10TH ANNUAL

DIGESTIVE DISEASES: NEW ADVANCES

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Hyatt Regency Jersey City On The Hudson

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Noninvasive Colorectal Cancer Screening: Who and How?

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National Colorectal Cancer Roundtable

Mount Sinai

American Cancer Society | National Colorectal Cancer Roundtable | 80% in every community

Disclosures

Steven Itzkowitz, MD, FACP, FACG, AGAF

- Research Support: Exact Sciences Corporation
- Advisory Board: Exact Sciences Corporation
- Research Support: Freenome
- Consultant: Geneoscopy

Topics Discussed

1. Current screening guidelines
2. Performance of screening tests
3. Review stool based tests
4. New tests on the horizon

USPSTF 2021: CRC Screening Guidelines

	Interval
Direct Visualization Tests:	
• Colonoscopy	10 years
• Sigmoidoscopy	5 years (or q10 yrs + FIT annually)
• CT colonography	5 years
Stool-based tests:	
• FOBT	1 year
• FIT	1 year
• sDNA-FIT	1-3 years

- Age 45-49: Grade B
- Age 50-75: Grade A
- Age 76-85: Grade C (individualize)

U.S. Preventive Services TASK FORCE

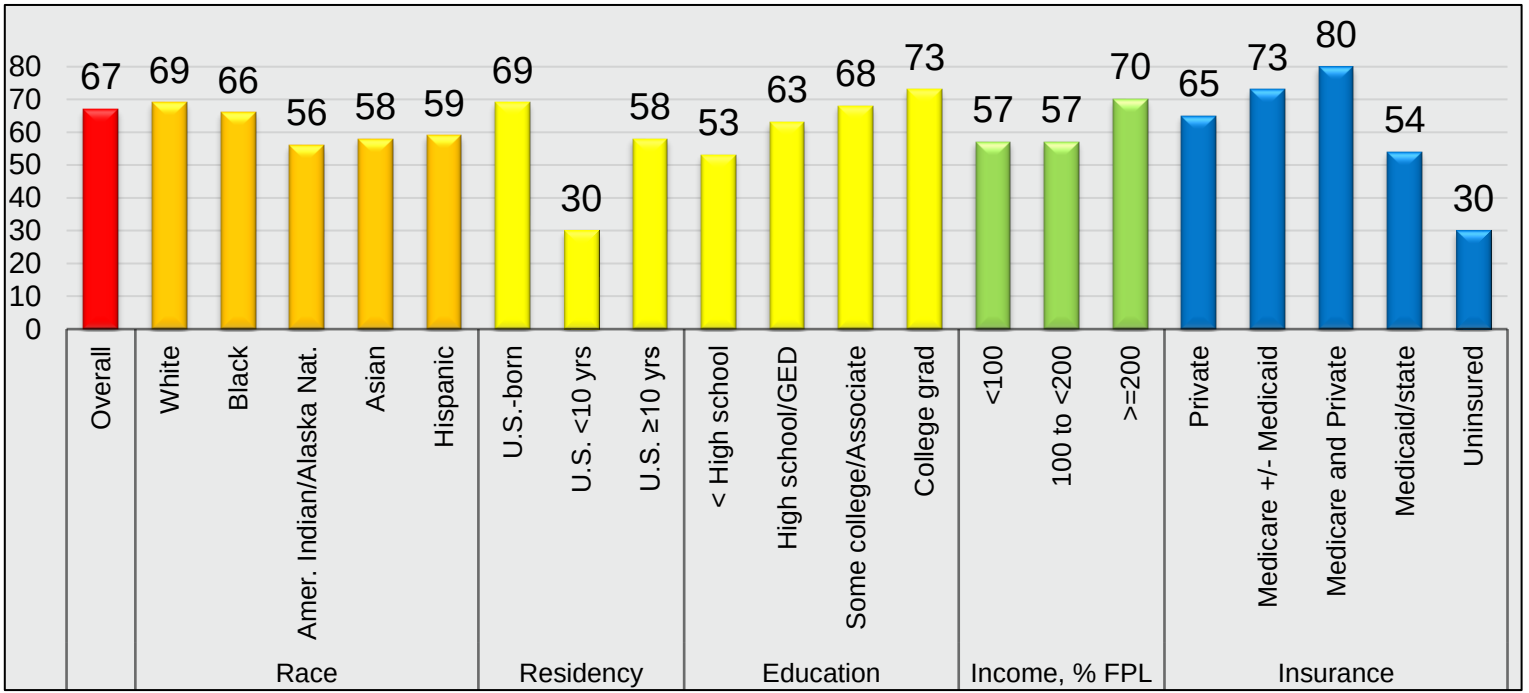
CRC Screening Test Performance

		Sensitivity		Specificity
		CRC	Adv. Adenoma	
Invasive Tests	Colonoscopy [1]	95%	95%	90%
	Sigmoidoscopy [1]	~50% (95% distal only)	~50% (95% distal only)	92%
	CT Colonography	96% [2]	94% [3]	86% [4]
Non-Invasive Tests	FIT-DNA [5]	92%	42%	87%
	FIT [1]	70%	22%	95%
	gFOBT (Hemoccult SENSA) [1]	70%	24%	93%
	gFOBT (Hemoccult II) [1]	40%	12%	98%

[1]Zauber et al. *AHRQ.* 2009; [2]Pickhardt et al. *Radiology.* 2011; [3]Pickhardt et al. *NEJM.* 2003; [4]Johnson et al. *NEJM.* 2008; [5]DeeP-C Study. *NEJM.* 2014.

Uptake Is Suboptimal, and Varies Greatly Across the Population

(Up-to-Date with CRC screening; National Health Interview Survey; 2018)



Slide courtesy Samir Gupta, MD.

CRC Screening at the Population Level

Effective Detection = S x C x A

S = Sensitivity

C = Compliance

A = Access

Criteria for the “Ideal” CRC Screening Tool

Sensitivity: (accurate detection)	Curable Stage CRC
	Critical Precursors (adenomas & SSPs)
	Right and left sided lesions
	Operator Independent
Compliance:	Noninvasive
	Safe
	Convenient & simple
	No prep or restrictions
Access:	Affordable
	Widely distributable

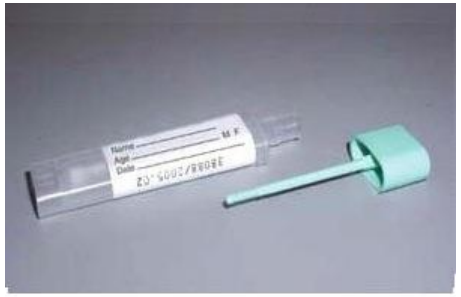
Colonoscopy Meets Some of the Criteria

		Colonoscopy
Sensitivity: (accurate detection)	Curable Stage CRC	+++
	Critical Precursors (adenomas & SSPs)	+++
	Right and left sided lesions	++
	Operator Independent	-
Compliance:	Noninvasive	-
	Safe	+/-
	Convenient & simple	-
	No prep or restrictions	-
Access:	Affordable	+/-
	Widely distributable	+/-

Stool-Based CRC Screening Tests

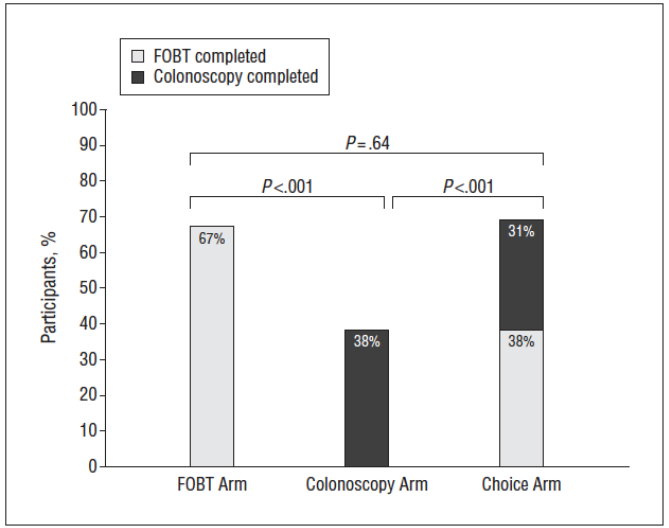
Fecal Occult Blood Test
(FOBT; Guaiac)

Fecal Immunochemical Test
(FIT; ELISA)



FIT-DNA (“Multi-Target Stool DNA”)
(Hgb; 10 DNA markers; Cologuard®)

Acceptability: Participation Varies Substantially by Test Offered



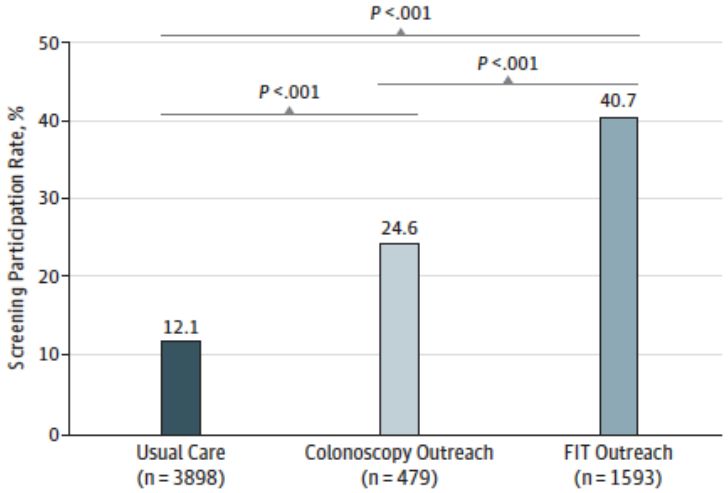
Arch Intern Med. 2012;172(7):575-582

ORIGINAL INVESTIGATION

Adherence to Colorectal Cancer Screening

A Randomized Clinical Trial of Competing Strategies

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



JAMA Internal Medicine Published online August 5, 2013

Original Investigation

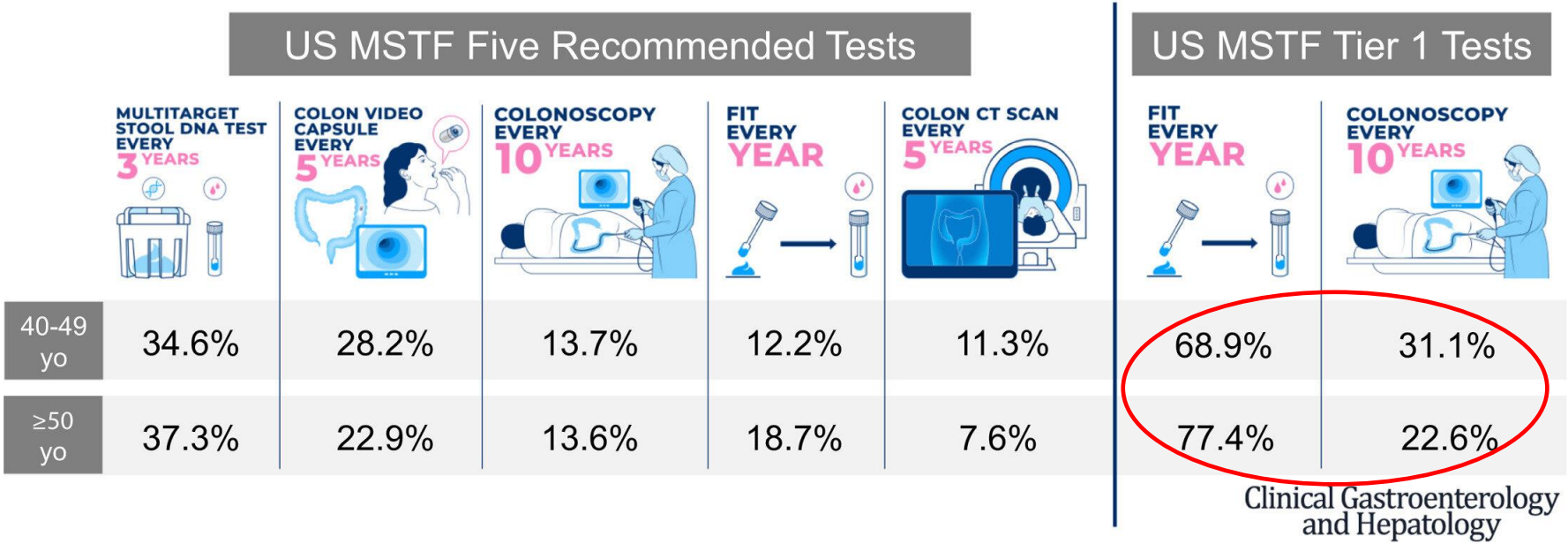
Comparative Effectiveness of Fecal Immunochemical Test Outreach, Colonoscopy Outreach, and Usual Care for Boosting Colorectal Cancer Screening Among the Underserved

A Randomized Clinical Trial

Samir Gupta, MD, MSCS; Ethan A. Halm, MD; Don C. Rockey, MD; Marcia Hammons, BSN; Mark Koch, MD; Elizabeth Carter, MD; Luisa Valdez, NRCMA; Liyue Tong, MS; Chul Ahn, PhD; Michael Kashner, PhD; Keith Argenbright, MD; Jasmin Tiro, PhD; Zhuo Geng, BA; Sandi Pruitt, PhD; Celette Sugg Skinner, PhD

Which Tests Do Patients Prefer?

Preferred CRC Screening Tests Among 1,000 Unscreened Americans



Makaroff et al. *Clin Gastroenterol Hepatol.* 21:520, 2023.

Summary: Stool-Based Tests

	FOBT (guaiac)	FIT	MT- sDNA
Analyte	Hemoglobin	Human Hgb	Human Hgb + DNA
At-home test	Yes	Yes	Yes
Diet/medication restriction	Yes	No	No
No. of samples	3	1	1
Detection of CRC	<50%	60-80%	80-92%
Detection of adenomas	<20%	40-60%	60-90% (size dep)
Detection of SSPs	Poor	Poor	Modest
Specificity	95-97%	94-96%	88-94%
Detection by site	Prox << Distal	Prox << Distal	Prox = Distal
Frequency	Yearly	Yearly	Q 3 yr
Adherence	23-50%	40-60%	Unknown
Cost	$20	$75	$600*

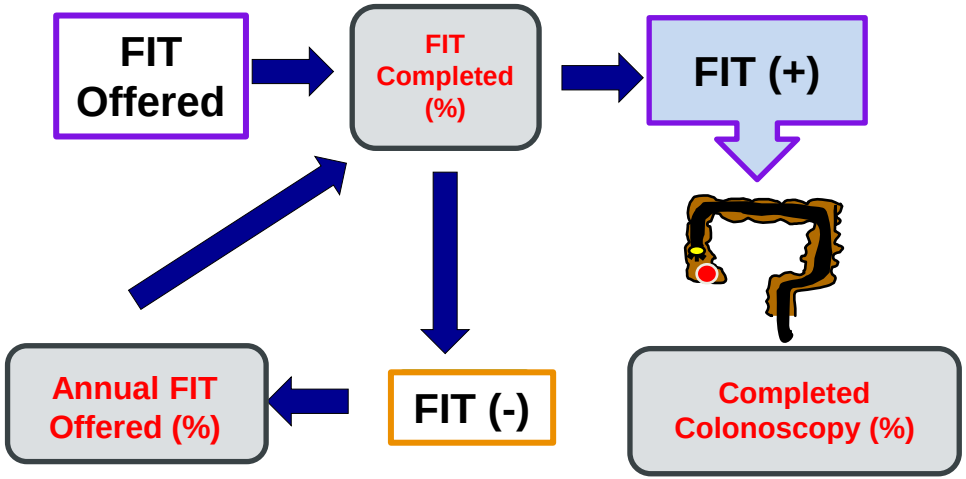
* Covered by Medicare & most Medicaid/commercial; Navigated test.

USMSTF: FIT Recommendations

- One-sample annual FIT
- Quantitative FIT (over qualitative)
- Favors lower threshold cut-off (i.e. ≤20 ug/g)
- Colonoscopy for FIT-positives
- Positive FIT/negative colonoscopy – no UGI workup
- No need to adjust diet or medications
- FIT should be done at home, not in-office digital rectal exam (DRE)
- Establish Quality Assurance Practices to monitor metrics:
  - FIT completion rate for those offered the test: 60%
  - Colonoscopy completion rate for positive FIT: ≥80%
  - ADR for FIT-positive colonoscopies: >45%(M); >35%(W)
  - Proportion FIT that cannot be processed by lab: <5%

Robertson et al. *Gastroenterology.* 152:1217, 2017.

FIT: Many Steps for Programmatic Adherence

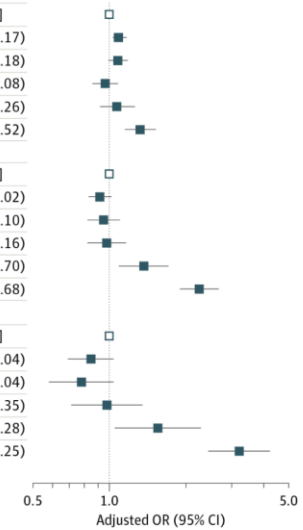


Quality Metrics (red)

Slide courtesy of David Lieberman, MD.

Timely Colonoscopy After a Positive Fit Is Very Important

Time to Colonoscopy After Positive FIT Result	No. of Cases/ Total No. of Patients Receiving Colonoscopy After Positive FIT Result	Rate (95% CI)[b]	Adjusted OR (95% CI)
Advanced adenoma			
8-30 d	2135/26 369	81 (78-84)	1 [Reference]
2 mo	2168/23 959	91 (87-94)	1.09 (1.03-1.17)
3 mo	779/8401	93 (87-99)	1.08 (0.99-1.18)
4-6 mo	429/5086	84 (77-92)	0.97 (0.86-1.08)
7-12 mo	189/1988	95 (82-108)	1.07 (0.92-1.26)
>12 mo	247/2130	116 (102-130)	1.32 (1.15-1.52)
Any colorectal cancer			
8-30 d	807/27 176	30 (28-32)	1 [Reference]
2 mo	685/24 644	28 (26-30)	0.92 (0.83-1.02)
3 mo	265/8666	31 (27-34)	0.95 (0.82-1.10)
4-6 mo	165/5251	31 (27-36)	0.98 (0.82-1.16)
7-12 mo	95/2083	46 (37-55)	1.37 (1.09-1.70)
>12 mo	174/2304	76 (65-86)	2.25 (1.89-2.68)
Advanced-stage colorectal cancer			
8-30 d	219/27 173	8 (7-9)	1 [Reference]
2 mo	173/24 642	7 (6-8)	0.85 (0.69-1.04)
3 mo	60/8664	7 (5-9)	0.78 (0.58-1.04)
4-6 mo	46/5249	9 (6-11)	0.98 (0.71-1.35)
7-12 mo	31/2082	15 (10-20)	1.55 (1.05-2.28)
>12 mo	72/2300	31 (24-38)	3.22 (2.44-4.25)



Corley et al. *JAMA*. 2017;317(16):1631-1641.

Time to Colonoscopy After Positive Stool Test: Real World data

- 32,769 patients
- De-identified administrative claims and EHR data
- 2015-2020
- Time to follow-up colonoscopy (FU-CY) after positive stool test:

90 days	180 days	360 days
43.3%	51.4%	56.1%

- Positive mt-sDNA, more likely than FIT to get FU-CY
  - (HR: 1.63; 95% CI 1.57-1.68)
- More comorbidities, less likely to get FU-CY
  - (H: 0.64; 95% 0.59-0.71)

Mohl et al. *JAMA Network Open.* 6:2023.

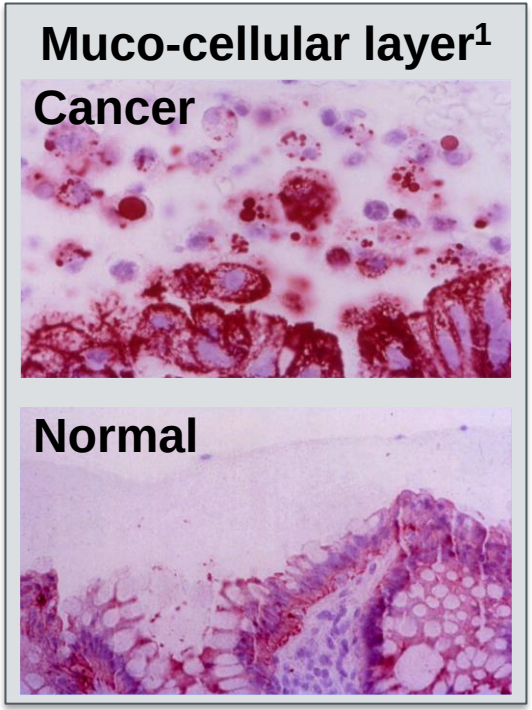
Adherence to Repeated FIT/FOBT Is Poor

	Test	Follow up	Study type	Adherence
Quintero (2014)	FIT	3 rounds	RCT	38%
Duncan (2014)	FIT	3 rounds	Population-based intervention (FIT mailed)	55%
Liss (2013)	FOBT	2 rounds	Retrospective	25%
Fenton (2010)	FOBT	2 rounds	Prospective observational	44%
Gellad (2011)	FOBT	4 rounds (5 years)	Retrospective	14%
Mandel (1993)	FOBT	11 rounds	RCT	46%

Biological Basis for Stool DNA

1) **Exfoliation; CRC, Adenoma**
   - Abundant
   - Continuous supply of DNA
   - Cancer > normal

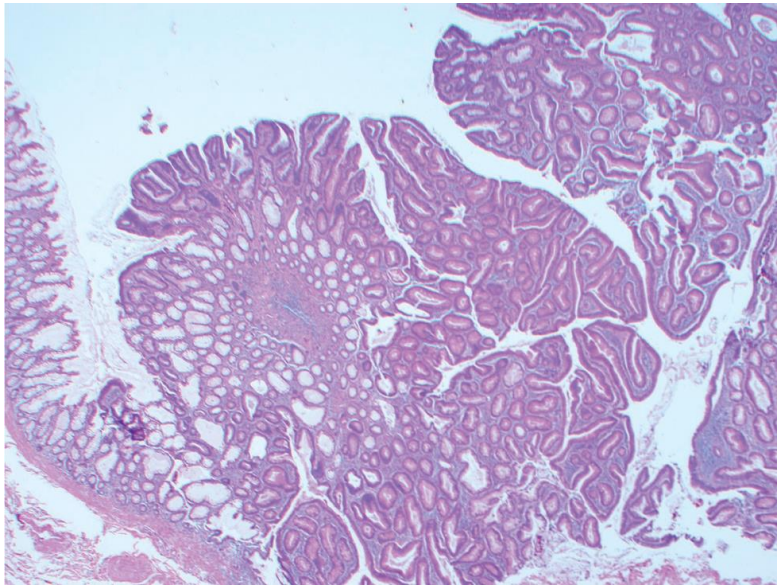
2) **DNA as marker**
   - Signature changes
   - Stable
   - Amplifiable



[1]Ahlquist et al. *Hum Pathol.* 2000 31:51.

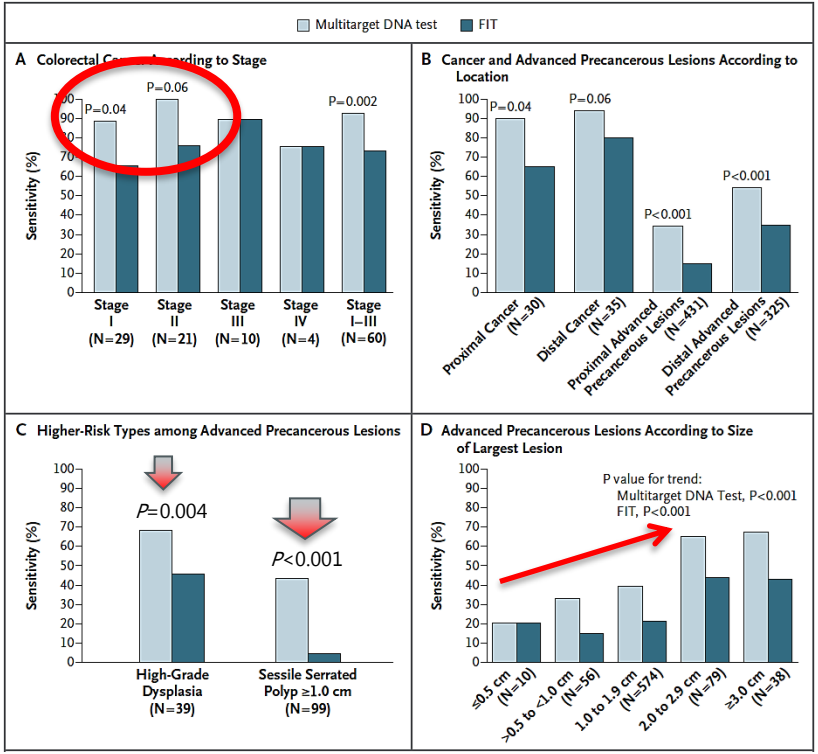
Surface Area of an Adenoma (Much Larger Than You'd Think!)

- Surface of adenoma = 200 x simple gross dimensions
- 2 cm adenoma = 800-1600 cm^2 in unfolded surface area



Berger and Ahlquist. *Pathology.* 44:80, 2012.

Deep-C: Subgroup Analysis Results



Imperiale TF et al. *N Engl J Med*. 2014;370(14):1287-1297.

New Stool-Based Tests

Study	Analyte	Sample Size	Pop'n	Preliminary Data
"BLUE-C" Study (Exact Sciences)	mt-sDNA 2.0 (DNA-FIT)	24,000	≥40	CRC sensitivity: 94% APL sensitivity: 43% HGD sensitivity: 75% Specificity: 93%
ColonoSight Test (Geneoscopy)	mt-RNA (RNA-FIT)	10,000	45-84	CRC sensitivity: 95% AA sensitivity: 62% Specificity: 85%

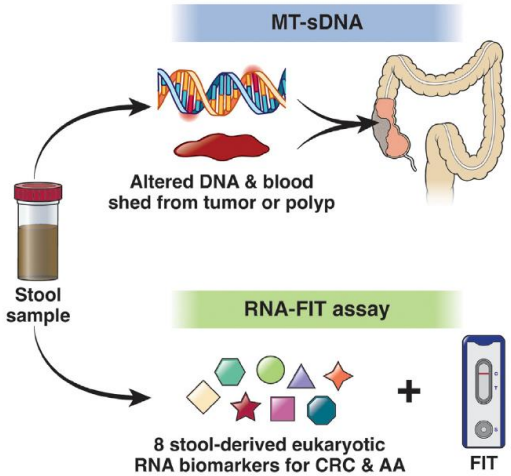


Figure 2. Altered DNA and proteins in blood shed from CRC and AA can be detected in stool samples of individuals using the MT-sDNA test. The geneoscopy assay (RNA-FIT) uses 8 stool-derived eukaryotic RNA biomarkers along with a FIT test for CRC and AA detection.

Hanna et al. *Clin Gastroenterol Hepatol.* 21:604;2023.

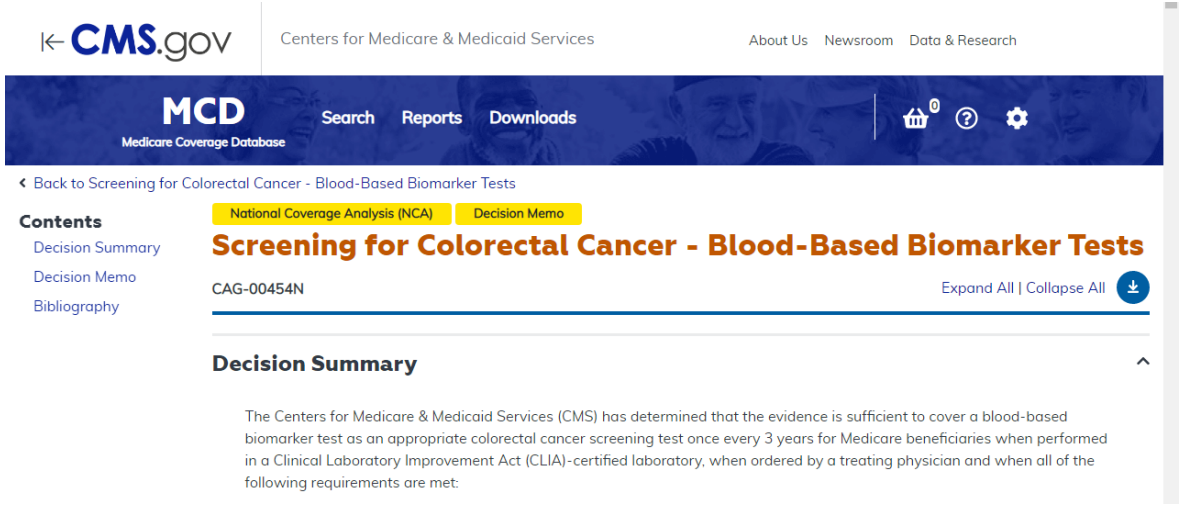
Comparison mt-sDNA tests: Deep-C vs Blue-C

	Deep-C	Blue-C (top line data)
Cancer sensitivity	92%	94%
Specificity • Negative colonoscopy • Including non-advanced findings	 • 90% • 87%	 • 93% • 91%
HGD sensitivity	69%	75%
Advanced precancer sensitivity	42%	43%

Exact Sciences website.

What About New Blood-Based Tests?

Blood-Based CRC Screening Tests: CMS National Coverage Decision



Sensitivity for CRC	74%
Specificity for CRC	90%
FDA approval	✓

Blood-Based Tests: Colorectal Cancer Specific

Study	Analyte	Sample Size	Pop'n	Primary Outcome
ECLIPSE (LUNAR2) (Guardant)	ct-DNA*	20,000	45-84	• Sensitivity CRC • Specificity AA
PREEMPT CRC (Freenome)	ct-DNA*; multiomics	25,000	45-85	• Sensitivity CRC • Specificity CRC

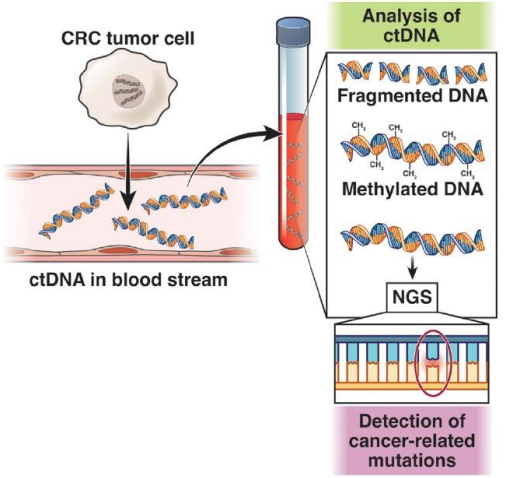


Figure 1. ctDNA-based assays are based on the detection of tumor cell–derived nucleic acids in the circulation. Next-generation sequencing is used to detect ctDNA fragments (with cancer-related mutations) and aberrantly methylated ctDNA.

*ct-DNA: circulating tumor DNA (derived from tumor); "liquid biopsy".
Different from: cf-DNA: *cell-free* DNA, which can come from non-tumor cells.
Hanna et al. *Clin Gastroenterol Hepatol.* 21:604;2023.

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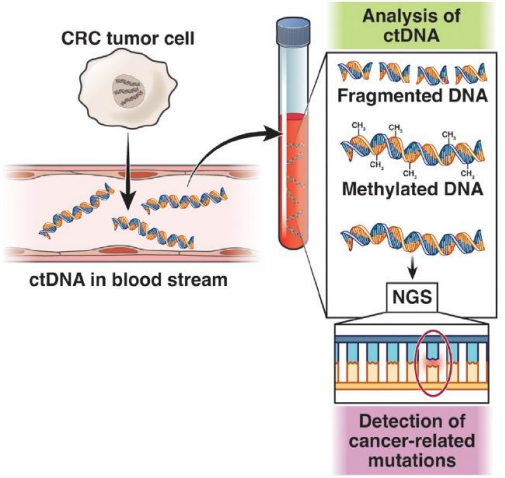
PREEMPT CRC (Freenome)	ct-DNA*; multiomics	25,000	45-85	Sensitivity and specificity CRC

Guardant:
CRC sensitivity: 83%
CRC specificity: 90%
AA sensitivity: 13%



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Multicancer Early Detection Tests (MCEDs) in the Pipeline

			Targeted Cancers															
Company	Assay	Technology	Lung	CRC	Breast	Pancreas	Liver	Esophagus	Stomach	Ovary	Prostate	Bladder	Kidney	Uterus	H&N	Lymphoma	Leukemia	Plasma Cell
Adela Bio	adela™	cfMeDIP-seq; cfDNA fragmentomics	■	■	■	■						■	■				■	
Biological Dynamics	Tr(ACE)	EV proteins; AI				■				■		■						
Bluestar Genomics	BluestarMCED	cfDNA 5hmC-seq; fragmentomics	■	■	■	■	■	■	■	■								
Burning Rock	OverC™	ELSA-seq	■	■		■	■	■		■								
Caris Life Sci	MI GPSai™	cfDNA/cfRNA NGS; AI	■	■	■				■				■	■				
Delfi Dignostics	DELFI	cfDNA fragmentomics	■	■		■			■	■								
Early Diagnostics	cf Methyl-Seq	cfDNA mC-NGS	■	■			■		■									
Exact Sciences	CancerSEEK	cfDNA NGS; protein markers	■	■	■	■	■	■	■	■								
Freenome	FMBT	Multi-Omics/AI	■	■	■	■	■	■	■	■	■	■	■	■				
Grail	Galleri™	CpG-cfDNA NGS	■	■		■	■	■	■	■		■			■	■		■
LungLifeAI	LungLB	CTC FISH; Imaging AI	■		■		■						■					
Natera	Signatera™	cfDNA NGS; protein markers	■	■	■	■	■					■		■				
Precision Epigenomics	Sentinel-10™	CpG-cfDNA qPCR	■	■	■	■	■											
20/20 Gene Systems	oneTEST	circul. Cancer Ag's; AI	■	■	■	■	■				■							

Slide courtesy Aasma Shaukat MD.
https://prevention.cancer.gov/.

How Will Blood Tests Fit in?

	Colonoscopy	FOBT (guaiac)	FIT	FIT- DNA	Blood tests
Sensitivity: (accurate detection)					
• Curable stage CRC	+	+/-	+/-	+	+
• Critical precursor lesions	+	-	-	+	+/-
• Both R & L sides	+	-	-	+	?
• Operator independent	-	-	+	+	+
Compliance:					
• Noninvasive & safe	-	+	+	+	+
• Simple and convenient	-	+/-	+/-	+	+
• No prep or restrictions	-	-	-	+	+
Access:					
• Affordable	+/-	+	+	+/-	??
• Widely distributable	+/-	+	+	+	+

Questions About Blood-Based Tests

- Which test to choose? (CRC specific, MCED)
- How to order? (information required)
- How complete? (navigation?)
- How to collect? (clinic, commercial lab, mobile phlebotomy, home)
- How to process? (commercial lab, central lab, regional labs
- How to interpret? (clinician? Staff?)
- How is follow-up colonoscopy ensured?
- Repeat interval for negative test?
- Follow-up of false positives?
- Comparative effectiveness
- Cost/coverage
- Adherence to two step process

Summary

1. Colonoscopy is often the preferred screening test, but many patients prefer non-invasive tests.
2. Important to offer a CHOICE to patients. That way they are more likely to complete the screening round.
3. If stool testing is done, it is important to set up systems to track positives and negatives for follow-up.
4. New stool and blood-based tests are coming soon. Many issues around how to integrate them into practice.

Mount Sinai

American Cancer Society | National Colorectal Cancer Roundtable | 80% by 2018

The best CRC screening test is…..
the one that gets done
(and gets done well).