
Baxter	SEER-Medicare	0.40 (0.37, 0.43)
Doubeni	Kaiser Permanente	0.33 (0.21, 0.52)
Kahi	US Veterans	0.39 (0.35, 0.43)

Nishiara R et al; *NEJM* 2013; 369:1095-1105
Baxter NN et al; *J Clin Oncol* 2012; 30:2664-2669
Doubeni CA et al; *Gut*. 2016;67(2):291-298
Kahi CH et al; *Annals Int Med* 2018 doi:10.7326/M17-0723

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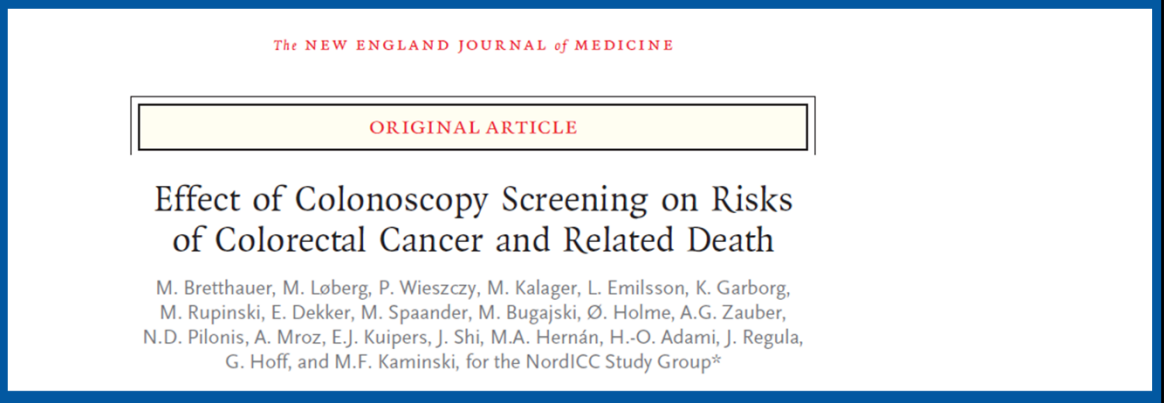
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

M. Bretthauer, M. Løberg, P. Wieszczy, 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*

Bretthauer et al, *N Engl J Med* 2022; 387:1547-1556

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Intention To Treat Analysis

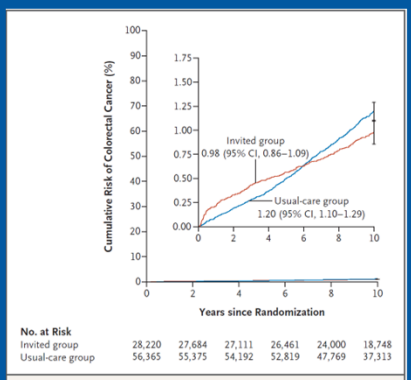

Figure 1. Cumulative Risk of Colorectal Cancer at 10 Years in Intention-to-Screen Analyses.

The inset shows the same data on an enlarged y axis. I bars indicate 95% confidence intervals.

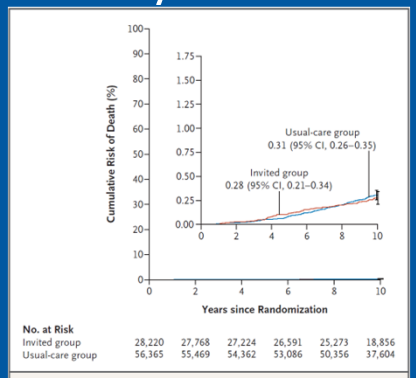

Figure 3. Cumulative Risk of Death from Colorectal Cancer at 10 Years in Intention-to-Screen Analyses.

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Table 2. Primary and Secondary End Points.

End Point	Invited Group		Usual-Care Group		Risk Difference (95% CI)	Risk Ratio (95% CI)
	Participants	10-Yr Risk (95% CI)	Participants	10-Yr Risk (95% CI)		
	number	*percent*	*number*	*percent*	*percentage points*	
Colorectal cancer	259	0.98 (0.86 to 1.09)	622	1.20 (1.10 to 1.29)	−0.22 (−0.37 to −0.07)	0.82 (0.70 to 0.93)
Death						
From colorectal cancer	72	0.28 (0.21 to 0.34)	157	0.31 (0.26 to 0.35)	−0.03 (−0.11 to 0.05)	0.90 (0.64 to 1.16)
From any cause	3036	11.03 (10.66 to 11.40)	6079	11.04 (10.78 to 11.30)	−0.01 (−0.47 to 0.44)	0.99 (0.96 to 1.04)

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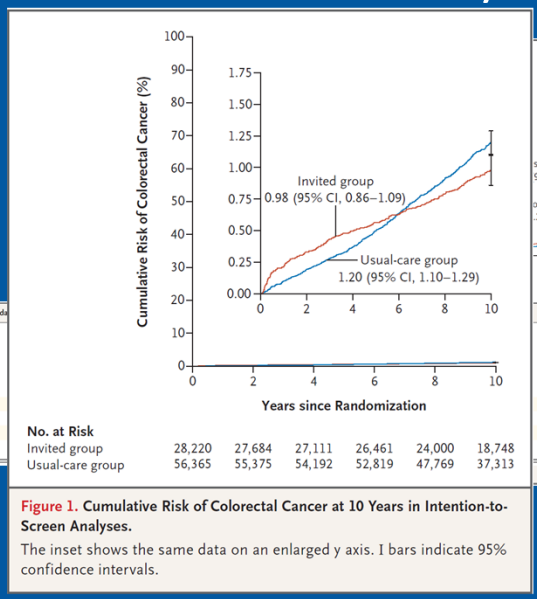
Intention To Treat Analysis



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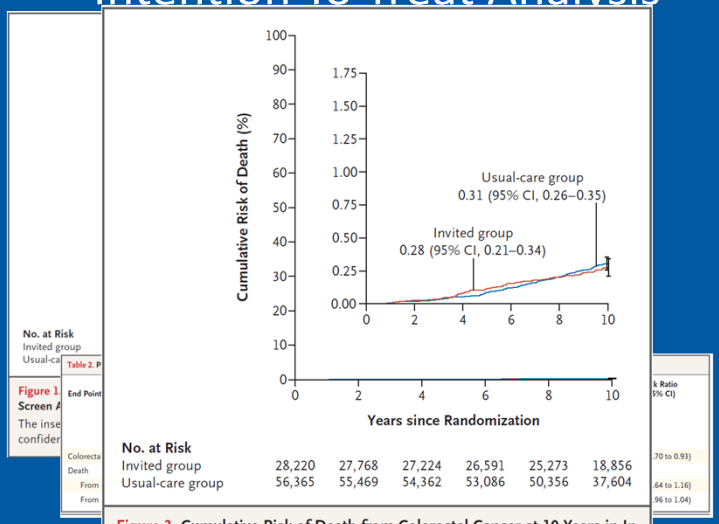

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Per Protocol

Outcome	Invitation to Screening		Control		
	Cases	10-year risk (%)	Cases	10-year risk (%)	Risk Ratio
CRC Incidence	102	0.84 (0.68, 1.00)	622	1.22 (1.13, 1.32)	0.69 (0.55, 0.83)
CRC Mortality	17	0.15 (0.09, 0.23)	157	0.30 (0.26, 0.36)	0.50 (0.27, 0.77)

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Bretthauer	Colonoscopy	Baseline	94,959 (Poland, Norway, Sweden)	10	10%

Mandel et al. *N Engl J Med* 1993:1365-71
Schoen et al. *J Natl Cancer Inst*. 2011:1310-22
Bretthauer et al, *N Engl J Med* 2022; 387:1547-1556

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JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Colorectal Cancer
US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

Recommended Strategies	Interval
High sensitivity FOBT or Fecal Immunochemical Test	Q 1 year
Stool DNA-FIT	Q1 to 3 years
Computed tomography colonography	Q 5 years
Flexible Sigmoidoscopy	Q 5 years
Flexible Sigmoidoscopy & FIT	FS q 10 & FIT annual
Colonoscopy	Q 10 years

Davidson MJ et al; JAMA 2021 Vol. 325 Issue 19 Pages 1965-1977

CONSENSUS GUIDELINE

Colorectal Cancer Screening: Recommendations for Physicians and Patients From the U.S. Multi-Society Task Force on Colorectal Cancer

Douglas K. Rex,[1] C. Richard Boland,[2] Jason A. Dominitz,[3] Francis M. Giardiello,[4] David A. Johnson,[5] Tonya Kaltenbach,[6] Theodore R. Levin,[7] David Lieberman,[8] and Douglas J. Robertson[9]

Table 4. Multi-Society Task Force Ranking of Current Colorectal Cancer Screening Tests

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 Gastroenterol* 2017 Vol. 112 Issue 7 Pages 1016-1030
Rex et al, *Gastroenterology* 2017 Vol. 153 Issue 1 Pages 307-323
Rex et al, *Gastrointest Endosc* 2017 Vol. 86 Issue 1 Pages 18-33

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Guideline

Thieme

Imaging alternatives to colonoscopy: CT colonography and colon capsule. European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) Guideline – Update 2020

ESGE ESGAR

Spada et all; Endoscopy 2020 Vol. 52 Issue 12 Pages 1127-1141

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CT Colonography

Features	Potential Drawbacks
Reasonable one-time sensitivity for cancer and advanced neoplasia (multiple studies)	Less reliable detection of medium sized (6-9 mm polyps) and serrated neoplasia
Some evidence of improved adherence relative to colonoscopy (COCOS)	Extracolonic findings & to a lesser degree radiation exposure
FDA indication for screening	

Capsule Endoscopy

Features	Potential Drawbacks
Reasonable one-time sensitivity for cancer and advanced neoplasia (fewer studies)	Significant bowel preparation required
Reasonable flat/serrated lesion detection	Longer read times-more difficult to accomplish same day colonoscopy
	No FDA indication for screening

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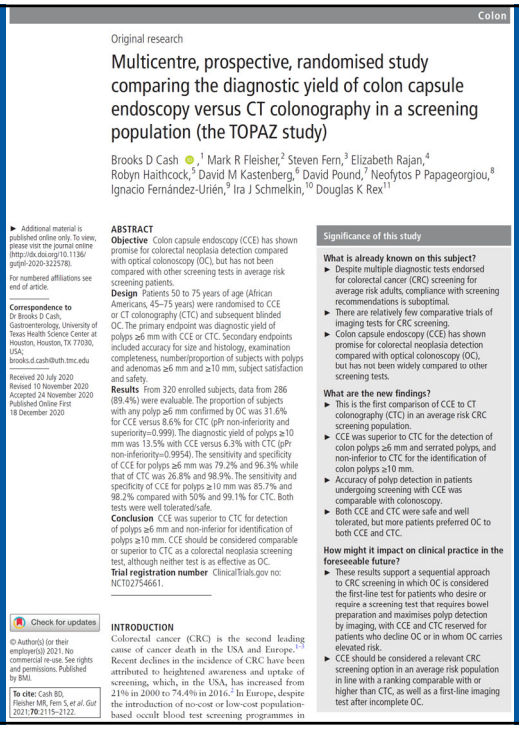

Colon

Original research

Multicentre, prospective, randomised study comparing the diagnostic yield of colon capsule endoscopy versus CT colonography in a screening population (the TOPAZ study)

Brooks D Cash ,[1] Mark R Fleisher,[2] Steven Fern,[3] Elizabeth Rajan,[4] Robyn Haithcock,[5] David M Kastenberg,[6] David Pound,[7] Neofytos P Papageorgiou,[8] Ignacio Fernández-Urién,[9] Ira J Schmelkin,[10] Douglas K Rex[11]

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2020-322578).

For numbered affiliations see end of article.

Correspondence to
Dr Brooks D Cash, Gastroenterology, University of Texas Health Science Center at Houston, Houston, TX 77030, USA;
brooks.d.cash@uth.tmc.edu

Received 20 July 2020
Revised 10 November 2020
Accepted 24 November 2020
Published Online First 18 December 2020

ABSTRACT

Objective Colon capsule endoscopy (CCE) has shown promise for colorectal neoplasia detection compared with optical colonoscopy (OC), but has not been compared with other screening tests in average risk screening patients.

Design Patients 50 to 75 years of age (African Americans, 45–75 years) were randomised to CCE or CT colonography (CTC) and subsequent blinded OC. The primary endpoint was diagnostic yield of polyps ≥6 mm with CCE or CTC. Secondary endpoints included accuracy for size and histology, examination completeness, number/proportion of subjects with polyps and adenomas ≥6 mm and ≥10 mm, subject satisfaction and safety.

Results From 320 enrolled subjects, data from 286 (89.4%) were evaluable. The proportion of subjects with any polyp ≥6 mm confirmed by OC was 31.6% for CCE versus 8.6% for CTC (pPr non-inferiority and superiority=0.999). The diagnostic yield of polyps ≥10 mm was 13.5% with CCE versus 6.3% with CTC (pPr non-inferiority=0.9954). The sensitivity and specificity of CCE for polyps ≥6 mm was 79.2% and 96.3% while that of CTC was 26.8% and 98.9%. The sensitivity and specificity of CCE for polyps ≥10 mm was 85.7% and 98.2% compared with 50% and 99.1% for CTC. Both tests were well tolerated/safe.

Conclusion CCE was superior to CTC for detection of polyps ≥6 mm and non-inferior for identification of polyps ≥10 mm. CCE should be considered comparable or superior to CTC as a colorectal neoplasia screening test, although neither test is as effective as OC.

Trial registration number ClinicalTrials.gov no: NCT02754661.

Check for updates

To cite: Cash BD, Fleisher MR, Fern S, *et al*. *Gut* 2021;**70**:2115–2122.

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer death in the USA and Europe.[1 2] Recent declines in the incidence of CRC have been attributed to heightened awareness and uptake of screening, which, in the USA, has increased from 21% in 2000 to 74.4% in 2016.[3] In Europe, despite the introduction of no-cost or low-cost population-based occult blood test screening programmes in

Significance of this study

What is already known on this subject?
- Despite multiple diagnostic tests endorsed for colorectal cancer (CRC) screening for average risk adults, compliance with screening recommendations is suboptimal.
- There are relatively few comparative trials of imaging tests for CRC screening.
- Colon capsule endoscopy (CCE) has shown promise for colorectal neoplasia detection compared with optical colonoscopy (OC), but has not been widely compared to other screening tests.

What are the new findings?
- This is the first comparison of CCE to CT colonography (CTC) in an average risk CRC screening population.
- CCE was superior to CTC for the detection of colon polyps ≥6 mm and serrated polyps, and non-inferior to CTC for the identification of colon polyps ≥10 mm.
- Accuracy of polyp detection in patients undergoing screening with CCE was comparable with colonoscopy.
- Both CCE and CTC were safe and well tolerated, but more patients preferred OC to both CCE and CTC.

How might it impact on clinical practice in the foreseeable future?
- These results support a sequential approach to CRC screening in which OC is considered the first-line test for patients who desire or require a screening test that requires bowel preparation and maximises polyp detection by imaging, with CCE and CTC reserved for patients who decline OC or in whom OC carries elevated risk.
- CCE should be considered a relevant CRC screening option in an average risk population in line with a ranking comparable with or higher than CTC, as well as a first-line imaging test after incomplete OC.

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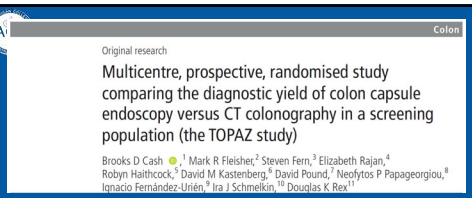

Colon

Original research

Multicentre, prospective, randomised study comparing the diagnostic yield of colon capsule endoscopy versus CT colonography in a screening population (the TOPAZ study)

Brooks D Cash ,[1] Mark R Fleisher,[2] Steven Fern,[3] Elizabeth Rajan,[4] Robyn Haithcock,[5] David M Kastenberg,[6] David Pound,[7] Neofytos P Papageorgiou,[8] Ignacio Fernández-Urién,[9] Ira J Schmelkin,[10] Douglas K Rex[11]

Modality	Proportion with polyps ≥ 6mm	Proportion with polyps ≥ 10 mm
Colon Capsule	42/133 (31.6%)	18/133 (13.5%)
CTC	11/128 (8.6%)	8/128 (6.3%)

N=286 evaluable participants

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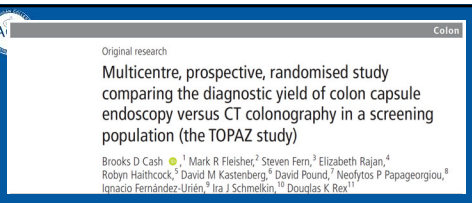
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N=286 evaluable participants

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Gastroenterology 2017;152:1217–1237

AGA SECTION

Recommendations on Fecal Immunochemical Testing to Screen for Colorectal Neoplasia: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer

Douglas J. Robertson,[1,2,*] **Jeffrey K. Lee**,[3,*] C. Richard Boland,[4] Jason A. Dominitz,[5] Francis M. Giardiello,[6] David A. Johnson,[7] Tonya Kaltenbach,[8] David Lieberman,[9] Theodore R. Levin,[10] and Douglas K. Rex[11]

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Advantages of FIT relative to Traditional FOBT

Biologic Advantage	Clinical Improvement
Directly measures human hemoglobin	• Highly sensitive for cancer even with single sample testing with some devices (**improved compliance**) • Maintains specificity even at higher levels of sensitivity (fewer false positive tests requiring definitive colon evaluation) • No need to adjust diet (**improved compliance**)

Robertson, DJ & Imperiale, TF; *Gastroenterology*. 2015;149(5):1286-93

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Advantages of FIT relative to Traditional FOBT

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Hemoglobin released from upper GI tract degraded in transit	• No need to adjust drug intake like NSAID's or anticoagulants (**improved compliance**) • Fewer false positives from the upper GI tract (i.e. improved specificity)

Robertson, DJ & Imperiale, TF; *Gastroenterology*. 2015;149(5):1286-93

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Advantages of FIT relative to Traditional FOBT

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Hemoglobin released from upper GI tract degraded in transit	• No need to adjust drug intake like NSAID's or anticoagulants (**improved compliance**) • Fewer false positives from the upper GI tract (i.e. improved specificity)
Hemoglobin measurement can be quantified	• Definition of a positive test can be matched to colonoscopy resources • Opportunity to use quantitative value to stratify risk
Hemoglobin measurement can be automated	• Reduces the likelihood that results are impacted by quality control issues • Facilitates high throughput (e.g. population based) screening efforts

Quantitative FIT

Robertson, DJ & Imperiale, TF; *Gastroenterology*. 2015;149(5):1286-93

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Advantages of FIT relative to Traditional FOBT

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Robertson, DJ & Imperiale, TF; *Gastroenterology*. 2015;149(5):1286-93

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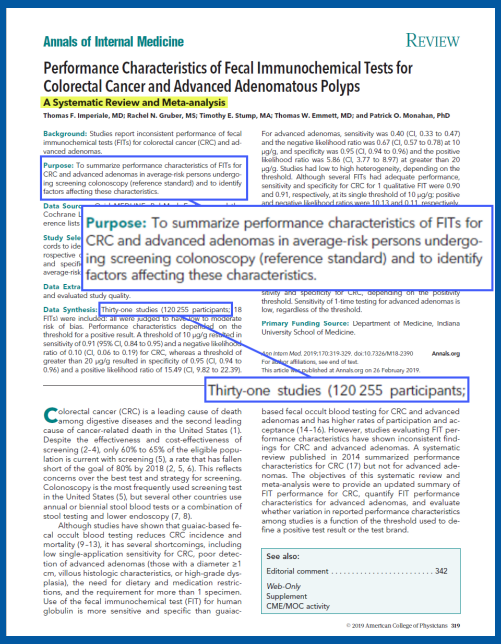

Annals of Internal Medicine REVIEW

Performance Characteristics of Fecal Immunochemical Tests for Colorectal Cancer and Advanced Adenomatous Polyps

A Systematic Review and Meta-analysis

Thomas F. Imperiale, MD; Rachel N. Gruber, MS; Timothy E. Stump, MA; Thomas W. Emmett, MD; and Patrick O. Monahan, PhD

Purpose: To summarize performance characteristics of FITs for CRC and advanced adenomas in average-risk persons undergoing screening colonoscopy (reference standard) and to identify factors affecting these characteristics.

Thirty-one studies (120 255 participants;

Imperiale et al, *Ann Intern Med* 2019 Vol. 170 Issue 5 Pages 319-329

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Test characteristics of FIT: Meta-analysis

FIT Threshold	Informative Studies	Outcome	Sensitivity	Specificity
20 µg/gm	14	Colorectal Cancer	0.75 (0.61, 0.86)	0.95 (0.92, 0.96)
20 µg/gm	15	Advanced Adenoma	0.25 (0.20, 0.31)	0.95 (0.93, 0.96)

Imperiale et al, *Ann Intern Med* 2019 Vol. 170 Issue 5 Pages 319-329

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Methylated genes
NDRG4
BMP3
KRAS

Hemoglobin

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FIT-Fecal DNA Test vs. FIT

	FIT-Fecal DNA Sensitivity	FIT Sensitivity
Cancer	92% (83-98)*	74% (62-84)
Advanced precancer	42% (39-46)**	24% (21-27)
Sessile serrated polyps ≥1cm	42%**	5%

N=9989
*p=0.002 **p<0.001

Imperiale et al NEJM 2014;370(14):1287

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FIT-Fecal DNA Test vs. FIT

	FIT-Fecal DNA Sensitivity	FIT Sensitivity
Cancer	92% (83-98)*	74% (62-84)
Advanced precancer	42% (39-46)**	24% (21-27)
Sessile serrated polyps ≥1cm	42%**	5%
	Specificity	Specificity
All nonadvanced lesions or normal exam	87% (86-87)**	95% (94-95)

N=9989
*p=0.002 **p<0.001

Imperiale et al NEJM 2014;370(14):1287

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Outline

- Does colorectal cancer screening work?
- Why consider strategies beyond colonoscopy?
- Non-invasive options
- Comparative effectiveness of most common strategies
- Colonoscopy vs FIT and FIT DNA
- FIT vs FIT DNA
- Future options including serology

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Comparative Effectiveness

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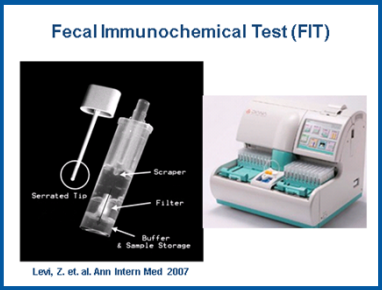
FIT vs. colonoscopy



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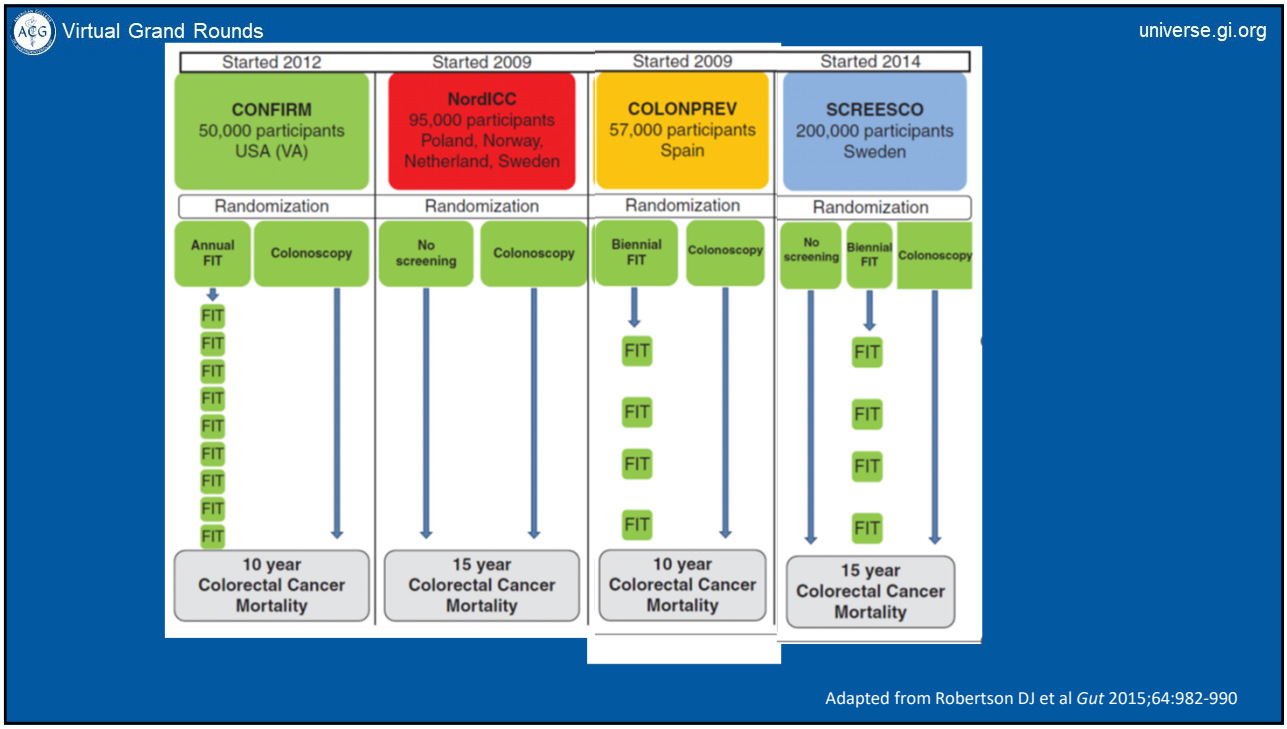
Virtual Grand Rounds
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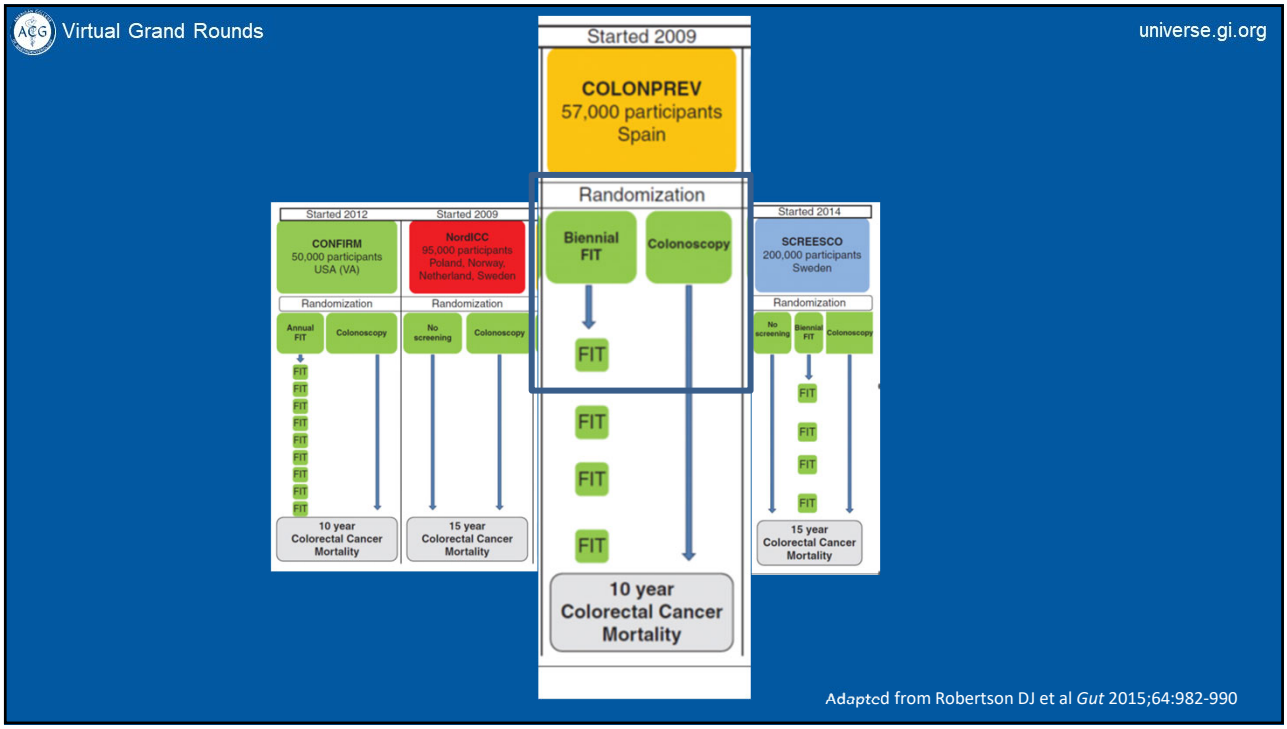
Started 2012
Started 2009
Started 2009
Started 2014
CONFIRM
50,000 participants
USA (VA)
NordICC
95,000 participants
Poland, Norway,
Netherland, Sweden
COLONPREV
57,000 participants
Spain
SCREESCO
200,000 participants
Sweden
Randomization
Randomization
Randomization
Randomization
Annual FIT
Colonoscopy
No screening
Colonoscopy
Biennial FIT
Colonoscopy
No screening
Biennial FIT
Colonoscopy
FIT
10 year Colorectal Cancer Mortality
15 year Colorectal Cancer Mortality
10 year Colorectal Cancer Mortality
15 year Colorectal Cancer Mortality
Adapted from Robertson DJ et al Gut 2015;64:982-990

57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Adapted from Robertson DJ et al Gut 2015;64:982-990

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Colonoscopy versus Fecal Immunochemical Testing in Colorectal-Cancer Screening

Enrique Quintero, M.D., Ph.D., Antoni Castells, M.D., Ph.D.,

	Colonoscopy (N=26,703)	FIT (N=26,599)
Participation		
Cancer Detection		
Advanced Adenoma		

N Engl J Med 2012;366:697

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Participation	24.6%	34.2%
Cancer Detection	30 (4 by crossover to FIT)	33 (1 by cross-over to colonoscopy)
Advanced Adenoma		

N Engl J Med 2012;366:697

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Advanced Adenoma	514	231

N Engl J Med 2012;366:697

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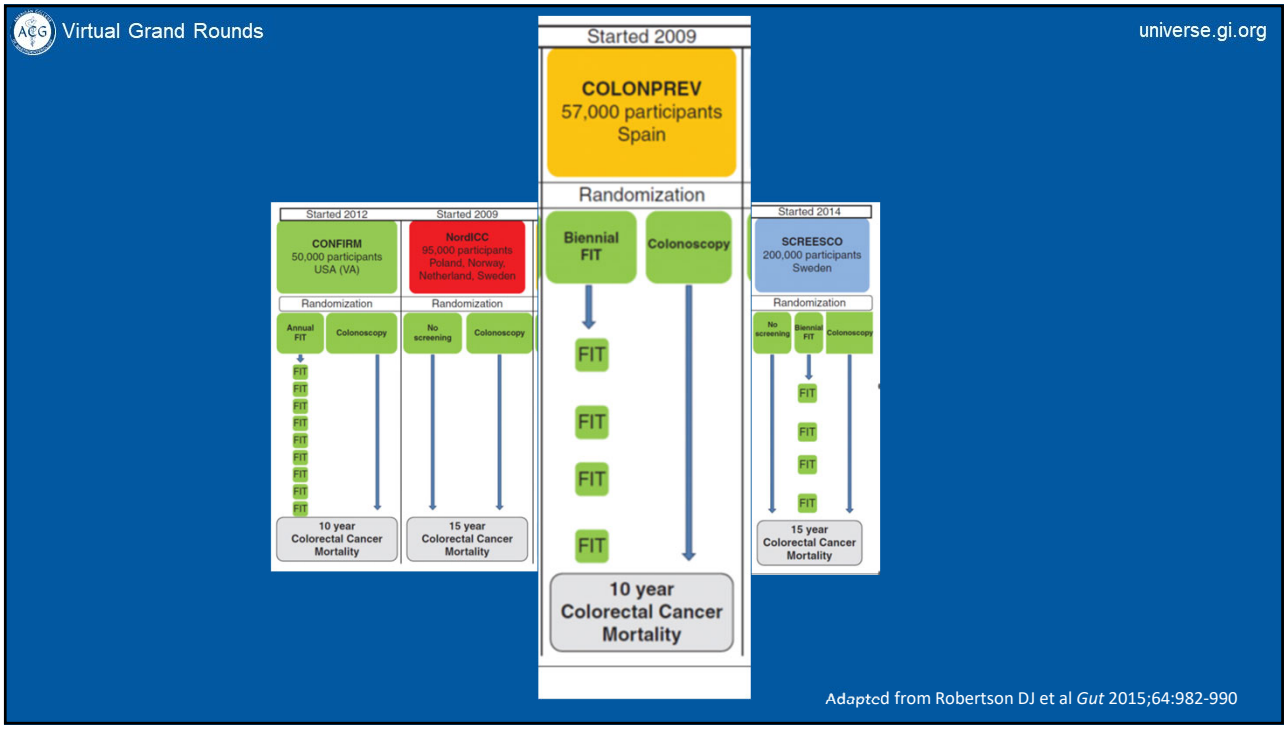
Virtual Grand Rounds
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Started 2009
COLONPREV
57,000 participants
Spain
Randomization
Biennial FIT
Colonoscopy
FIT
FIT
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FIT
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Annual FIT
Colonoscopy
10 year Colorectal Cancer Mortality
Started 2009
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Randomization
No screening
Colonoscopy
15 year Colorectal Cancer Mortality
Started 2014
SCREESCO
200,000 participants
Sweden
Randomization
No screening
Biennial FIT
Colonoscopy
15 year Colorectal Cancer Mortality
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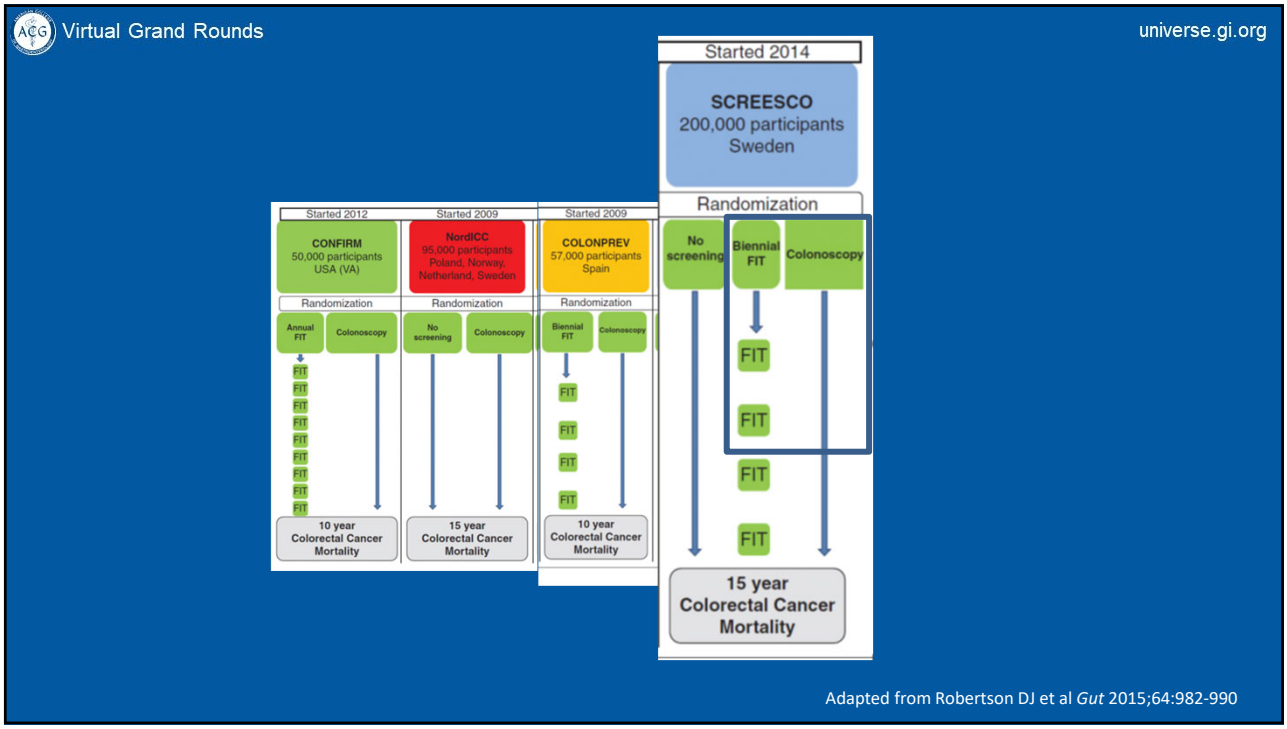
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Adapted from Robertson DJ et al Gut 2015;64:982-990

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Once-only colonoscopy or two rounds of faecal immunochemical testing 2 years apart for colorectal cancer screening (SCREESCO): preliminary report of a randomised controlled trial

.org

Intention To Screen Analysis

	Colonoscopy (N=31,400)	FIT (N=60,300)	Relative Risk
Participation	10,679 (35.1%)	33,383 (55.5%)†	NR
Cancer Detection			
Advanced Adenoma			

† % of those received a FIT (N=60,137)

Forsberg et al *Lancet Gastroenterol Hepatol* 2022;7:513-521

65

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Participation	10,679 (35.1%)	33,383 (55.5%)†	NR
Cancer Detection	49 (0.16%)	121 (0.20%)	0.78, 95% CI 0.56, 1.09
Advanced Adenoma			

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Forsberg et al Lancet Gastroenterol Hepatol 2022;7:513-521

66

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Participation	10,679 (35.1%)	33,383 (55.5%)†	NR
Cancer Detection	49 (0.16%)	121 (0.20%)	0.78, 95% CI 0.56, 1.09
Advanced Adenoma	637 (2.05%)	968 (1.61%)	**1.27,** **95 % CI 1.15, 1.41**

† % of those received a FIT (N=60,137)

Forsberg et al Lancet Gastroenterol Hepatol 2022;7:513-521

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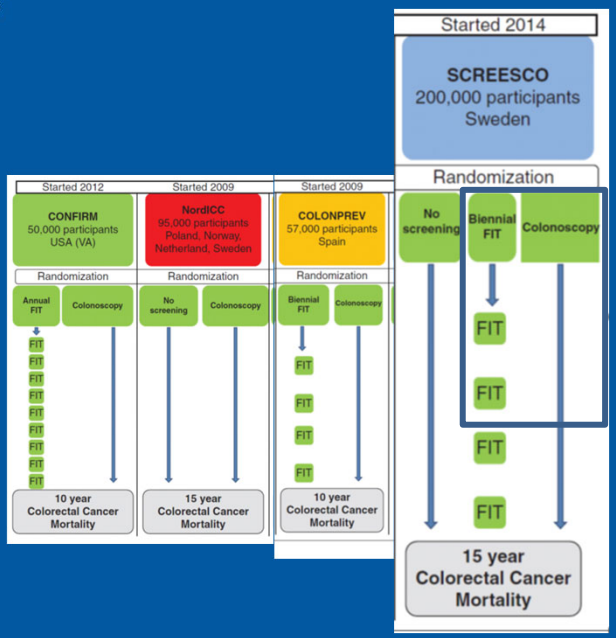

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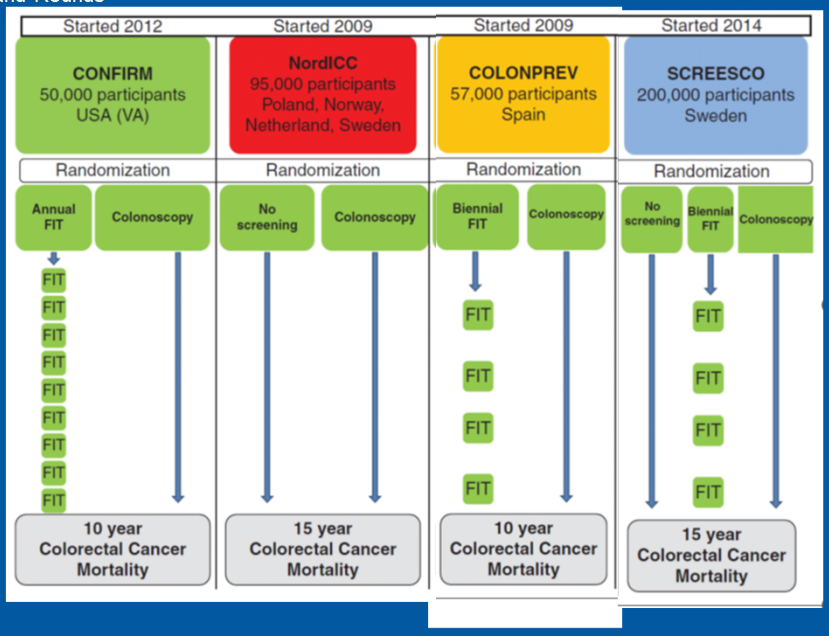

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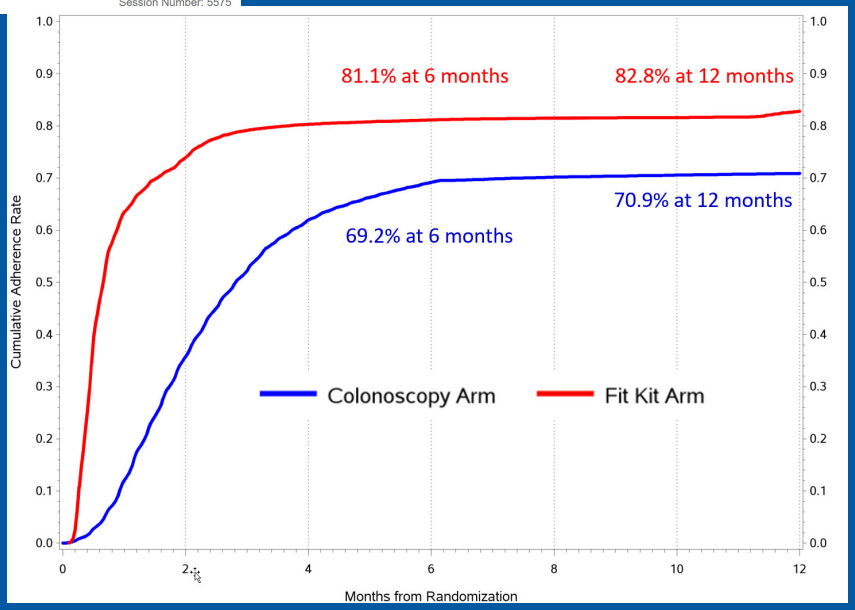
1258: COLONOSCOPY ADHERENCE IN A MULTI-CENTER STUDY OF COLORECTAL CANCER (CRC) SCREENING

Tue, May 09 W190a - McCormick Place

4:00pm - 4:15pm (Central) Session Number: 5575



CONFIRM

Dominitz JD & Robertson DJ et al; DDW Abstract 1258

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Comparative Effectiveness

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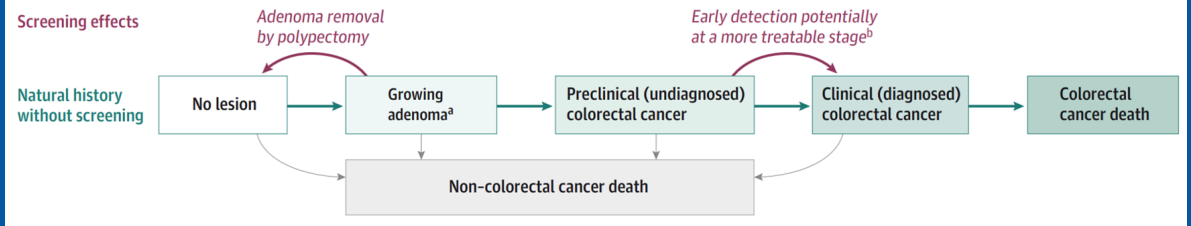
Comparative Effectiveness

Figure 1. Natural History of Colorectal Cancer and the Effects of Screening as Simulated by SimCRC, MISCAN, and CRC-SPIN



Adapted from Knudsen, AB et al *JAMA* 2021 Vol. 325 Issue 19 Pages 1998-2011

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[C] Benefit: CRC deaths averted per 1000 individuals screened*

Screening Modality and Frequency	CRC Deaths Averted* if Start Screening at Age 50 by Model and Average Across Models			
	SimCRC	CRC-SPIN	MISCAN	Average
Stool tests				
FIT 1y				
Direct visualization tests				
COL 10y				

[E] Burden: Lifetime number of colonoscopies per 1000 individuals screened*

Screening Modality and Frequency	Lifetime No. of Colonoscopies* if Start Screening at Age 50 by Model and Average Across Models			
	SimCRC	CRC-SPIN	MISCAN	Average
Stool tests				
FIT 1y				
Direct visualization tests				
COL 10y				

Adapted from Knudsen, AB et al *JAMA* 2021 Vol. 325 Issue 19 Pages 1998-2011

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[C] Benefit: CRC deaths averted per 1000 individuals screened*

Screening Modality and Frequency	CRC Deaths Averted* if Start Screening at Age 50 by Model and Average Across Models			
	SimCRC	CRC-SPIN	MISCAN	Average
Stool tests				
FIT 1y	27	24	23	25
Direct visualization tests				
COL 10y	29	26	25	27

[E] Burden: Lifetime number of colonoscopies per 1000 individuals screened*

Lifetime No. of Colonoscopies* if Start

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[E] Burden: Lifetime number of colonoscopies per 1000 individuals screened*

Screening Modality and Frequency	Lifetime No. of Colonoscopies* if Start Screening at Age 50 by Model and Average Across Models			
	SimCRC	CRC-SPIN	MISCAN	Average
Stool tests				
FIT 1y	1423	1619	1445	1496
Direct visualization tests				
COL 10y	3414	3500	3476	3464

Adapted from Knudsen, AB et al *JAMA* 2021 Vol. 325 Issue 19 Pages 1998-2011

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Screening Modality and Frequency	CRC Deaths Averted* if Start Screening at Age 50 by Model and Average Across Models			
	SimCRC	CRC-SPIN	MISCAN	Average
Stool tests				
FIT 1y	27	24	23	25
Direct visualization tests				
COL 10y	29	26	25	27

[E] Burden: Lifetime number of colonoscopies per 1000 individuals screened*

Screening Modality and Frequency	Lifetime No. of Colonoscopies* if Start Screening at Age 50 by Model and Average Across Models			
	SimCRC	CRC-SPIN	MISCAN	Average
Stool tests				
FIT 1y	1423	1619	1445	1496
Direct visualization tests				
COL 10y	3414	3500	3476	3464

In 1000 individuals a strategy of colonoscopy relative to FIT averts 2 death at a cost of roughly 2000 extra colonoscopy

Adapted from Knudsen, AB et al *JAMA* 2021 Vol. 325 Issue 19 Pages 1998-2011

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Table 4. Key Question 3: Summary of Serious Harms and Extracolonic Findings From Screening

Modality	Outcome	No. of studies	No. of participant	Events per 10 000 procedures (95% CI)
Screening colonoscopy	Serious bleeding	20	5 172 508	14.6 (9.4-19.9)
	Perforation	26	5 272 600	3.1 (2.3-4.0)

In 1000 individuals a strategy of colonoscopy relative to FIT averts 2 death at a cost of roughly 2000 extra colonoscopy

Adapted from Knudsen, AB et al *JAMA* 2021 Vol. 325 Issue 19 Pages 1998-2011& Lin, LA et al JAMA 2021 Vol. 325 Issue 19 Pages 1978-1998

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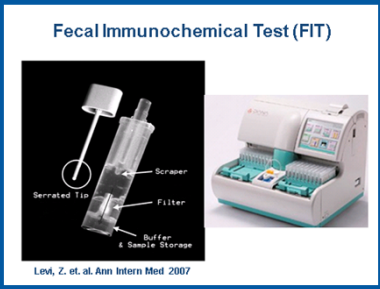
FIT vs. MT-DNA



How to use your Cologuard kit

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Figure 33. Benefits, Harms and Burden of Colorectal Cancer Screening Strategies Highlighted by the USPSTF in 2016 (With Screening From Ages 50 to 75 Years) and the Change in Outcomes When Screening Is Started at Age 45 Instead of At Age 50

[C] Benefit: CRC deaths averted per 1000 individuals screened*

Screening Modality and Frequency	CRC Deaths Averted* if Start Screening at Age 50 by Model and Average Across Models				Additional CRC Deaths Averted* if Start Screening at Age 45 by Model and Average Across Models			
	SimCRC	CRC-SPIN	MISCAN	Average	SimCRC	CRC-SPIN	MISCAN	Average
Stool tests								
FIT 1y	27	24	23	25	+1	+1	+0.6	+1
sDNA-FIT 1y	29	26	25	27	+1	+1	+0.6	+1
sDNA-FIT 3y†	26	23	22	24	+1	+1	+0.6	+1
Direct visualization tests								
COL 10y	29	26	25	27	+2	+1	+1	+1
CTC 5y	29	25	23	26	+1	+1	+0.5	+0.9
SIG 5y	25	22	23	23	+1	+0.9	+0.4	+0.9
SIG 10y + FIT	29	26	25	26	+1	+1	+0.9	+1

CRC Deaths Averted by Age to Begin Screening, Model Average

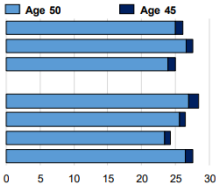

Figure 33. Benefits, Harms and Burden of Colorectal Cancer Screening Strategies Highlighted by the USPSTF in 2016 (With Screening From Ages 50 to 75 Years) and the Change in Outcomes When Screening Is Started at Age 45 Instead of At Age 50

[E] Burden: Lifetime number of colonoscopies per 1000 individuals screened*

Screening Modality and Frequency	Lifetime No. of Colonoscopies* if Start Screening at Age 50 by Model and Average Across Models				Additional Colonoscopies* if Start Screening at age 45 by Model and Average Across Models			
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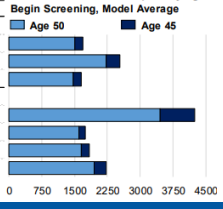

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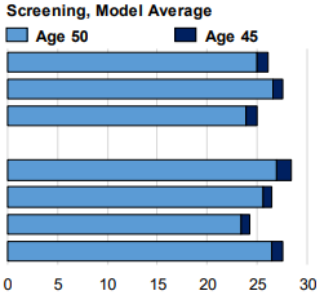

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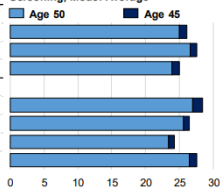

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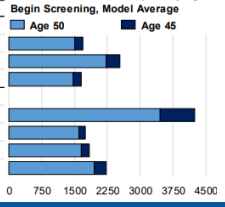

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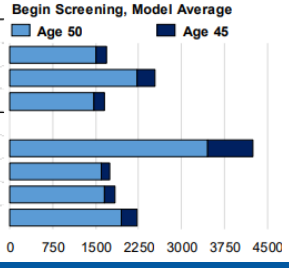

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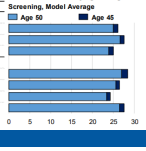

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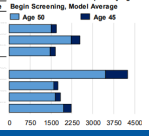

In 1000 individuals a strategy of FIT relative to MT-DNA averts 1 death at a cost of roughly 20 extra colonoscopy

Davidson MJ et al; *JAMA* 2021 Vol. 325 Issue 19 Pages 1965-1977

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How to use your Cologuard kit

In 1000 individuals a strategy of colonoscopy relative to FIT averts 2 death at a cost of roughly 2000 extra colonoscopy

In 1000 individuals a strategy of FIT relative to MT-DNA averts 1 death at a cost of roughly 20 extra colonoscopy

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Outline

- Does colorectal cancer screening work?
- Why consider strategies beyond colonoscopy?
- Non-invasive options
- Comparative effectiveness of most common strategies
- Colonoscopy vs FIT and FIT DNA
- FIT vs FIT DNA
- Future options including serology

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Future of Non-Invasive CRC Screening

- Modify current screening tests
- Modify approach to current screening tests
- Implement new screening tests

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Test characteristics of FIT: Meta-analysis

FIT Threshold	Informative Studies	Outcome	Sensitivity	Specificity
20 µg/gm	14	Colorectal Cancer	0.75 (0.61, 0.86)	0.95 (0.92, 0.96)
20 µg/gm	15	Advanced Adenoma	0.25 (0.20, 0.31)	0.95 (0.93, 0.96)

Imperiale et al, *Ann Intern Med* 2019 Vol. 170 Issue 5 Pages 319-329

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Adjusting FIT positivity threshold

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Imperiale et al, *Ann Intern Med* 2019 Vol. 170 Issue 5 Pages 319-329

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COLOGUARD® 2.0

Exact Sciences aims to build on the success of Cologuard® through the development of Cologuard 2.0, a stool DNA test with enhanced performance characteristics without losing the simplicity and convenience of an at-home test. The goals with Cologuard 2.0 are to increase test performance and further improve the patient experience to reinforce Cologuard as the best-in-class non-invasive screening option. Samples collected from the BLUE-C clinical trial will be used to establish the performance characteristics of Cologuard 2.0 and support a submission for FDA approval.

NCT 04144738

https://www.exactsciences.com/Pipeline-and-Data/Cologuard-2-0 accessed 5/13/2023

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Future of Non-invasive CRC Screening

- Modify current non-invasive screening tests
- Modify approach to current screening tests
- Implement new non-invasive screening tests

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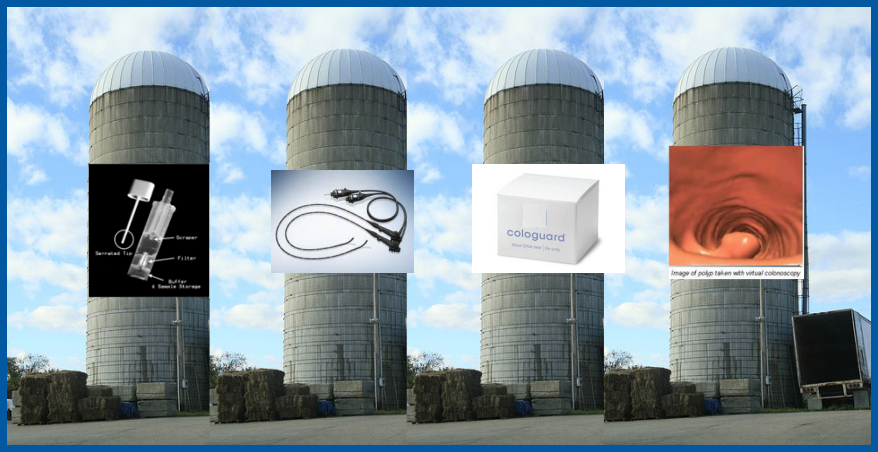
How We Generally Think About CRC Screening Options



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Risk Scores for Predicting Advanced Colorectal Neoplasia in the Average-risk Population: A Systematic Review and Meta-analysis

Le Peng, MM, PhD[1,2], Korbinian Weigl, MPH, PhD[1,2,3], Daniel Boakye, MPH, PhD[1,2] and Hermann Brenner, MD, MPH[1,3,4]

- 22 studies (17 original risk scores)
- Commonly included factors: age, sex, family history, BMI and smoking
- Area under the curve ranged from 0.62, 0.77

Score	Interpretation
0.5	No discrimination
0.7-0.8	Acceptable
0.8-0.9	Excellent
>0.9	Outstanding

Peng et al, *Am J Gastroenterol* 2018 Vol. 113 Issue 12 Pages 1788-1800
Mandrekar JN. *Journal of Thoracic Oncology*. 2010;5(9):1315-6

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A Risk-Scoring System Combined With a Fecal Immunochemical Test Is Effective in Screening High-Risk Subjects for Early Colonoscopy to Detect Advanced Colorectal Neoplasms

Han-Mo Chiu,[1] Jessica Y. L. Ching,[2] Kai Chun Wu,[3] Rungsun Rerknimitr,[4] Jingnan Li,[5]

- Applied the Asia Pacific Colorectal Screening Scoring System to asymptomatic individuals (n=5657)
  - 4434 based on lower risk score sent to FIT
    - *503* FIT positive
  - *1766* based on higher risk score sent to colonoscopy
- Using this approach, 71% with advanced neoplasia and **95% of those with cancer** underwent early colonoscopy

Gastroenterology. 2016;150(3):617-625

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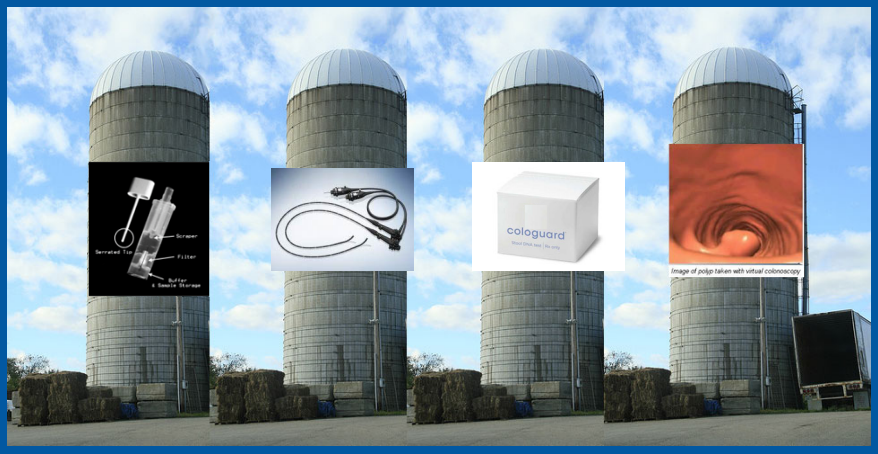
How We Generally Think About CRC Screening Options



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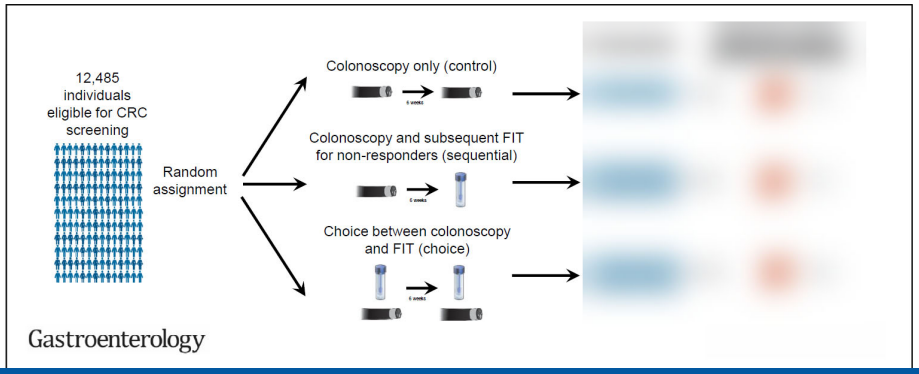
Participation in Competing Strategies for Colorectal Cancer Screening: A Randomized Health Services Study (PICCOLINO Study)

Nastazja Dagny Pilonis,[1,2] Marek Bugajski,[1,2] Paulina Wieszczy,[1,2] Maciej Rupinski,[1,2] Malgorzata Pisera,[1,2] Edyta Pawlak,[1] Jaroslaw Regula,[1,2] and Michal Filip Kaminski[1,2,3]

[1]The Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [2]Medical Center for Postgraduate Education, Warsaw, Poland; and [3]Institute of Health and Society, University of Oslo, Oslo, Norway



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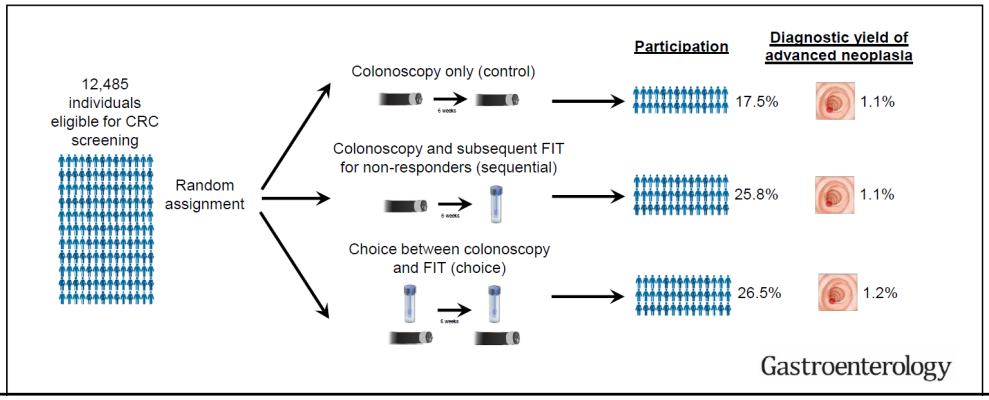

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Future of CRC Screening

- Modify current screening tests
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- Implement new screening tests

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Domain	Options
"Where"	**Blood** Stool Urine Breath
"What"	Genetic/Epigenetic Signals circulating tumor cells cell free DNA methylation micoRNA Germline markers low penetrance SNP's Volatile Organic Metabolites
"How"	Single vs Multi-marker panels AI/Deep Learning Reverse Transcriptase PCR Genome Wide Association Studies

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Table 1 | Representative genes commonly methylated and silenced in CRC

Gene	Protein	Function*	Effect of loss of function
APC	Adenomatous polyposis coli	Wnt signaling pathway inhibition	Increased Wnt/β-catenin signaling
MLH1	MutL homolog 1	DNA mismatch repair	Microsatellite instability
MGMT	O-6-methylguanine-DNA methyltransferase	Repair of alkylation DNA damage	Increased G>A mutation frequency
RASSF1A	Ras association domain family 1 (isoform A)	Negative RAS effector, proapoptotic, microtubule stabilization	Increased RAS/RAF/MAP kinase signaling, death-receptor-dependent apoptosis
SLC5A8	Sodium solute symporter family 5 member 8	Sodium and short chain fatty acid transporter, suppresses colony formation	Not known
RUNX3	Runt-related transcription factor 3	Transcription factor	Decreased TGF-β/BMP signaling
MINT1[‡]	Methylated in tumor locus 1	NA	NA
MINT31[‡]	Methylated in tumor locus 31	NA	NA
SFRP1	Secreted frizzled-related protein 1	Wnt antagonist	Increased Wnt/β-catenin signaling
SFRP2	Secreted frizzled-related protein 2	Wnt antagonist	Increased Wnt/β-catenin signaling
CDH1	E-cadherin	Calcium dependent cell–cell adhesion glycoprotein	Loss of cell adhesion, possible increased Wnt/β-catenin signaling
CDH13	Cadherin 13	Selective cell recognition and adhesion, antiapoptotic	Increased PI3K/Akt/mTOR signaling, MAPK signaling
CRABP1	Retinoic-binding protein 1	Carrier protein for transport of retinol, promotes apoptosis	Not known
CDKN2A/p16	Cyclin-dependent kinase inhibitor 2A	Regulates cell cycle G1 progression	Increased cell proliferation
HLTF	Helicase-like transcription factor	dsDNA translocase, fork remodeling activity, ubiquitin ligase	Impaired DNA repair
CDKN2A (P14, ARF)	p14(ARF)	Inhibits E3 ubiquitin ligase	Decreased p53 stabilization and activation
ESR1	Estrogen receptor 1	Ligand-activated transcription factor	Loss of estrogen receptor signaling
TIMP3	Tissue inhibitor of metalloproteinase 3	Inhibition of MMPs and ADAMs	Increased EGFR signaling, TNF signaling
CXCL12	Chemokine (CXC motif) ligand 12	Alpha chemokine	Increased tumor cell metastases
ID4	Inhibitor of DNA binding 4	Transcription factor	Not known
IRF8	Interferon regulatory factor 8	Transcription factor	Interferon signaling
THBS1/TSP1	Thrombospondin 1	Cell-to-cell and cell-to-matrix adhesive glycoprotein	Decreased TGF-β1 signaling
DAPK	Death associated protein kinase	Induction of cell death	Interferon gamma signaling, TNF alpha signaling, Fas/APO1 signaling
VIM	Vimentin	Stablizing cytoskeleton	No known biological effect
SEPT9	Septin 9	GTPase, formation of filaments	Impaired cytokinesis and loss of cell cycle control

*Many of these gene products have multiple functions. The listed function in this table is the one most commonly cited as the one responsible for CRC formation. ‡MINTs are 'methylated in tumor' loci, and are not specific genes. Abbreviations: ADAM, A Disintegrin and Metalloproteinase; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; TNF, tumor necrosis factor.

Figure adapted from Nat Rev Gastroenterol Hepatol. 2011 Oct 18;8(12):686-700.

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Sept 9 Serology PRESEPT Study

N=6874

Outcome	N detected by Sept 9	N Total in Population	Sensitivity
Cancer	27	53	50.9%
Cancer by Stage			
I	8	22	36.4%
II	8	14	57.1%
III	7	12	58.3%
IV	4	5	80.0%
Advanced Adenoma	30	314	9.6%
Nonadvanced Adenoma	16	209	7.7%

Detects only 50% of cancers with better detection of late stage cancer

Church et al, *Gut* 2014;63:317

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Blood Test Increases Colorectal Cancer Screening in Persons Who Declined Colonoscopy and Fecal Immunochemical Test: A Randomized Controlled Trial

Peter S. Liang,[1,2] Anika Zaman,[1,2] Anne Kaminsky,[1] Yongyan Cui,[2] Gabriel Castillo,[2] Craig T. Tenner,[1,2] Scott E. Sherman,[1,2] and Jason A. Dominitz[3,4]

[1]Department of Medicine, VA New York Harbor Health Care System, New York, New York; [2]Department of Medicine, NYU Langone Health, New York, New York; [3]Department of Medicine, VA Puget Sound Health Care System, Seattle, Washington; and [4]Department of Medicine, University of Washington School of Medicine, Seattle, Washington

BACKGROUND & AIMS: The septin 9 blood test is indicated for colorectal cancer screening in individuals who decline first-line tests, but participation in this context is unclear. We conducted a randomized controlled trial to compare reoffering colonoscopy and fecal immunochemical test (FIT) alone versus also offering the blood test among individuals who declined colonoscopy and FIT.

METHODS: Screen-eligible Veterans aged 50–75 years who declined colonoscopy and FIT within the previous 6 months were randomized to letter and telephone outreach to reoffer screening with colonoscopy/FIT only (control), or additionally offering the blood test as a second-line option (intervention). The primary outcome was completion of any screening test within 6 months. The secondary outcome was completion of a full screening strategy within 6 months, including colonoscopy for those with a positive noninvasive test.

RESULTS: Of 359 participants who completed follow-up, 9.6% in the control group and 17.1% in the intervention group completed any screening (7.5% difference; $P = .035$). Uptake of colonoscopy and FIT was similar in the 2 groups. The full screening strategy was completed in 9.0% and 14.9% in the control and intervention groups, respectively (5.9% difference; $P = .084$).

CONCLUSIONS: Among individuals who previously declined colonoscopy and FIT, offering a blood test as a secondary option increased screening by 7.5% without decreasing uptake of first-line screening options. However, completion of a full screening strategy did not increase. These findings indicate that a blood test is a promising method to improve colorectal cancer screening, but obtaining a timely colonoscopy after a positive noninvasive test remains a challenge (ClinicalTrials.gov number, NCT03598166).

P. S. Liang et al ; Clin Gastroenterol Hepatol 2023

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Blood Test Increases Colorectal Cancer Screening in Persons Who Declined Colonoscopy and Fecal Immunochemical Test: A Randomized Controlled Trial

Peter S. Liang,[1,2] Anika Zaman,[1,2] Anne Kaminsky,[1] Yongyan Cui,[2]
Gabriel Castillo,[2] Craig T. Tenner,[1,2] Scott E. Sherman,[1,2] and Jason A. Dominitz[3,4]

[1]Department of Medicine, VA New York Harbor Health Care System, New York, New York; [2]Department of Medicine, NYU Langone Health, New York, New York; [3]Department of Medicine, VA Puget Sound Health Care System, Seattle, Washington; and [4]Department of Medicine, University of Washington School of Medicine, Seattle, Washington

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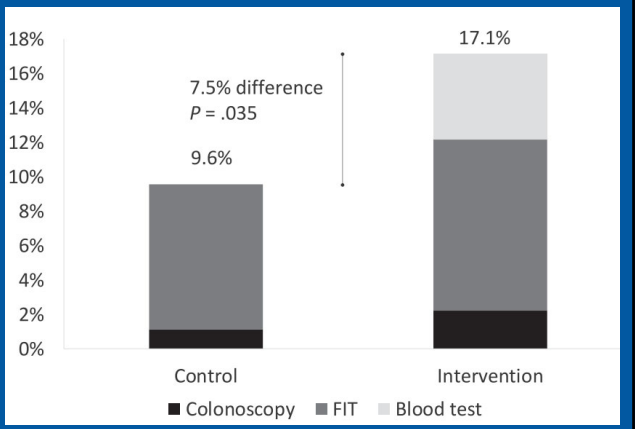

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Examples of Blood Based Tests in Development

Company/Test	Method (Name)	CRC vs. Multicancer	Current Trial	Comments
Freenome	Cell free DNA, protein/AI	CRC specific	PREEMPT NCT04369053	N=25000 with completion target 2022
Guardant	Circulating Tumor DNA (LUNAR)	CRC specific	ECLIPSE NCT04136002	N=10000 with target completion 2024
CancerSeek	Circulating Tumor DNA; Proteins	Multi-cancer	NCT04213326	Large Case/Control study with target completion 2022
GRAIL	Circulating Tumor DNA; Proteins	Multi-cancer	PATHFINDER NCT04241796	

A. Shaukat and T. R. Levin, *Nat Rev Gastroenterol Hepatol* 2022

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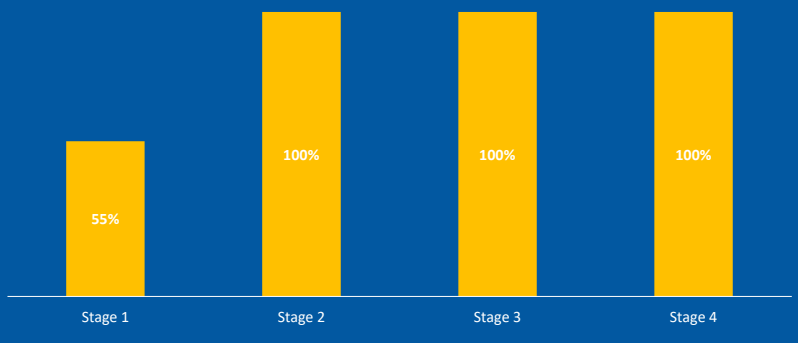
ECLIPSE (NCT 04136002) Cell Free DNA Serology



Overall Sensitivity for cancer = 80%

Overall Specificity for absence of cancer or advanced lesions = 90%

Overall Sensitivity for advanced lesions = 13%

Chung D et al; DDW abstract 913e

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Multi-cancer early detection tests (MCEDs)

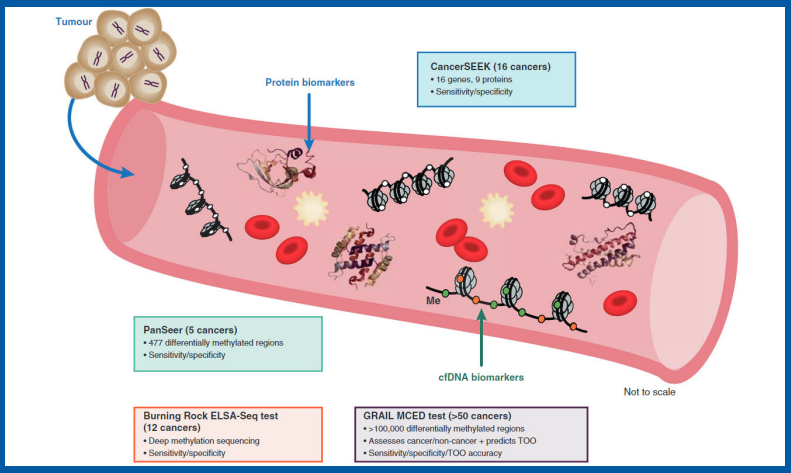

Image from Br J Cancer 2021 Vol. 124 Issue 9 Pages 1475-1477

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CANCER

Detection and localization of surgically resectable cancers with a multi-analyte blood test

- "CancerSEEK"
  - Uses PCR based assays to assess multiple regions of "driver genes" (circulating tumor DNA) commonly mutated in 8 cancer types
  - Combined with an immunoassay platform of 39 proteins known to be important in carcinogenesis
  - Applied in 1005 non metastatic cancer patients and 812 healthy controls

Cohen et al, *Science* 2018;359:926-930

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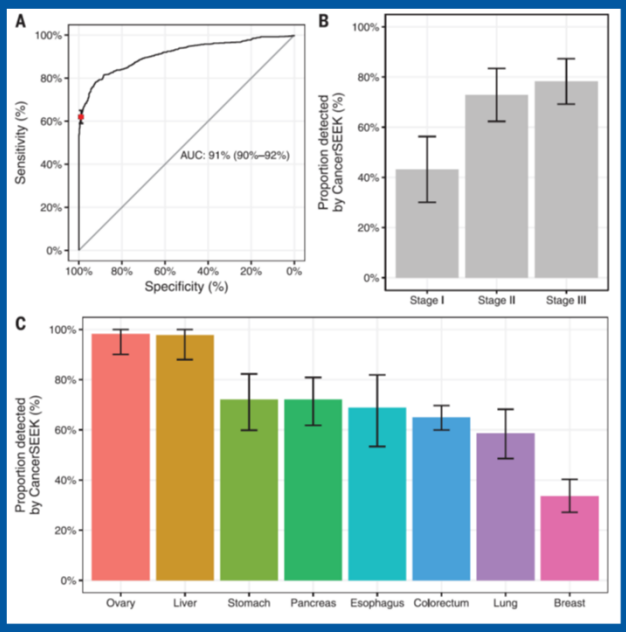

Cohen et al, *Science* 2018;359:926-930

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Pathfinder Study-NCT04241796

- Evaluate a MCED (> 50 cancer types) with a blood test incorporating cfDNA and machine learning
  - Outcomes include test characteristics and diagnostic testing burden
- Results
  - N=6621; 92 (1.7%) with a positive result
  - Within one year
    - 35/92 found with cancer

Diagnostic Testing	True Positives (N=35)	False Positives (N=57)
> 1 imaging test; %	90.9	93.0
> 1 invasive proc; %	81.8	29.8
Median time to resolution	57 days	162 days

Schrag, D., et al. Annals of Oncology 33 (2022): S961.

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Conclusions

- Colorectal cancer screening works
  - Randomized Controlled trials of Colonoscopy, FS and FOBT
- There are options beyond colonoscopy
- Comparative Effectiveness
  - A close call with trials coming
- Future of screening
  - Improvement in current tests, personalization and new blood-based options on the horizon

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Questions

Douglas J. Robertson, MD, MPH

T.R. Levin, MD, FACG

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Health and Nutrition Circle
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