
2023 SCSG
GI SYMPOSIUM

Hot Topics From DDW23: Colon and Lower GI Abstracts (Part 2)

Folasade May, MD, PHD, MPhil

Samir Gupta, MD, MSCS

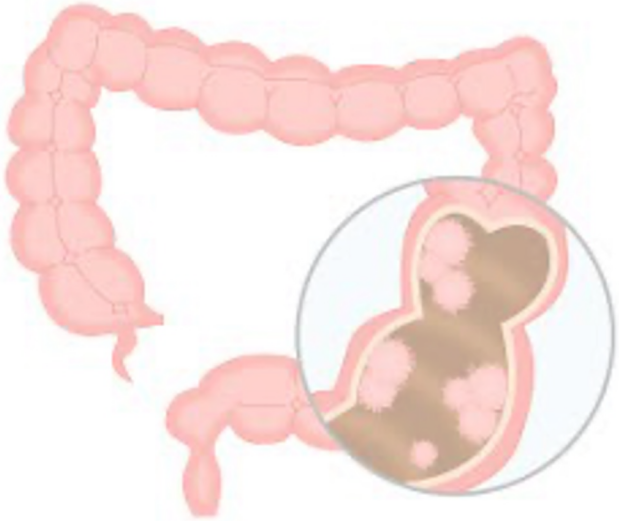
Disclosures

Consultant/Advisor for:	Geneoscopy; InterVenn; Universal Diagnostics; CellMax Life
Grant/Research support:	National Institutes of Health, National Cancer Institute; Epigenomics; Freenome
Employee of:	UC San Diego; Veterans Health Administration

Presentation Overview

- Evidence for changing epidemiology of CRC
- CRC disparities
- High risk CRC groups
- Artificial intelligence and colonoscopy
- New in CRC screening tests
- Risk stratification for CRC
- CRC screening interventions

New in CRC Screening Tests



Comparative Effectiveness of CRC Screening Tests

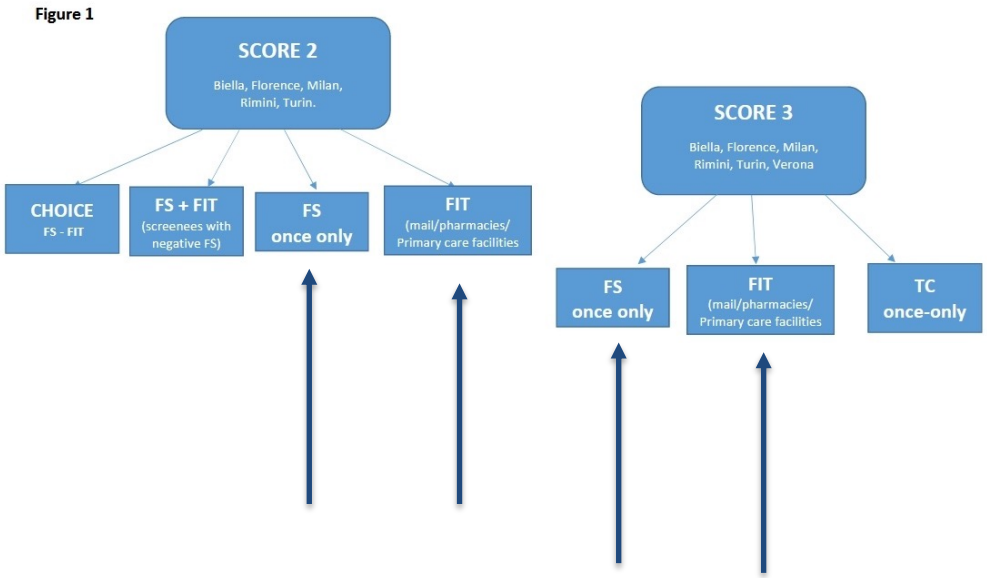
- Few studies with head-to-head comparisons of impact of non-invasive vs. endoscopic screening on risk for incident and fatal CRC
- Working hypothesis is that more endoscopic tests should be more effective

COLORECTAL CANCER SCREENING WITH REPEATED FECAL IMMUNOCHEMICAL TEST VERSUS SIGMOIDOSCOPY. INCIDENCE AND MORTALITY FOLLOW-UP OF THE ITALIAN MULTICENTER TRIALS #887

Carlo Senore, Emilia Riggi, Paola Armaroli, Marco Zappa, Cristiano Crosta, Manuel Zorzi, Franco Ferrero, Orietta Giuliani, Carmen Visioli, Arrigo Arrigoni, Nereo Segnan

- Aim: Compare colorectal (CRC) incidence and mortality at 15-year follow-up among subjects enrolled in the FS and FIT arms in the SCORE2 (1) and SCORE 3 (2) trials
- Methods:
  - 2 RCTs 1999-2004 among average risk 55 to 64 year olds
  - Restricted analysis to subjects invited to undergo FIT every 2 years (n=23,896) or one time sigmoidoscopy (n=11,236)
  - Colonoscopy for abnormal FIT or ≥ 3 adenomas or any adenoma ≥10mm
  - Primary outcome: CRC incidence and mortality through up to 15 years follow up

Figure 1



Results

- FIT Participation 29-32% first round, and at least once on f/u for 48% (average 3 FITs)
- Sigmoidoscopy participation 30%
  - 46% of responders and 19% of non-responders in the FS arm also did FIT

Incidence	**FIT**				**FS**						
	322,090 person-years				150,040 person-years						
	Cases	**Rate&**	Lower	Upper	Cases	**Rate&**	Lower	Upper	RR*	95% CI	P-value
CRC all sites	626	**194.4**	179.7	210.2	238	**158.62**	139.7	180.1	**0.85**	0.73-1.00	0.04
Mortality	**FIT**				**FS**						
	325.380 person-years				151.320 person-years						
	Cases	**Rate&**	Lower	Upper	Cases	**Rate&**	Lower	Upper	RR*	95% CI	P-value
CRC all sites	131	**40.3**	33.9	47.8	48	**31.7**	23.9	42.1	**0.85**	0.61-1.18	0.33
All causes	3812	**1171.5**	1134.9	1209.3	1612	**1065.3**	1014.5	1118.6	**0.97**	0.91-1.03	0.31

Data courtesy of Dr. Carlo Senore

Implications

- Among the first data comparing impact of a strategy of FIT vs endoscopic sigmoidoscopy-based screening on CRC incidence and mortality
- Suggest superiority of endoscopic screening with respect to incidence
- Await final report and results from more ongoing studies

Blood-Based CRC Screening Tests: Approach

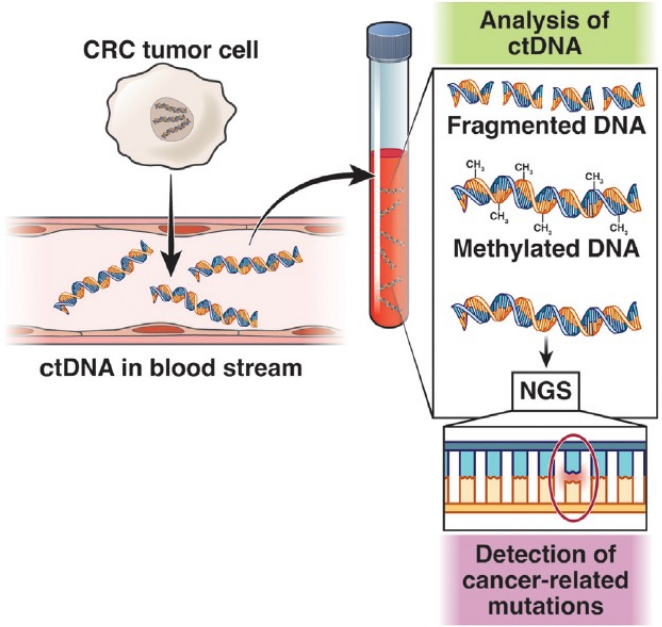


Figure 1. ctDNA-based assays are based on the detection of tumor cell–derived nucleic acids in the circulation. Next-generation sequencing is used to detect ctDNA fragments (with cancer-related mutations) and aberrantly methylated ctDNA.

Clinical Gastroenterology and Hepatology 2023;21:604–616

NARRATIVE REVIEW

Charles J. Kahi, Section Editor

Emerging Tests for Noninvasive Colorectal Cancer Screening

Marina Hanna,[1] Neelendu Dey,[1,2,3] and William M. Grady[1,2]

[1]Department of Medicine, University of Washington, Seattle, Washington; [2]Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, Washington; and [3]Microbiome Research Initiative, Fred Hutchinson Cancer Center, Seattle, Washington

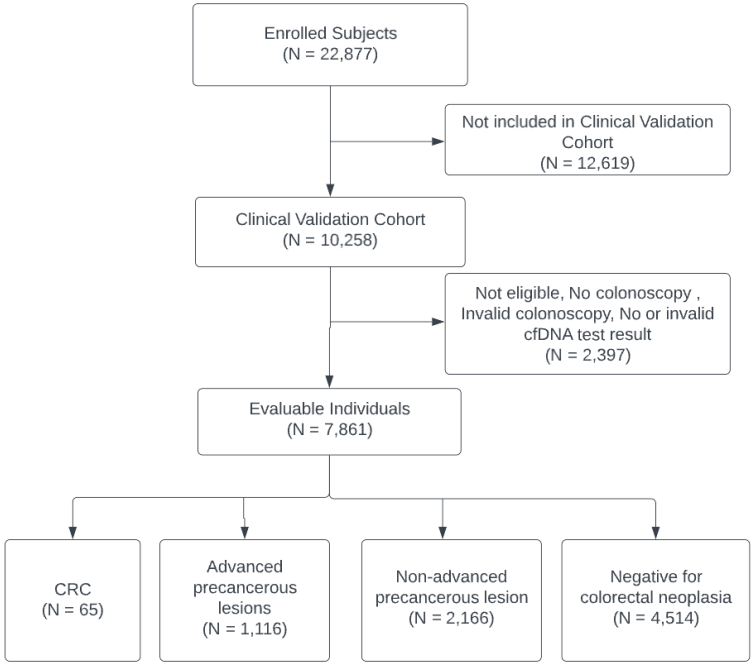
CLINICAL VALIDATION OF A CELL-FREE DNA BLOOD-BASED TEST FOR COLORECTAL CANCER SCREENING IN AN AVERAGE RISK POPULATION #913e

Daniel Chung, Darrell Mason Gray[2] Joel Greenson, Samir Gupta, Craig Eagle, Sylvia Hu, Amirali Talasaz, Rachel Blankson Issaka, Harminder Singh, Frank A. Sinicrope[1], William Grady

Aim: Evaluate performance of a cell-free DNA (cfDNA) blood-based CRC screening test in an average-risk population.

Methods:

- Average risk, age ≥ 45 y, presenting for screening colonoscopy 2019-2022 (n=265 sites)
- Blood collected pre-bowel prep
- Primary outcomes: CRC sensitivity and specificity
- Secondary outcome: Sensitivity for advanced precancerous lesions (adenoma with size ≥ 10mm, villous histology, or high grade dysplasia; sessile serrated lesion ≥ 10 mm)
- Assay algorithm analyzing DNA methylome and fragmentation patterns locked pre-analysis and analysis conducted blind to case/control status
- Down-sampled entire study cohort of 22,877 individuals to identify all CRC cases (n=65) and random age and sex stratified sample of controls (n=7,796)
- Case-control analysis

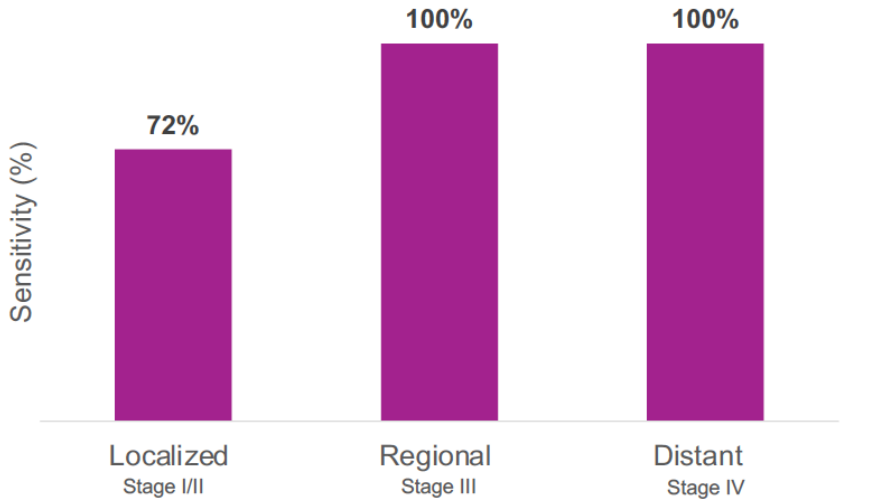


Results – Demographics

Characteristic	Clinical Validation Cohort (N=10,258)	Evaluable Subjects (N=7,861)
Age (years)		
Mean (SD)	60.6 (9.13)	60.3 (9.14)
Min, Max	45, 90	45, 84
Age Group (years)	N (%)	N (%)
45-49	776 (7.6)	640 (8.1)
50-69	7,161 (69.8)	5,495 (69.9)
70+	2,321 (22.6)	1,726 (22.0)
Sex		
Female	5,493 (53.5)	4,218 (53.7)
Race		
American Indian or Alaska Native	19 (0.2)	14 (0.2)
Asian	685 (6.7)	560 (7.1)
Black or African American	1,353 (13.2)	931 (11.8)
Native Hawaiian or Other Pacific Islander	24 (0.2)	19 (0.2)
White	7,939 (77.4)	6,167 (78.5)
Other / Multiple / Missing	238 (2.3)	170 (2.2)
Ethnicity		
Hispanic or Latino	1,561 (15.2)	1,044 (13.3)

Results – Sensitivity

- Sensitivity CRC:
  - 83% (54/65, 95% CI 72–90%)
- Specificity for the absence of CRC or APL:
  - 90% (5,982/6,680; 95% CI 89–90%)
- Sensitivity for APL:
  - 13% (147/1,116; 95% CI 11-15%)
- Met pre-specified endpoints for CRC sensitivity/specificity



Stage I*	Stage II	Stage III	Stage IV
55% (12/22)	100% (14/14)	100% (16/16)	100% (10/10)

*Assumes 5 incompletely staged malignant polyps are Stage I disease (1/5 detected)

LARGE MULTI-COHORT STUDY SHOWS ACCURATE DETECTION OF EARLY-STAGE COLORECTAL CANCER AND ADVANCED ADENOMA PATIENTS USING CELL-FREE DNA METHYLATION AND FRAGMENTATION SIGNALS *Pol Canal Noguer, Kristi Kruusmaa, James Macalister Kinross, Vivian Erklavec Zajec, Špela Zavodnik, Alejandro Requena Bermejo, Francesco Mattia Mancuso, Marina Manrique López, Primoz Knap, Marko Chersicola, Pablo Pérez Martínez, Fernando Trincado Alonso, Carme Nolla Colomer, Aasma Shaukat*

Aim: Assess the diagnostic accuracy of a test utilizing cell-free DNA (cfDNA) methylation, fragmentation characteristics of selected cancer-related biomarker regions, tumor-derived signal deduction and a machine learning algorithm to refine a blood test for the early detection of CRC and advanced adenomas (AA).

Methods:

- Prospective, international observational case control
- Blood collected prior to colonoscopy or surgery
- 170 early stage (I-II), 128 late-stage (III-IV) CRC cases
- 149 advanced adenoma cases
- 550 age, gender and country of origin matched colonoscopy controls (n=155 negative; n=337 benign findings; n=58 non-advanced adenoma)
- Panel of targeted biomarkers was previously identified through tissue- and plasma-based discovery and verification workflow
- Algorithm was not locked prior to analysis (training analysis)
- Primary outcomes: CRC sensitivity, AA sensitivity, specificity

Results

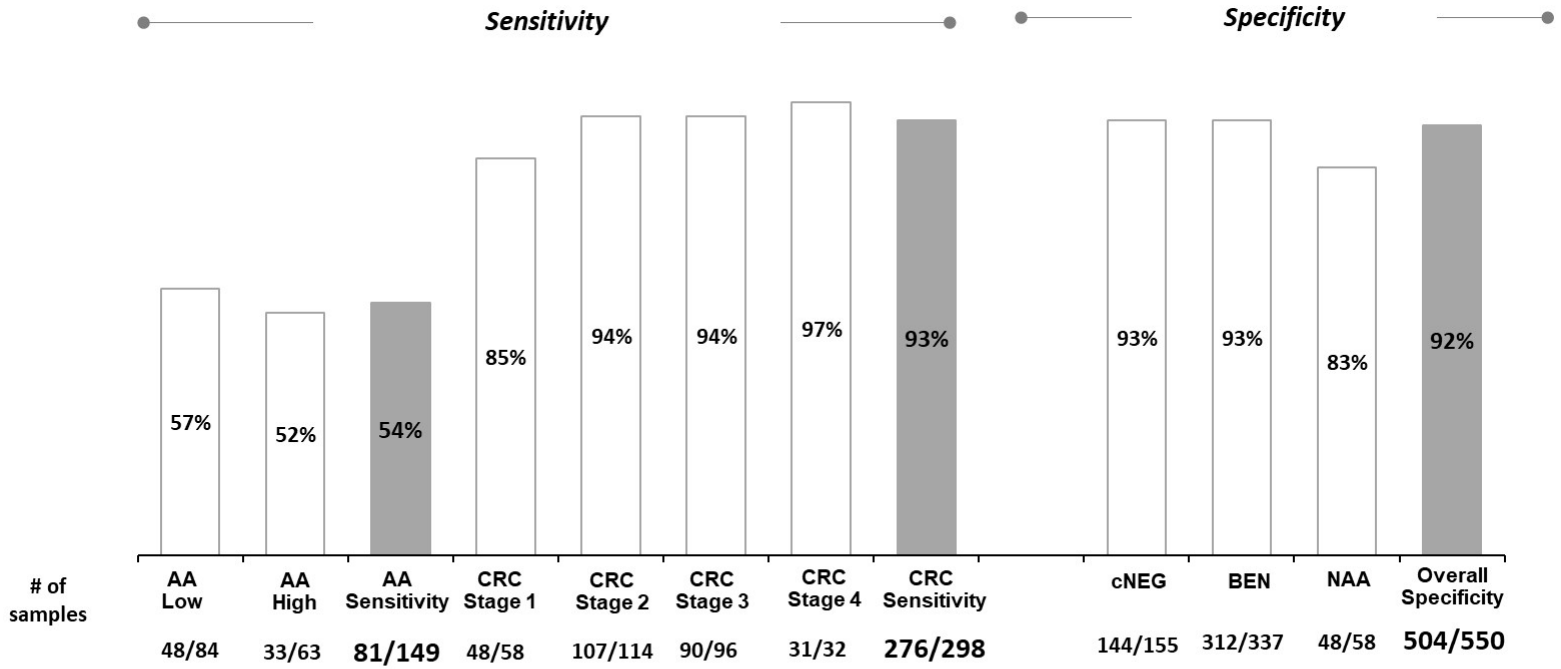
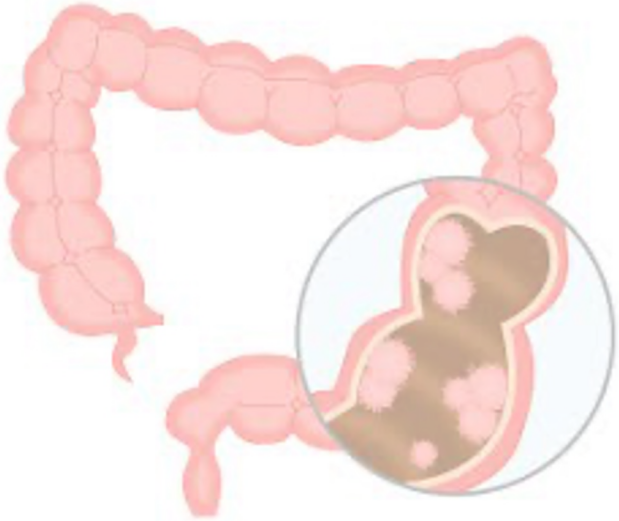


Fig.1 Sensitivity and specificity values for prediction outcomes. AA Low- advanced adenomas with low grade dysplasia, >= 1cm; AA High- advanced adenomas with high grade dysplasia; CRC- colorectal cancer; cNEG- patients with no colonoscopy findings; BEN- patients with bening colonscopy findings such as: diverticulosis, hemorrhoids, previously undiagnosed gastrointential diseases, inflammatory and/or hyperplastic polyps; NAA- non-advanced adenomas

Implications: Blood-Based Tests

- Likely to have at least one blood-based test FDA approved and Centers for Medicare/Medicaid Services covered in the next 1-2 years
- Sensitivity and specificity for CRC comparable or better than FIT
- Adequacy for early-stage CRC and advanced adenomas uncertain
- Potential impacts:
  - Increased participation
  - Increased CRC detection
    - Even with lower sensitivity for early stage CRC due to increased population coverage
  - Possible reduced CRC prevention if blood-based participation displaces participation in FIT, sDNA-FIT, or colonoscopy

Risk Stratification for CRC



RISK OF ADVANCED NEOPLASIA AFTER POLYPECTOMY IN ADULTS <50 AND ≥50 YEARS: DATA FROM THE MGB COLONOSCOPY COHORT #Tu1092

Jean Carlos Padilla Aponte, Mingyang Song, Georgios Polychronidis, Markus Dines Knudsen

Background:

- Incidental detection of adenomas in individuals under age 50 undergoing routine diagnostic colonoscopy common
- Unclear whether young-onset detection confers increased risk for colorectal neoplasia

Aim:

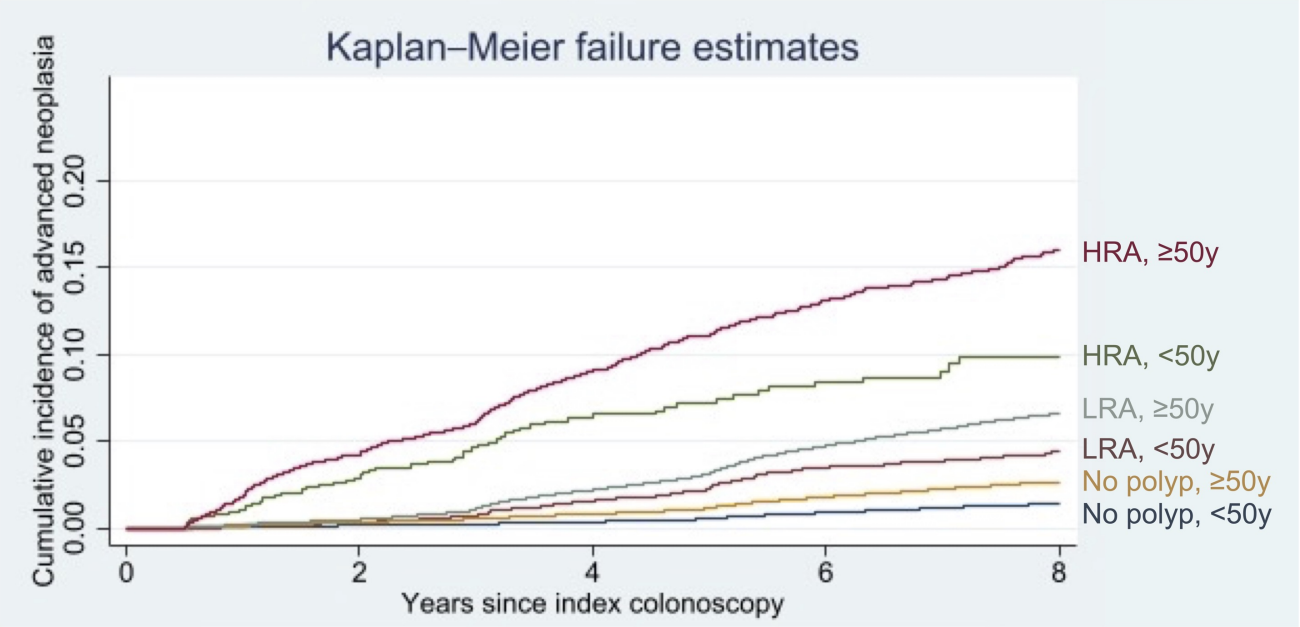
- Assess the subsequent risk of advanced neoplasia in patients under 50 who had undergone a polypectomy at their index colonoscopy, compared to older individuals

Methods:

- Longitudinal cohort study of 188,175 individuals exposed to colonoscopy 2007-2017 at Mass General Brigham system
- Primary outcome: advanced neoplasia (CRC, advanced adenoma, or ≥10 mm serrated polyps), stratified by baseline colonoscopy finding
- Median follow up 5.7 years

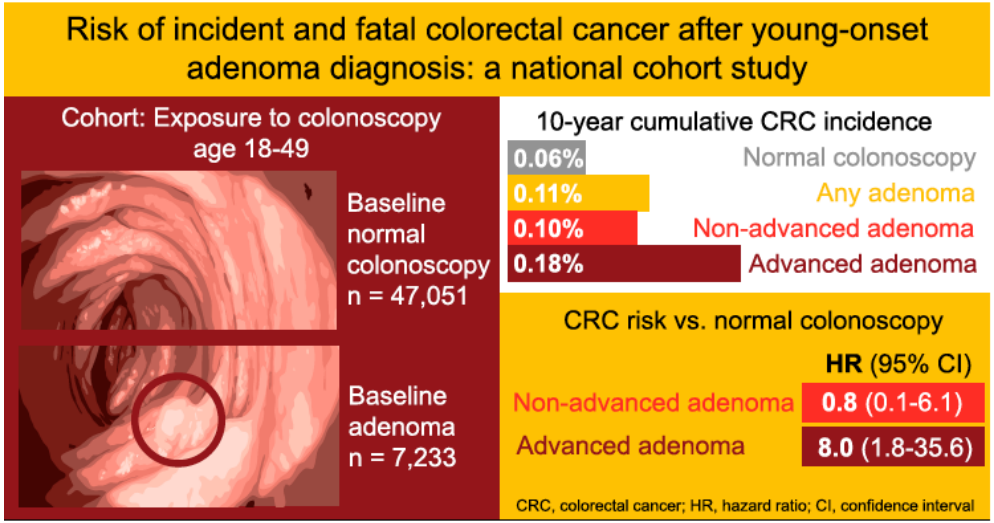
Results

	Risk for AN baseline low risk adenoma vs. normal	Risk for AN baseline high risk adenoma vs. normal
Age < 50	1.02 (.95 - 1.09)	1.28 (1.14 - 1.44)
Age ≥50	.96 (.92 - 1.01)	1.21 (1.13 - 1.01)



Implications

- Individuals with young onset adenoma likely do not need more aggressive surveillance than currently recommended guidelines
- Caveat:
  - Family history of colorectal cancer, multiple/large polyps



KNOWN COLORECTAL CANCER POLYGENIC RISK SCORE IS ASSOCIATED WITH BASELINE SCREENING COLONOSCOPY FINDINGS BUT NOT FOLLOW UP COLONOSCOPY OUTCOMES

Brian Sullivan Xuejun Qin Thomas S. Redding, David Weiss, Julie Upchurch, Kellie J. Sims, Jason A. Dominitz, Annjanette Stone, Christina D. Williams, David A. Lieberman, Elizabeth R. Hauser

Background:

- Polygenic risk scores (PRS), which calculate genetic risk for colorectal cancer (CRC), may help prioritize individuals for more intensive versus less intensive CRC screening and surveillance.

Aim:

- Assess association of a PRS with prevalent and incident advanced neoplasia (AN) in a population undergoing screening colonoscopy and follow up.

Methods:

- Department of Veterans Affairs Cooperative Studies Program #380 cohort
- Sample of individuals with and without advanced neoplasia at baseline and follow up colonoscopy
- PRS was based on 136 pre-specified CRC-risk single nucleotide polymorphisms

Results

Whole Cohort		
	Advanced Neoplasia Odds Ratio (95% CI)*	**p-value**
Prevalent Advanced Neoplasia (total n = 594)	5.01 (1.69,15.18)	0.004
Incident Advanced Neoplasia (total n = 354)	2.64 (0.45,15.82)	0.28
Cohort with Family History Excluded		
Prevalent Advanced Neoplasia (total n=460)	4.54 (1.29,16.43)	0.0197
Incident Advanced Neoplasia (total n=267)	2.54 (0.37,18.00)	0.344

* Models adjusted for race (based on genetic ancestry by principal component analysis), sex, and age [at last colonoscopy or first colonoscopy with advanced neoplasia].
# Quintile cutoffs calculated by the distribution of the PRS among healthy control participants. Data courtesy of Brian Sullivan, MD

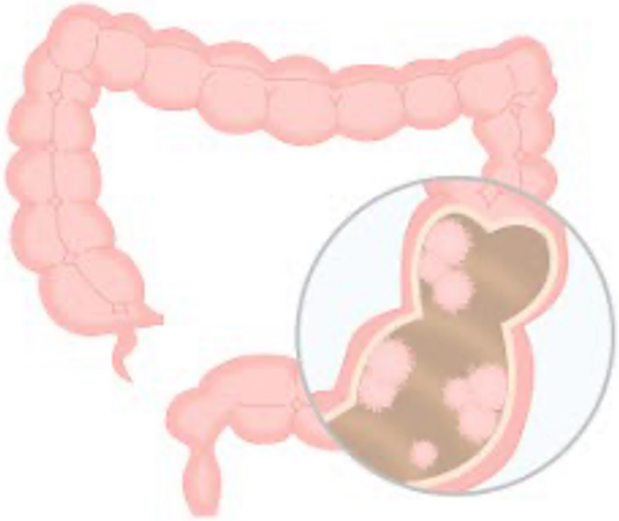
Results: Performance as triage tool

	AN at Screening (n=171)		Number of Initial Colonoscopies (n=594)
PRS Test "Positivity" Cutpoint of CRC Risk	Sensitivity	Specificity	Proportion of colonoscopy Saved as Initial Test
Quintile 1	91.8%	20.1%	99/594=**16.6%**
Quintile 2	70.2%	40.0%	220/594=37.0%
Quintile 3	43.9%	60.0%	350/594=58.9%
Quintile 4	24.6%	79.9%	467/594=78.6%

Implications

- Polygenic risk scores may have a role in risk stratification
  - Triage to non-invasive tests vs colonoscopy
  - Triage to early initiation of screening

CRC Screening Interventions



COMPARISON OF FOUR POPULATION HEALTH INTERVENTIONS TO INCREASE COLORECTAL CANCER SCREENING IN YOUNG ADULTS: RESULTS OF A RANDOMIZED TRIAL

Artin Galoosian[1,2,3], Daniel Croymans[1,3], Hengchen Dai[4], Silvia Saccardo[5], Craig R. Fox[1,4], Greg Goshgarian[6], Maria Han[1,3], Sadie De Silva[1,2,3], Sitaram Vangala[1], Folasade (Fola) Popoola May[2,7,8]

Background:

- Screening newly recommended for age 45 to 49
- Best strategies for rapid implementation and uptake uncertain

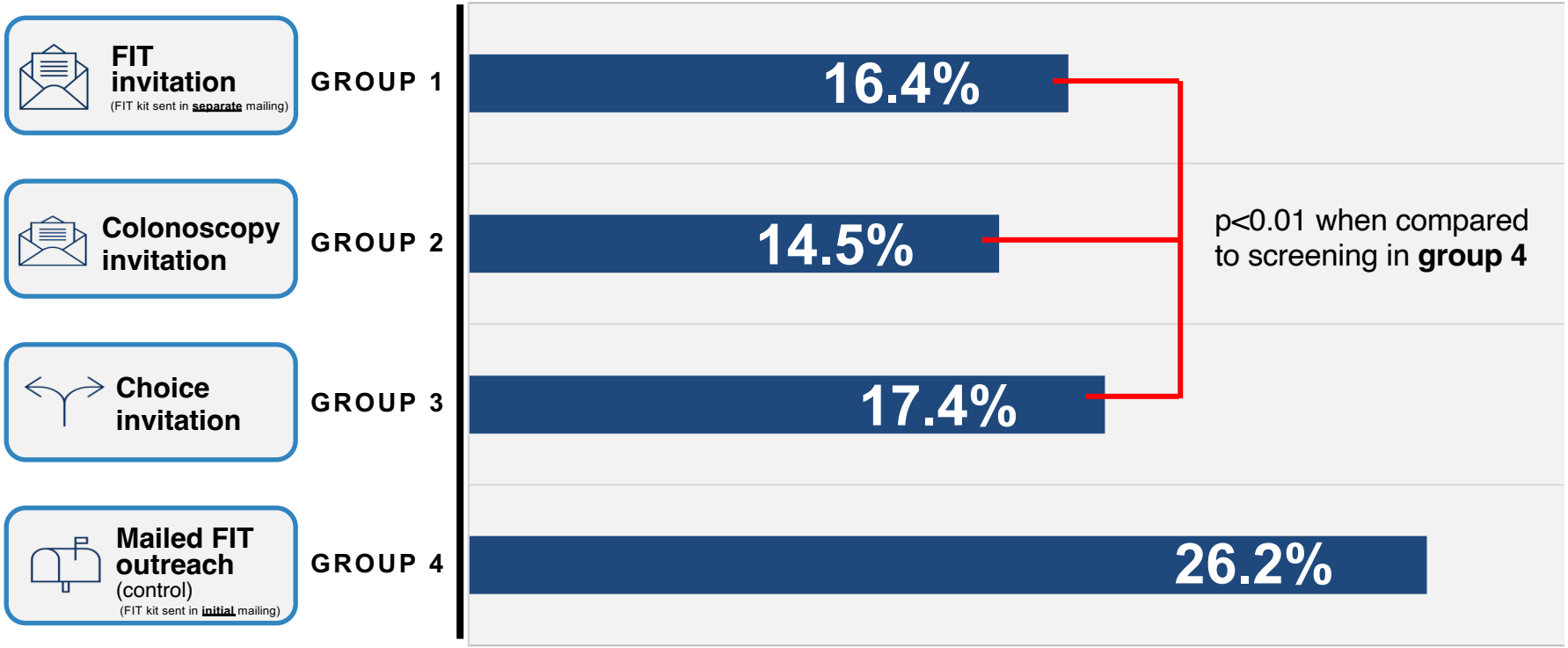
Aim:

- Compare 4 different outreach strategies to maximize screening participation among patients aged 45-49 in a diverse health system.

Methods:

- UCLA health patients age 45-49 assigned to a primary care clinician
- N=20,509 randomly assigned to:
    1) Fecal immunochemical test (FIT) invitation (option to request mailed FIT);
    2) Colonoscopy invitation (option to request colonoscopy);
    3) Choice between FIT and colonoscopy; or
    4) Mailed FIT outreach (standard of care)
- All invitations were sent to patients via the electronic patient portal and received one initial text message and one reminder text message two weeks later.
- Primary outcome: completion of any CRC screening at 26 weeks

Results: Overall Screening Completion Rate Was 18.6%



Slide courtesy of Dr. Folasade May

DDW2023 Digestive Disease Week®

Summary

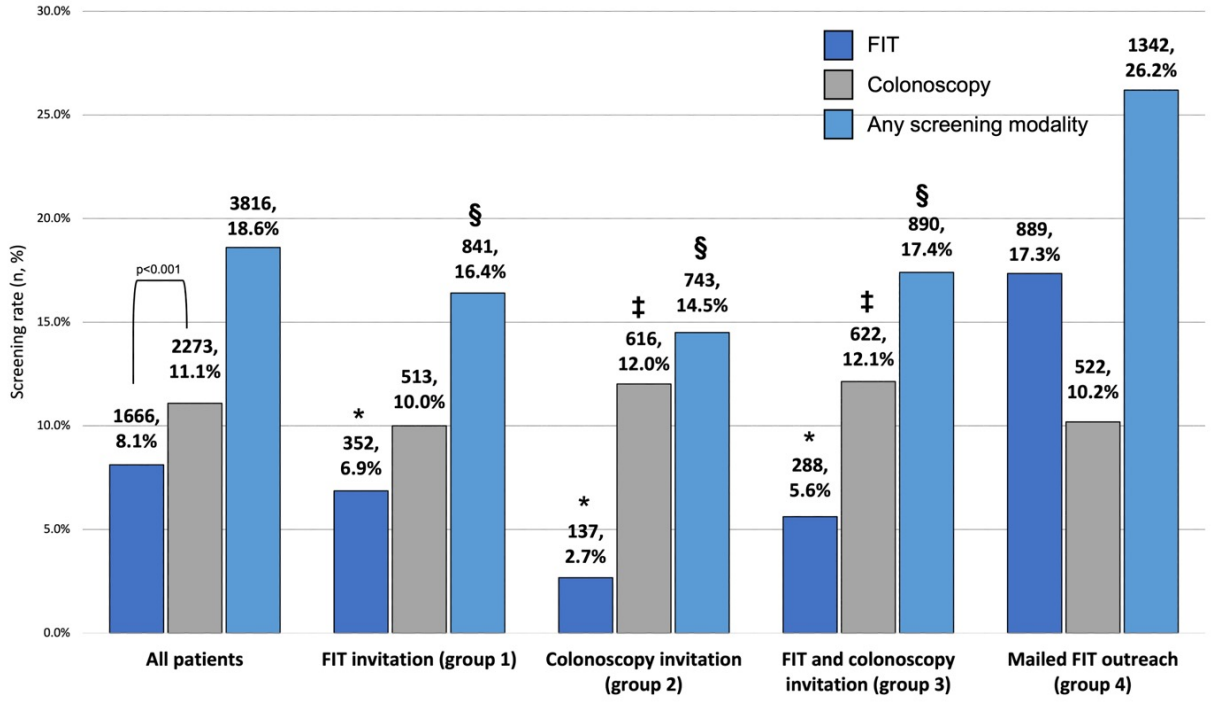
- Emerging data suggests endoscopic screening superior to non-invasive screening
- Novel blood-based tests with performance similar to FIT are likely to be approved
- Individuals with early onset adenoma do not require special follow up beyond current guidelines
- Genetic-based risk stratification strategies are promising for risk stratification
- Best way to get newly eligible people rapidly up to date may be to offer mailed FIT


Thank You!
s1gupta@health.ucsd.edu

Back up information/slides

Results

Figure: Screening participation overall and by screening modality for each intervention group, N=20,509



* indicates p<0.01 compared to FIT in group 4
‡ indicates p<0.01 compared to colonoscopy in group 4
§ indicates p<0.01 compared to any screening modality in group 4