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# The Next generation Cologuard test - will this stimulate its use in Europe?

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I have no conflicts of interest related to this presentation

I work with the organized screening programs in the Canton of Vaud,  
Switzerland

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# Original Cologuard

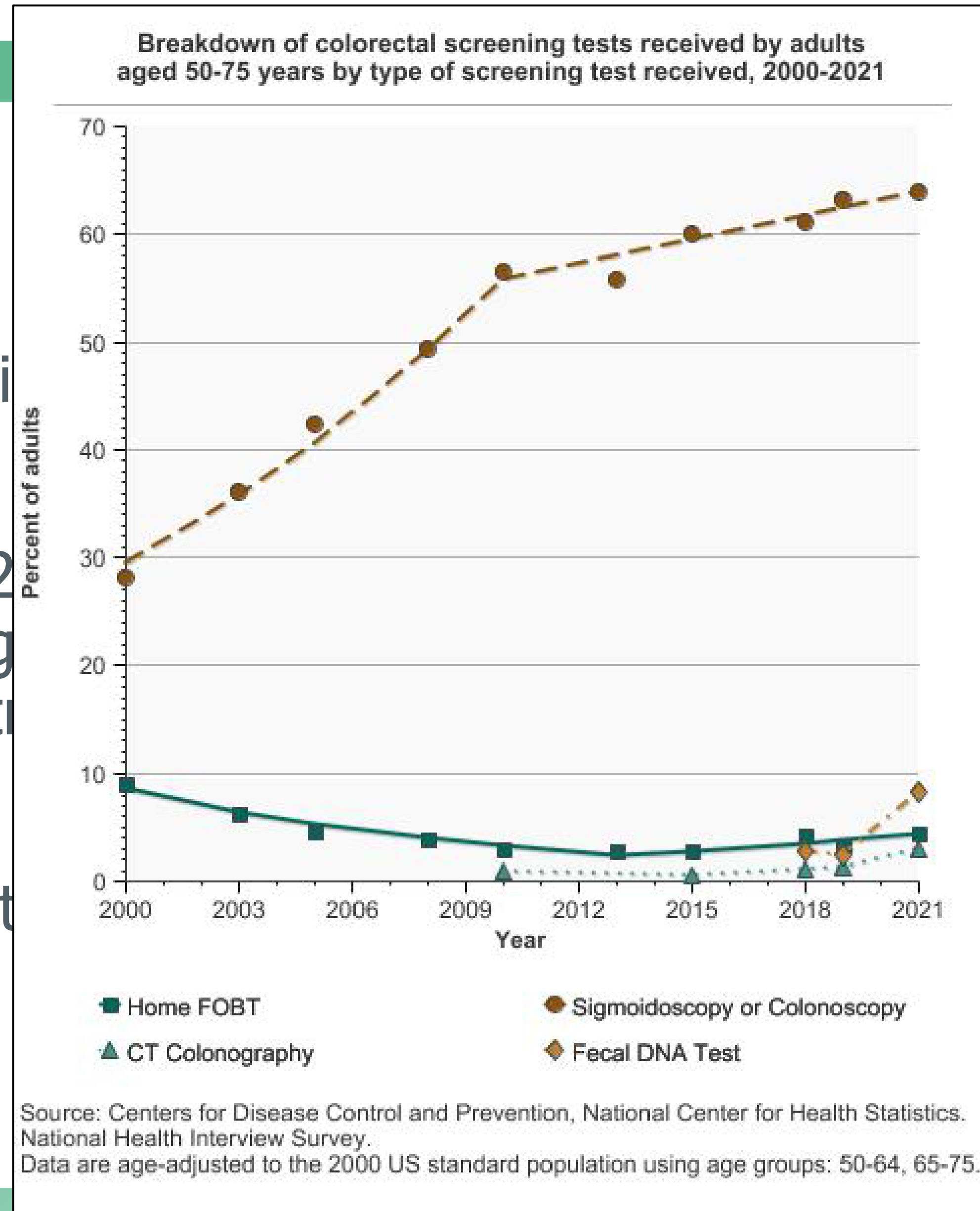
- Molecular assays for aberrantly methylated BMP3 and NDRG4 promoter regions, mutant KRAS, and  $\beta$ -actin (a reference gene for human DNA quantity)
- Combined with a proprietary logistic regression algorithm
- Collection of an entire bowel movement
- All tests processed centrally in Madison, Wisconsin
- Not currently available or approved for use outside the USA





# Original Cologuard

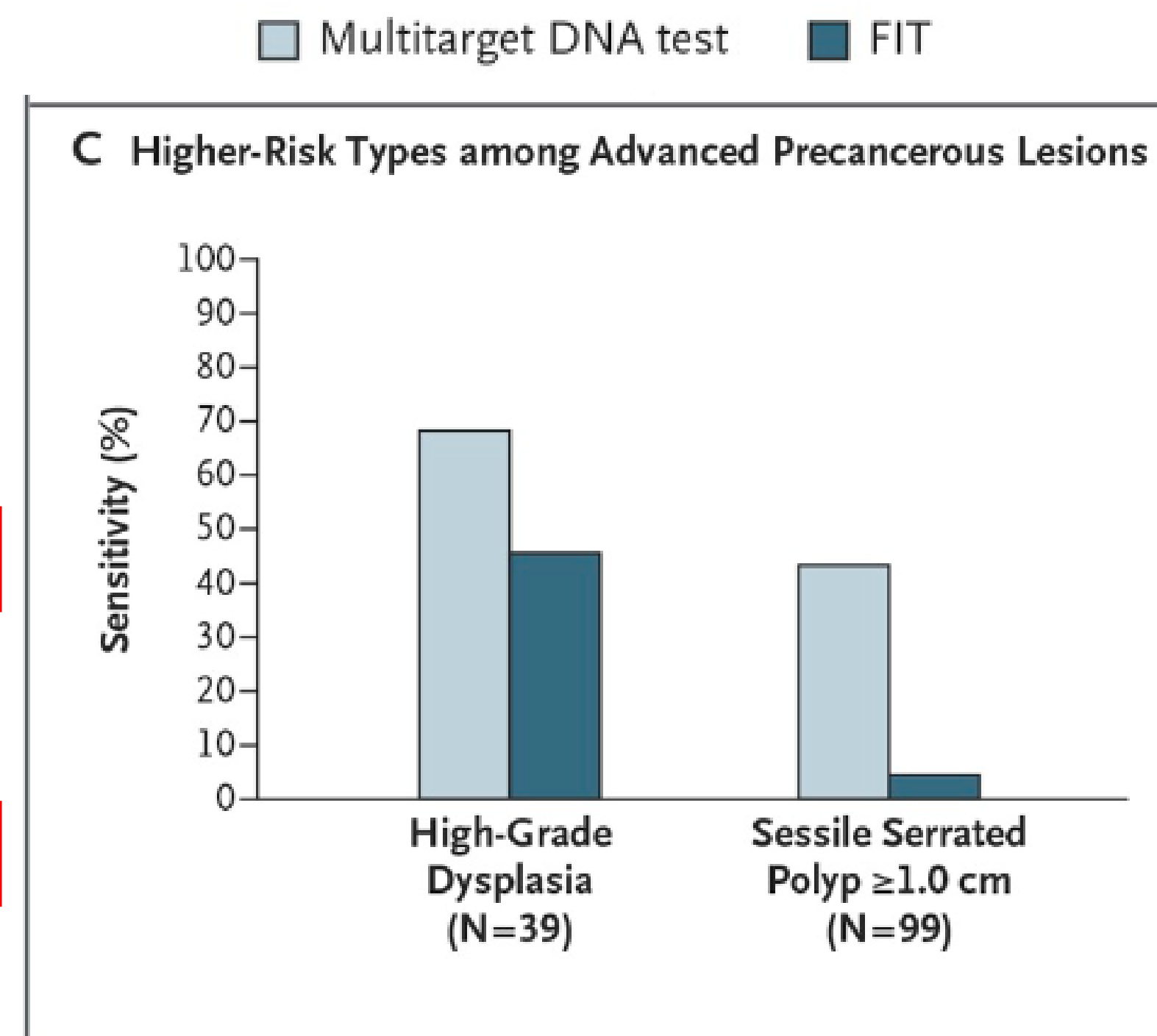
- Developed by Exact Sciences
- FDA approval and Medicare reimbursement simultaneously in 2014
- Recommended by USPSTF in 2016  
„Clinicians should consider engaging patients in making about the screening strategy and completion”
- Integrated into HEDIS quality tool
- Recent increase in use



# Original Cologuard Test

**Table 1. Sensitivity and Specificity of the Multitarget Stool DNA Test and the Fecal Immunochemical Test (FIT) for the Most Advanced Findings on Colonoscopy.**

Most Advanced Finding	Colonoscopy (N = 9989)	Multitarget DNA Test (N = 9989)		FIT (N = 9989)	
		Positive Results	Sensitivity (95% CI)	Positive Results	Sensitivity (95% CI)
		<i>no.</i>	<i>no.</i>	<i>no.</i>	<i>no.</i>
Colorectal cancer					
Any	65	60	92.3 (83.0–97.5)	48	73.8 (61.5–84.0)
Stage I to III*	60	56	93.3 (83.8–98.2)	44	73.3 (60.3–83.9)
Colorectal cancer and high-grade dysplasia	104	87	83.7 (75.1–90.2)	66	63.5 (53.5–72.7)
Advanced precancerous lesions†	757	321	42.4 (38.9–46.0)	180	23.8 (20.8–27.0)
Nonadvanced adenoma	2893	498	17.2 (15.9–18.6)	220	7.6 (6.7–8.6)
			Specificity (95% CI)		Specificity (95% CI)
All nonadvanced adenomas, non-neoplastic findings, and negative results on colonoscopy	9167	1231	86.6 (85.9–87.2)	472	94.9 (94.4–95.3)
Negative results on colonoscopy	4457	455	89.8 (88.9–90.7)	162	96.4 (95.8–96.9)



# What impact in a screening population?

One-time test in a population with 0.5% CRC prevalence and 4% advanced adenoma prevalence

	FIT-DNA	FIT (OC-Sensor at 20 µg/g)
CRCs detected (/1,000)	5	4
AAs detected (/1,000)	17	10
Positive tests among people without CRC or AA (/1,000)	127	48

RESEARCH ARTICLE

## Cost-effectiveness of a multitarget stool DNA test for colorectal cancer screening of Medicare beneficiaries

Steffie K. Naber<sup>1</sup>\*, Amy B. Knudsen<sup>2</sup>, Ann G. Zauber<sup>3</sup>, Carolyn M. Rutter<sup>4</sup>, Sara E. Fischer<sup>3aa</sup>, Chester J. Pabiniak<sup>5</sup>, Brittany Soto<sup>3ab</sup>, Karen M. Kuntz<sup>6</sup>, Iris Lansdorp-Vogelaar<sup>1</sup>

### Results

Compared to no screening, triennial mtSDNA screening resulted in 82 (range: 79–88) LYG per 1,000 simulated individuals. This was more than for five-yearly sigmoidoscopy (80 (range: 71–89) LYG), but fewer than for every other simulated strategy. At its 2017 reimbursement rate of \$512, mtSDNA was the most costly strategy, and even if adherence were 30% higher than with other strategies, it would not be a cost-effective alternative. At a substantially reduced reimbursement rate (\$6–18), two models found that triennial mtSDNA testing was an efficient and potentially cost-effective screening option.

<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0220234>



# BLUE-C Trial - Design

- 23,494 participants included between 2019 and 2023 at 194 study locations in the United States
- Representative screening population
- Adults  $\geq 40$  years presenting for screening colonoscopy asked to complete mt-sDNA 2.0 and FIT tests
- Sponsored by Exact Sciences and lead by Thomas Imperiale





# BLUE-C Trial – high-level results

	Cologuard in DeeP-C study <sup>1</sup>	Next-gen Cologuard in BLUE-C study <sup>2</sup>
Specificity including non-advanced findings	87	91
Specificity including no findings	90	93
Cancer sensitivity	92	94
High-grade dysplasia sensitivity	69	75
Advanced precancer sensitivity	42	43

One-time test with 0.5% CRC prevalence  
and 4% advanced adenoma prevalence

	mt-sDNA 2.0	FIT-DNA	FIT (OC-Sensor at 20 µg/g)
CRCs detected (/1,000)	5	5	4
AAs detected (/1,000)	17	17	10
Positive tests among people without CRC or AA (/1,000)	85	127	48

<https://www.exactsciences.com/newsroom/press-releases/next-generation-cologuard-test-demonstrates-94-percent-sensitivity>





# What about ColoAlert ?

- Developed and distributed by Mainz Biomed Germany GmbH. Shipped for free in Germany
- Analyses samples for KRAS-mutations, BRAF-mutations, total amount of human DNA and occult blood
- Single case-control study
- Adenomas poorly described
- 85% cancer sensitivity (vs 68% with ColoScreen FIT) and 92% specificity (vs 96% with FIT)
- Not ready for widespread use (my opinion!)

Clin. Lab. 2018;64:1719-1730  
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## ORIGINAL ARTICLE

### **Early Detection of Colorectal Cancer: a Multi-Center Pre-Clinical Case Cohort Study for Validation of a Combined DNA Stool Test**

Matthias M. Dollinger<sup>1,\*</sup>, Susanna Behl<sup>2,\*</sup>, Wolfgang E. Fleig<sup>3,\*</sup>

<https://mainzbiomed.com/coloalert/>  
<https://www.coloalert.com/pages/what-is-coloalert>



# Performance of non-invasive tests in development

- Guardant DNA blood test: high-level results show 83% CRC and 13% AA sensitivity; 90% specificity (ECLIPSE study)
  - Freenome multiomics blood test: completed enrollment of 35'000 participants, but results not yet reported (PREEMPT CRC study)
  - Some MCED tests also detect CRC. Case-control sensitivity of Galleri blood test reported as 74% in a case-control study
  - mtFIT stool test: AA sensitivity of 38% vs 28% for traditional FIT with equal 96% specificity in an 'enriched screening population' of 1284 persons
- Prospective validation now underway with 15,000 participants in the Dutch screening program

<https://investors.guardanthealth.com/press-releases/press-releases/2022/Guardant-Health-announces-positive-results-from-pivotal-ECLIPSE-study-evaluating-a-blood-test-for-the-detection-of-colorectal-cancer/default.aspx>

<https://pubmed.ncbi.nlm.nih.gov/33506766/>

<https://www.acpjournals.org/doi/10.7326/m20-8270>

<https://clinicaltrials.gov/study/NCT05314309>



# Discussion

- Based on press release information, the next-generation Cologuard has similar sensitivity and improved specificity to the existing test
- Specificity is important, but the next-generation Cologuard is unlikely to be more cost-effective than FIT and important logistical hurdles remain
- It is unlikely to change our approach to screening in Europe in the near future
- Non-invasive stool and blood tests







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