Colorectal cancer screening: great opportunities and new challenges

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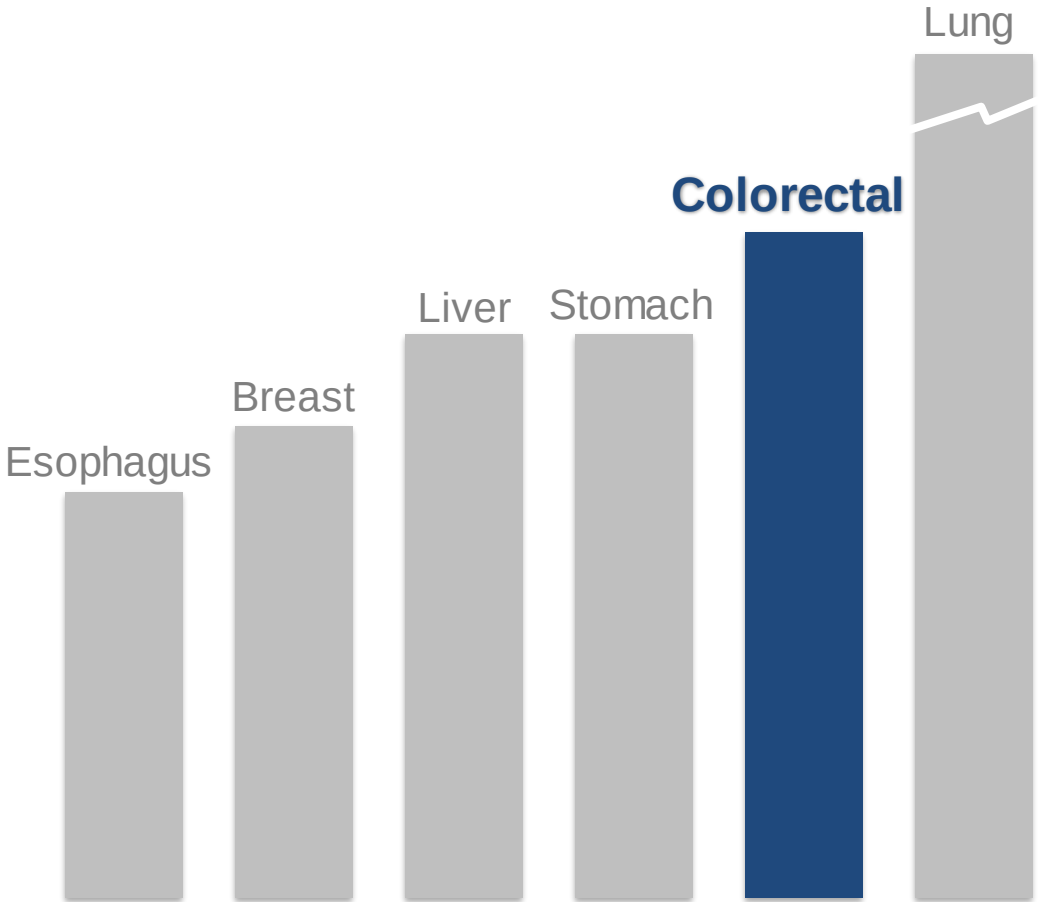
Colorectal cancer: second deadliest cancer

880,800
annual deaths

1,850,000
annual new diagnoses



GLOBOCAN 2018

Detecting CRC earlier is crucial

Diagnosed in stages I or II

9/10 survive 5 years

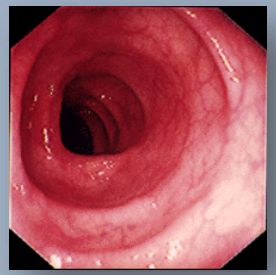
Diagnosed in stage IV

1/10 survives 5 years

SEER 18 2009-2015

Colorectal cancer natural history

Advanced colorectal neoplasm



Normal mucosa

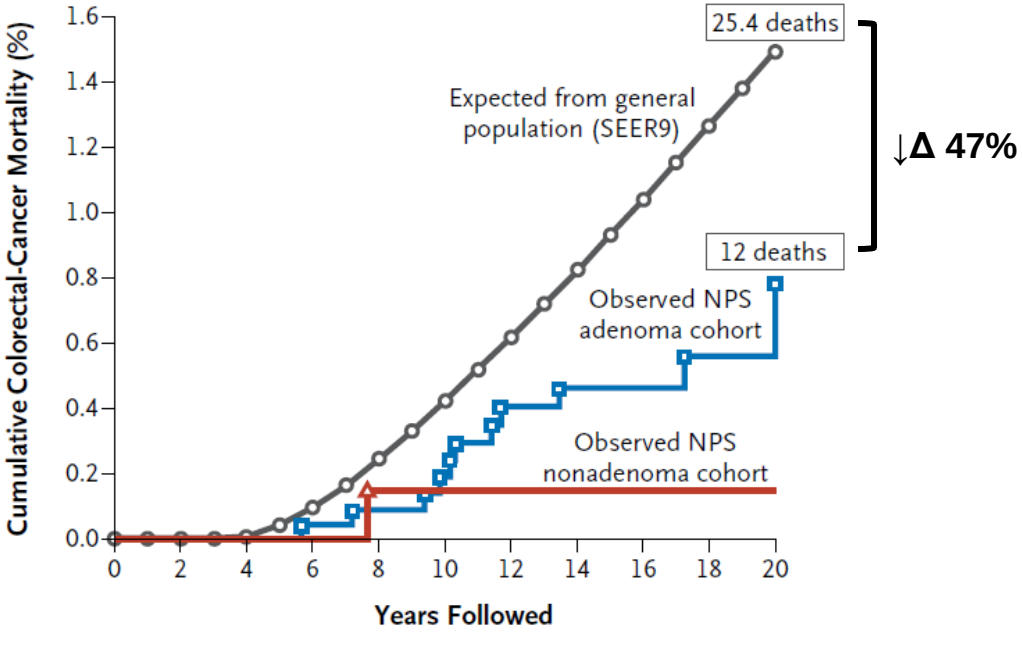
Non-advanced adenoma

Advanced adenoma

Colorectal cancer

≈10 years

Endoscopic polypectomy: CRC mortality

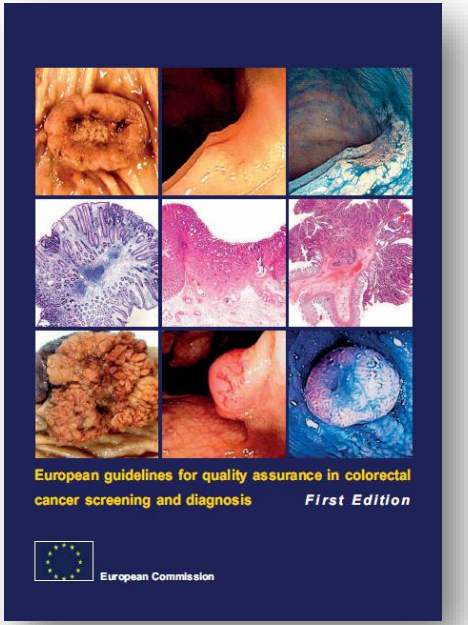


No. at Risk

Adenoma	2602	2358	2100	1808	1246	461
Nonadenoma	773	733	678	632	420	164

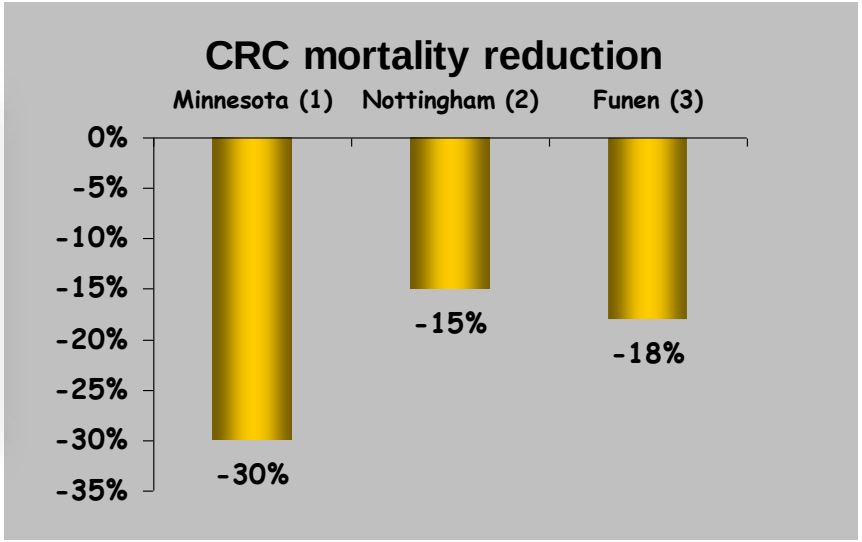
Zauber *et al.* NEJM 2012

Population-based scenario



"In order to maximize the impact of the intervention and ensure high coverage and equity of access, only **organized screening programs** should be implemented, **as opposed to case-finding or opportunistic screening**"

Screening in average-risk population: fecal occult blood testing (FOBT)

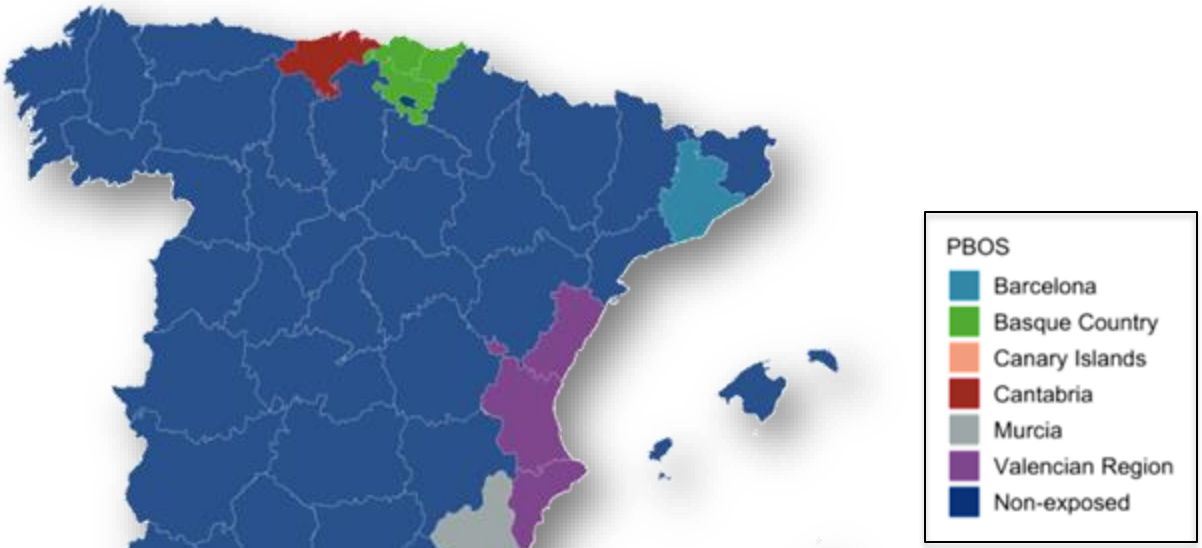


Evidence: 1a
Recommendation: A

[1]Mandel *et al.* NEJM 1993
[2]Hardcastle *et al.* Lancet 1996
[3]Kronborg *et al.* Lancet 1996

CRC screening implementation in Spain

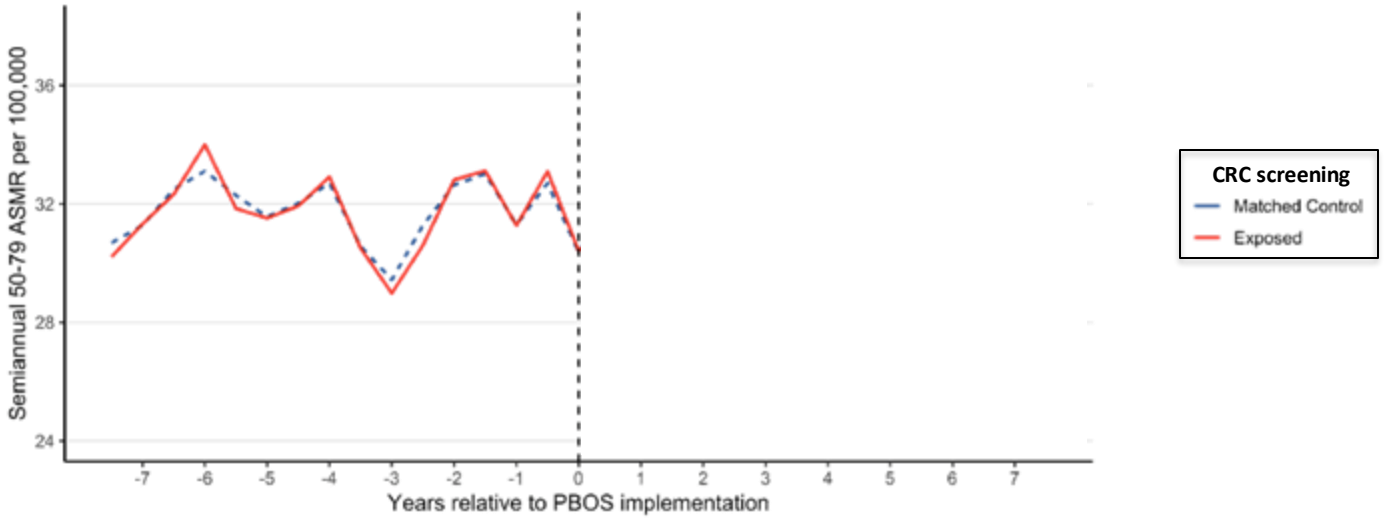
Provinces with population-based organized screening programs implemented prior to 2010



Serra-Burriel *et al*. Intl J Epidemiol 2020

Effect of CRC screening on CRC mortality

Average CRC age-standardized mortality rates (ASMR)
for population aged 50 to 79 with respect to screening implementation



Estimated changes on CRC ASMR per 100,000 inhabitants <u>at 7th year</u>
-2.94 (95% CI: -1.15, -4.73; p=0.0013; relative reduction -9.00%)

Serra-Burriel *et al*. Intl J Epidemiol 2020

Screening in average-risk population: colonoscopy

Screening in average-risk population: colonoscopy

Meta-analysis of 6 observational studies
(*per protocol* analysis)

	RR (95%CI)
CRC incidence	0.31 (0.12 - 0.77)
CRC mortality	0.32 (0.23 - 0.43)

Evidence: 2b
Recommendation: B

Brenner *et al.* BMJ 2014

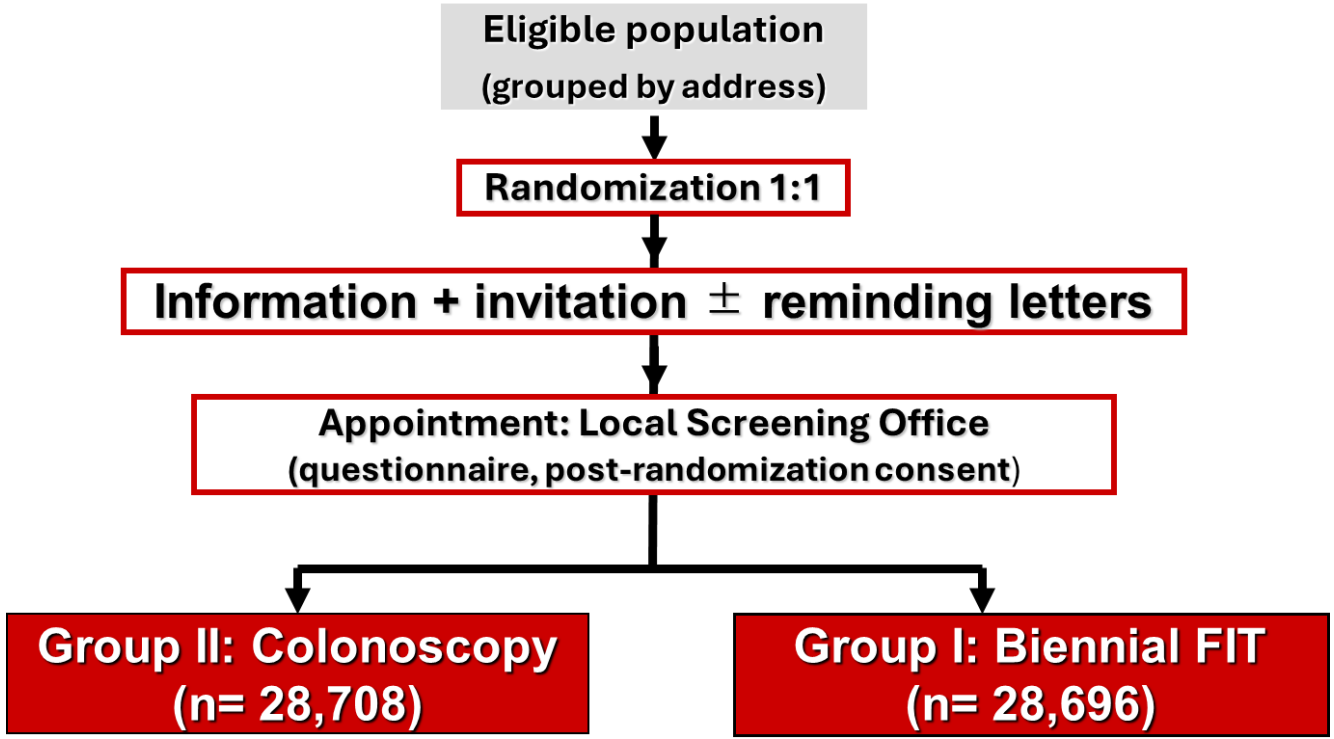
RCT on colonoscopy-based screening

- **NordICC study:**
  - Colonoscopy *vs.* usual care
  - Norway, Poland, The Netherlands, and Sweden

- **ColonPrev study:**
  - Colonoscopy *vs.* biennial FIT
  - Spain

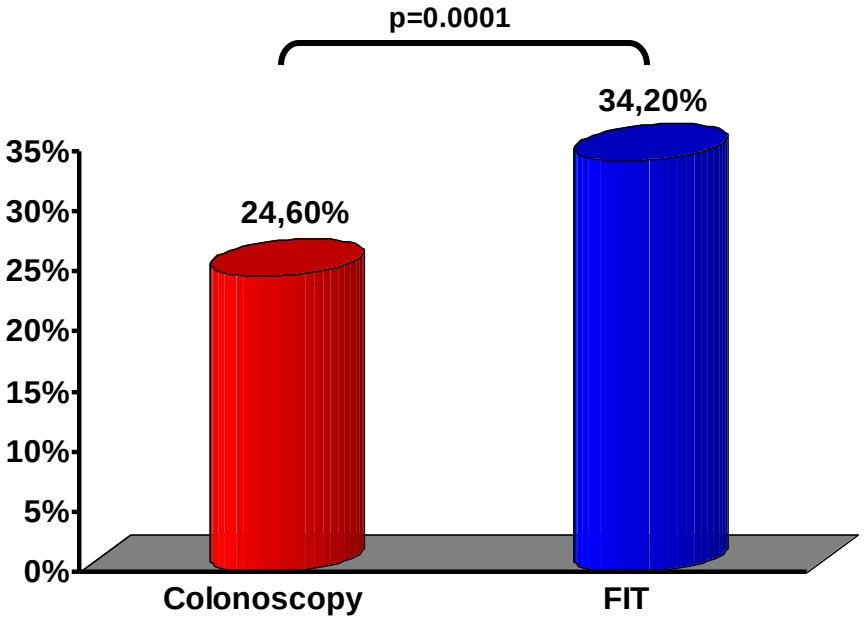
- **CONFIRM study:**
  - Colonoscopy *vs.* annual FIT
  - US (Veterans Administration)

The ColonPrev Study



Screening participation

(intention-to-screen analysis)

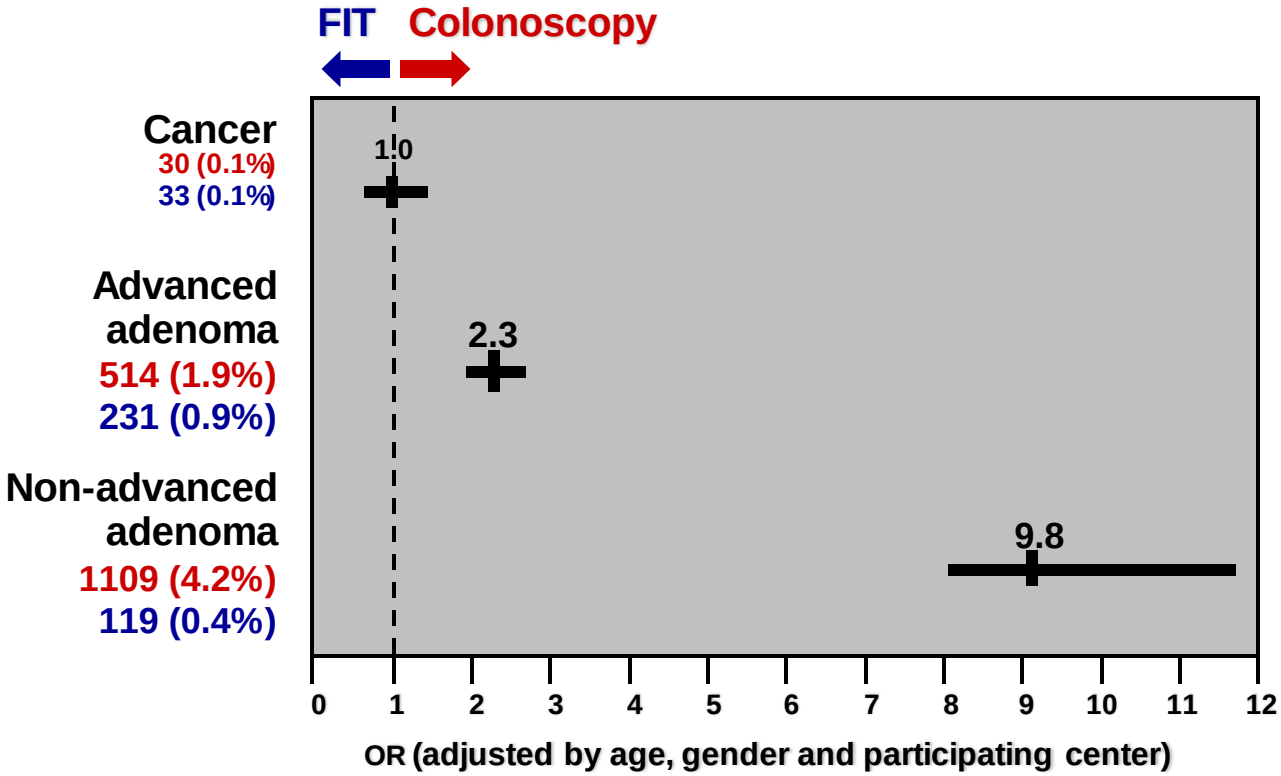


OR, 0.63 (95% CI, 0.60-0.65)

Quintero & Castells *et al*. NEJM 2012

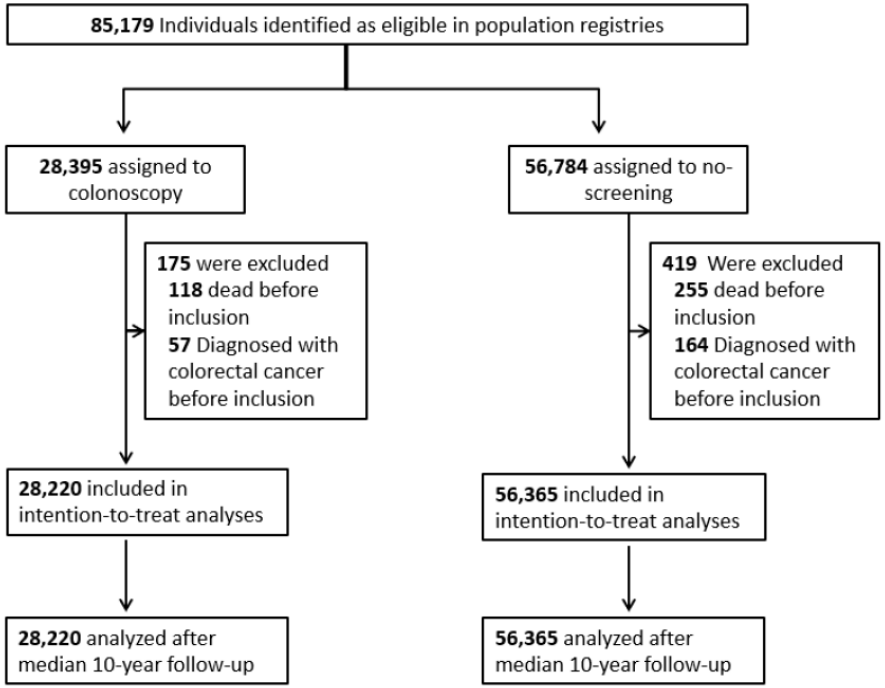
Diagnostic yield

(intention-to-screen analysis)



Quintero & Castells *et al*. NEJM 2012

The NordICC Study

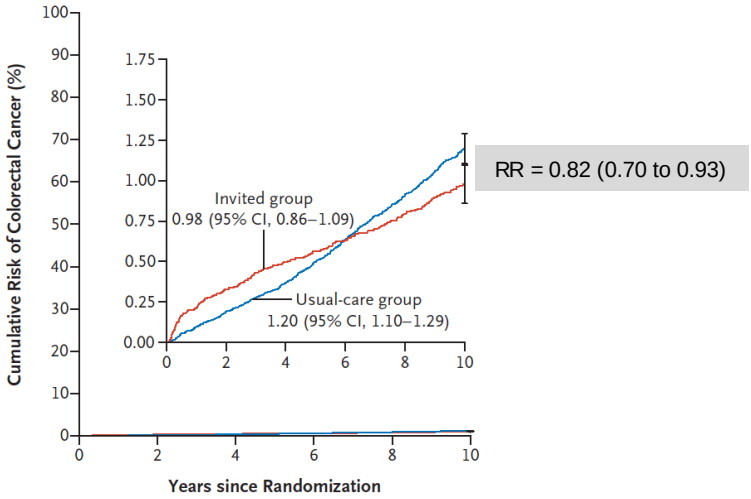


Bretthauer *et al*. NEJM 2022

The NordICC Study

Intention-to-screen analysis

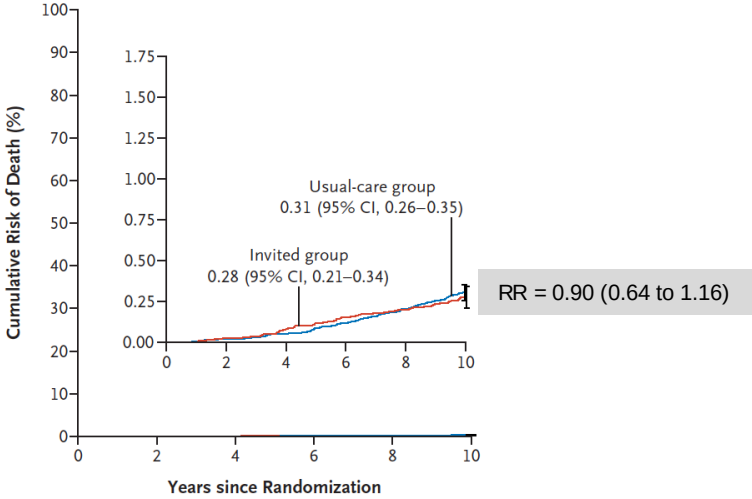
Incidence of CRC



RR = 0.82 (0.70 to 0.93)

No. at Risk						
Invited group	28,220	27,684	27,111	26,461	24,000	18,748
Usual-care group	56,365	55,375	54,192	52,819	47,769	37,313

CRC-related mortality



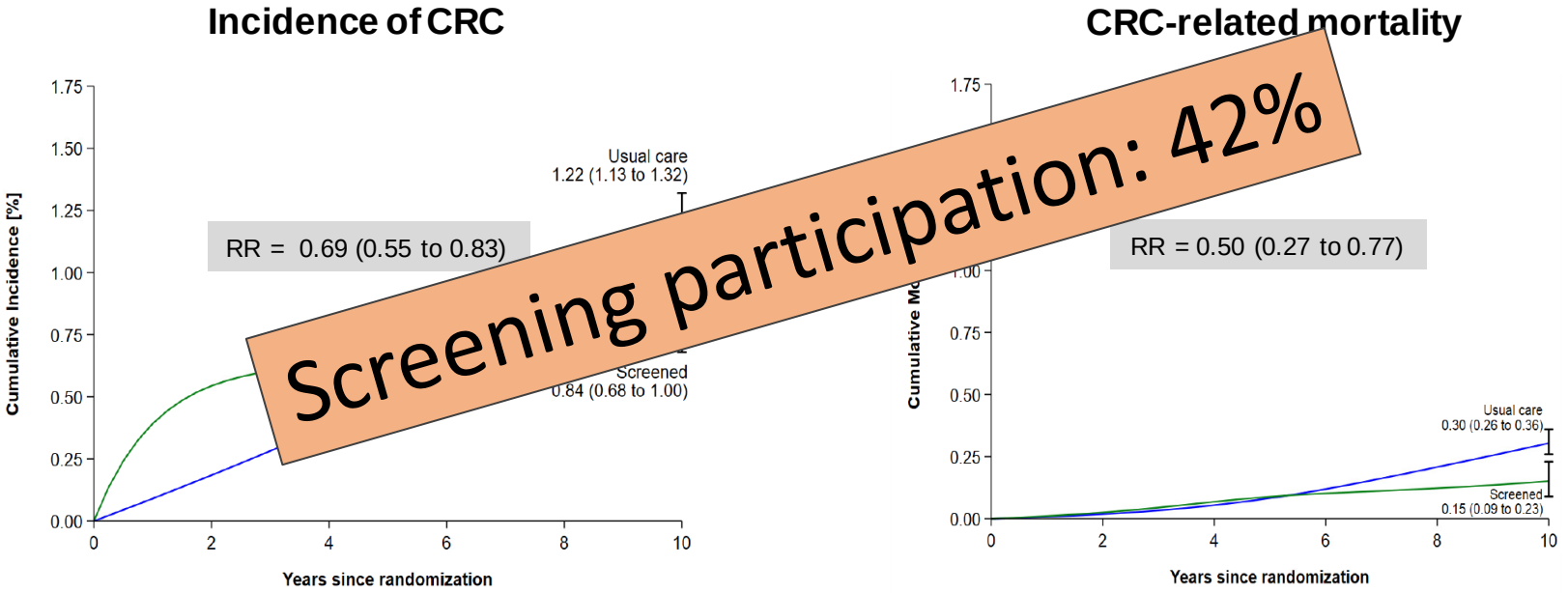
RR = 0.90 (0.64 to 1.16)

No. at Risk						
Invited group	28,220	27,768	27,224	26,591	25,273	18,856
Usual-care group	56,365	55,469	54,362	53,086	50,356	37,604

Bretthauer *et al*. NEJM 2022

The NordICC Study

Adjusted *per-protocol* analysis



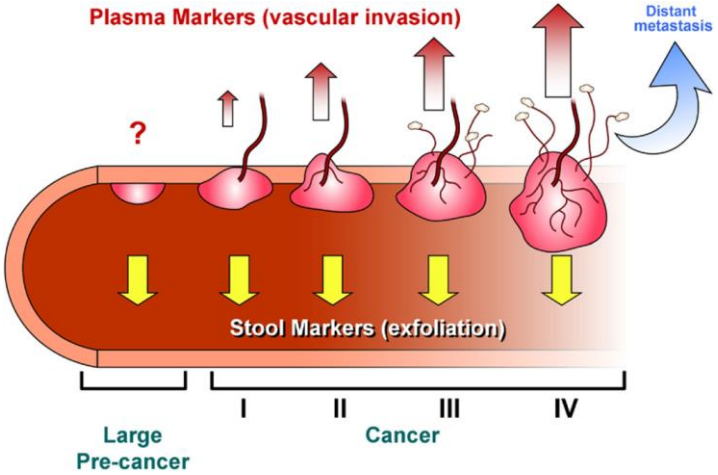
Bretthauer *et al*. NEJM 2022

Screening in a population-based scenario

Screening success = Test sensitivity x Compliance x Accessibility

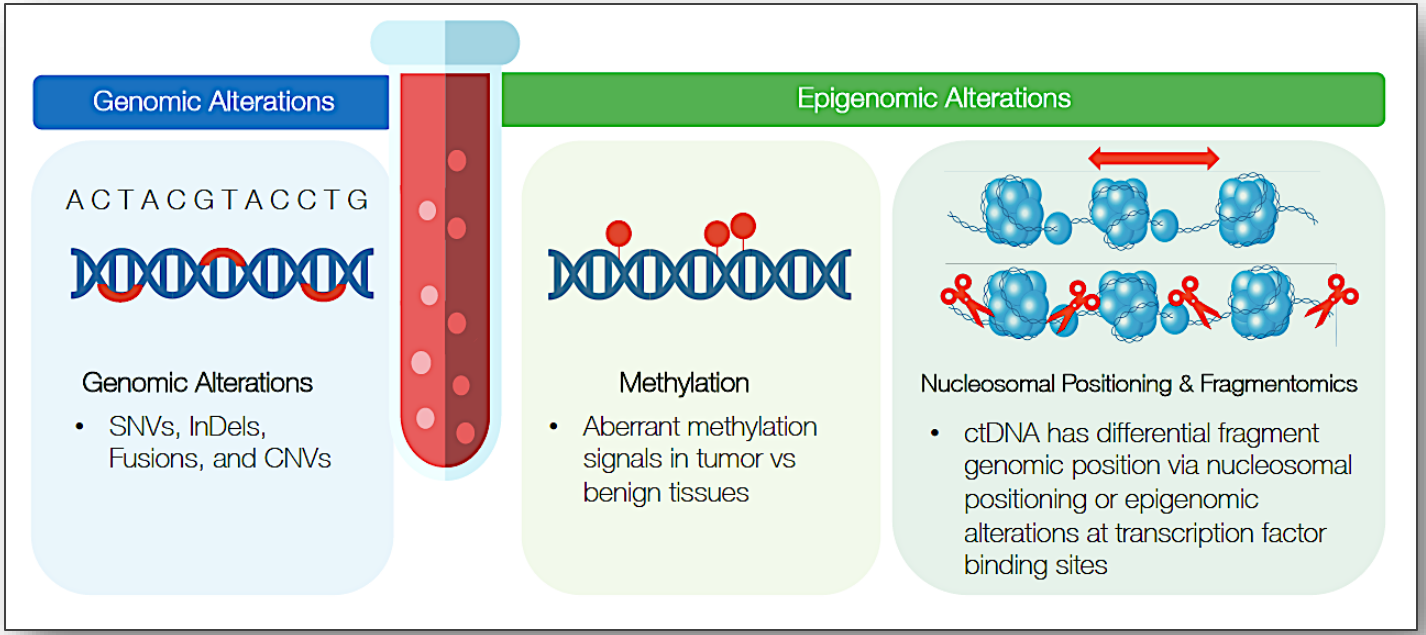
CRC molecular biomarkers

- The analysis of molecular markers representing the **genetic and epigenetic alterations associated with CRC** is an attractive strategy
- Exfoliation of neoplastic cells in the **feces** is a continuum process in patients with colorectal neoplasia
- Tumor cells and tumor markers also enter into the **blood** in patients with colorectal neoplasia



Ahlquist *et al*. Clin Gastroenterol Hepatol 2012

Multimodal ctDNA blood-based test



GUARDANT

Multimodal cfDNA blood-based CRC screening test (Eclipse study)

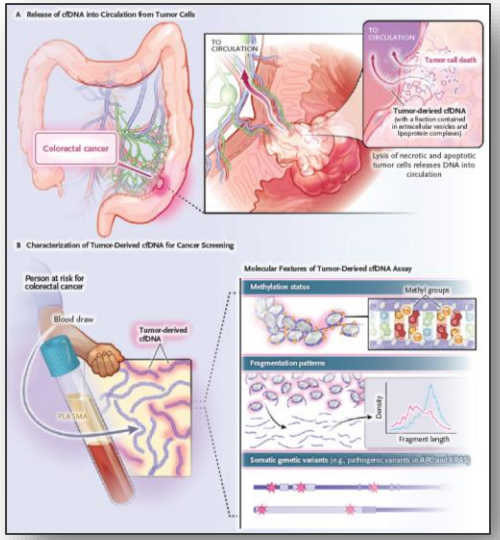


Table 2. Sensitivity and Specificity of the Cell-free DNA (cfDNA) Blood-Based Test for the Most Advanced Findings on Colonoscopy.*

Variable	Most Advanced Finding on Colonoscopy	cfDNA Blood-Based Test	
		Positive Test	Sensitivity (95% CI)
	no.	*no.*	%
Colorectal cancer			
Any	65	54	83.1 (72.2–90.3)
Stage I, II, or III*	48	42	87.5 (75.3–94.1)
Advanced precancerous lesions†	1116	147	13.2 (11.3–15.3)
			Specificity (95% CI)
Nonadvanced adenomas, nonneoplastic findings, and negative colonoscopy	6680	698	89.6 (88.8–90.3)
Nonneoplastic findings and negative colonoscopy	4514	457	89.9 (89.0–90.7)

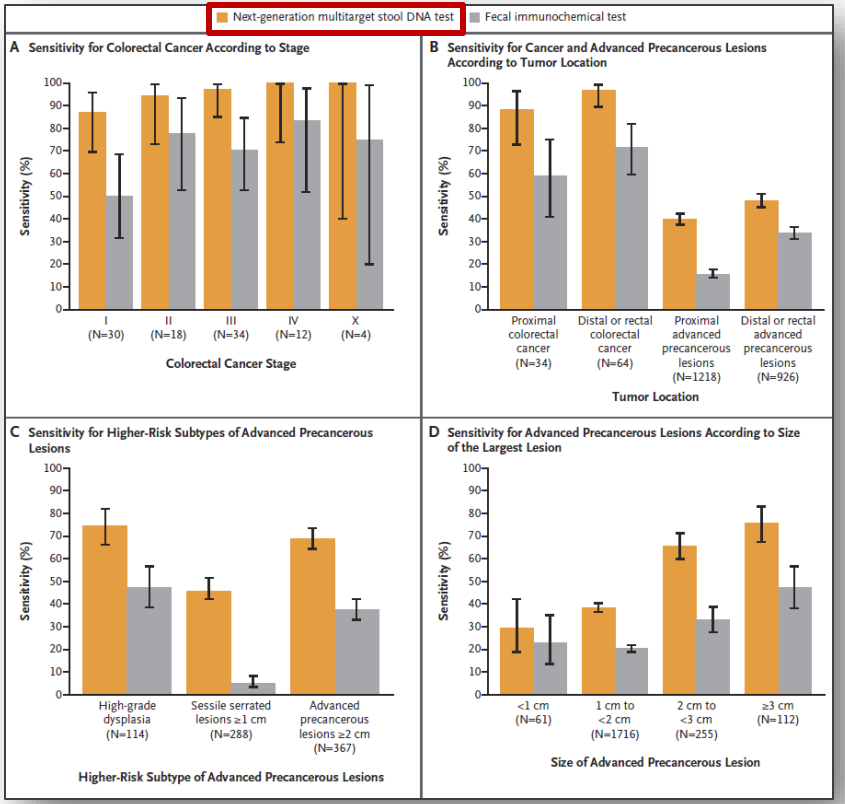
Chung *et al*. NEJM 2024

Screening in a population-based scenario

Screening success = Test sensitivity x Compliance x Accessibility

Fecal DNA testing (BLUE-C study)

Cologuard®



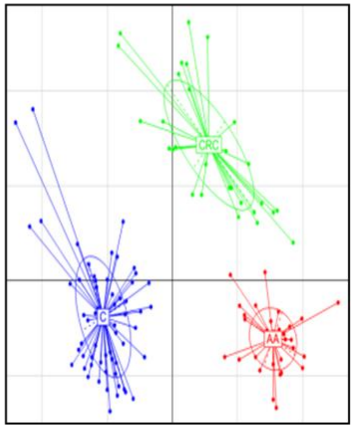
Imperiale *et al*. NEJM 2024

Fecal miRNA testing (miRFec study)

Discovery phase (tissue samples)

Patients undergoing surgical or endoscopic resection (CRC/AA)

NGS miRNA analysis (CRC, 30; AA, 32)



Selection of **21 miRNA** commonly up-regulated in both CRC and AA

Validation phase (fecal samples)

CRC, 11
AA, 28
N, 39

Technical validation

9 miRNA up-regulated in feces

Clinical validation

FIT-positive participants in CRC screening program

N, 217 | NAA, 136 | AA, 347 | CRC, 67

CRC+AA *vs.* N+NAA

- ↑ **miR-421**
- ↑ **miR-27a-3p**
- ↑ **miR-130b-3p**

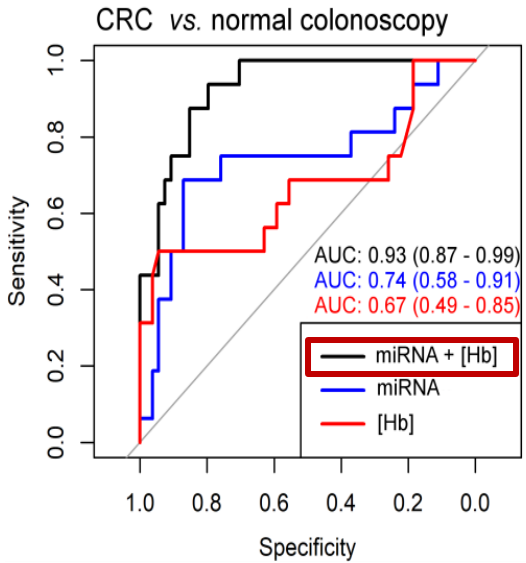
Duran-Sanchon *et al*. Gastroenterology 2020

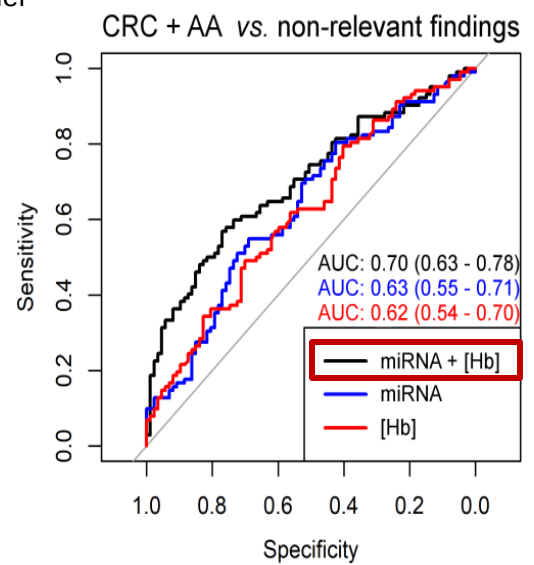
Fecal miRNA testing (miRFec study)

Fecal miRNA-based predictive model

Machine learning algorithm → Variables

- **miR-421**
- **miR-27a-3p**
- Fecal hemoglobin concentration
- Age
- Gender





Duran-Sanchon *et al*. Gastroenterology 2020

Summary

- **Fecal immunochemical testing** is an adequate approach for an organized screening program.
- **Colonoscopy** is the most accurate method for CRC screening, but its usefulness may be limited in a population-based scenario.
- Comparison of effectiveness of FIT- and colonoscopy-based screening in terms of **CRC mortality reduction** should wait the results of ongoing RCT.
- **Biomarker-based screening strategies** may improve CRC prevention: new-generation stool DNA/miRNA testing seems to offer better performance than FIT, whereas blood-based test may favor screening participation.

Conclusion

"The best test is the one that gets done."

Sidney Winawer, MD

Thank you for your attention!!!