Concurrent Session F

Blood-Based Colorectal Cancer Testing: State of the Science

American Cancer Society | NATIONAL COLORECTAL CANCER ROUNDTABLE

9:55 AM to 11:10 AM

Blood-Based Colorectal Cancer Testing: State of the Science

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Emerging Noninvasive GI Cancer Detection Tests: ctDNA Based Screening Tests

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Emerging Noninvasive GI Cancer Detection Tests:

ctDNA Based Screening Tests

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UNIVERSITY of WASHINGTON

Early Detection Research Network

TBEL

Disclosure Information

- Freenome — Advisory Board Member
- SEngine — Advisory Board Member
- Guardant Health — Advisory Board Member
- Diacarta — Consultant
- Natera — Advisory Board Member
- Clinical trial support: LucidDx Technologies

Non FDA Approved use of products in this presentation:

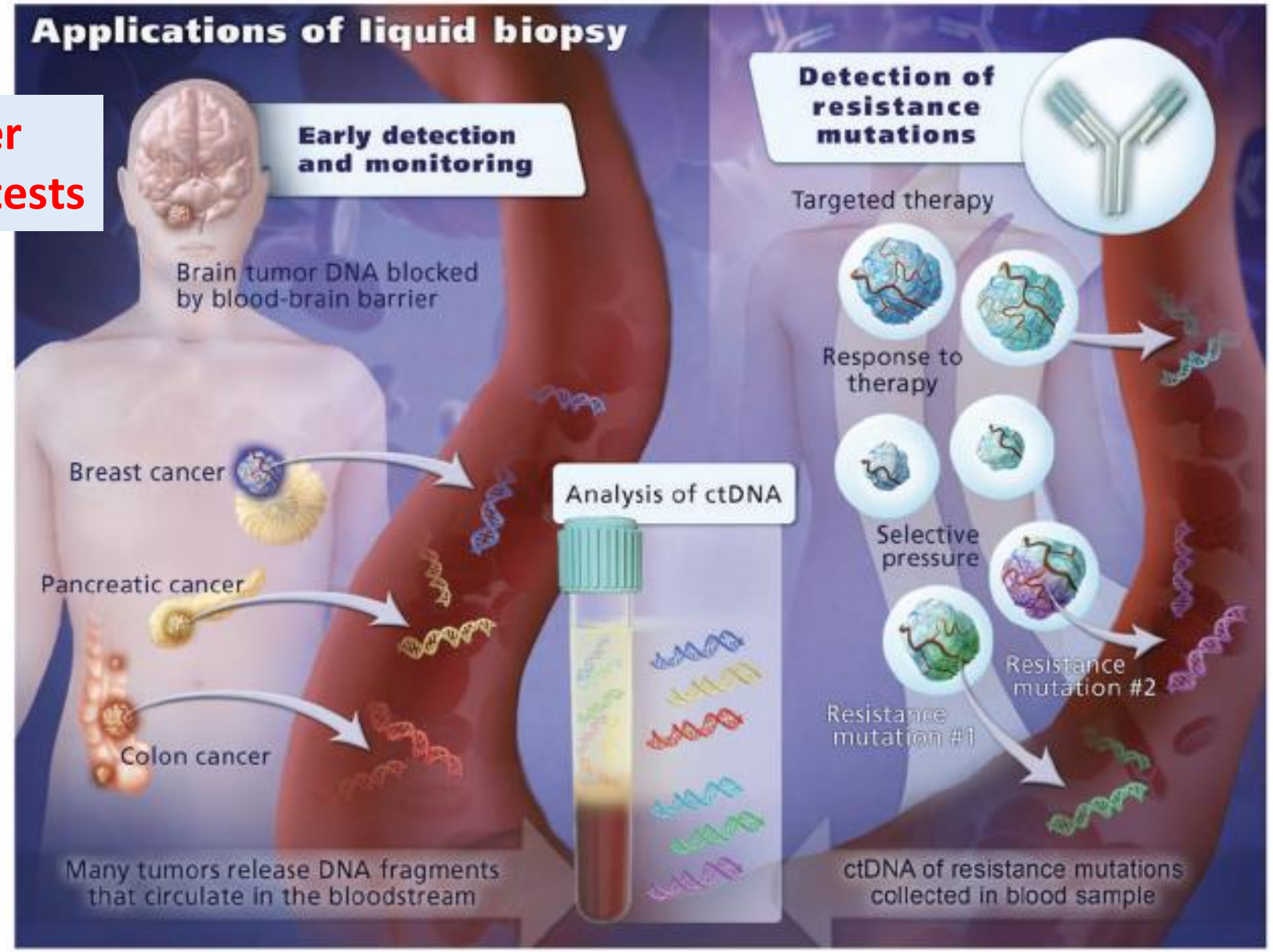
Galleri test

ctDNA Colorectal Cancer Test Overview

- . Test technology
- ctDNA based CRC tests
- MCED tests
  - Test landscape
  - Test performance for CRCs and other GI cancers
  - Test clinical utility

“Liquid Biopsies” and Cancer Detection

Early cancer Screening tests



Bettegowda, 2014

Overview: ctDNA and MCED test technology

- Biomarker assays based on panels of:
  - proteins
  - ctDNA: mutations, methylated DNA, chromatin fragments
  - ctDNA + proteins

- Emerging markers:
  - exosomal RNA and DNA
  - circulating microbial DNA
  - autoantibodies

- These tests depend on AI informed patterns of specific cancers.

ctDNA CRC screening tests

- Shield
  - Guardant Health

- ctDNA and protein assay
  - Freenome

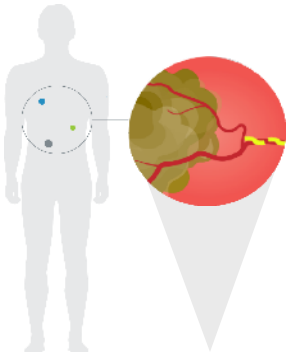
- Epiprocolon (*mSEPT9*)
  - Epigenomics

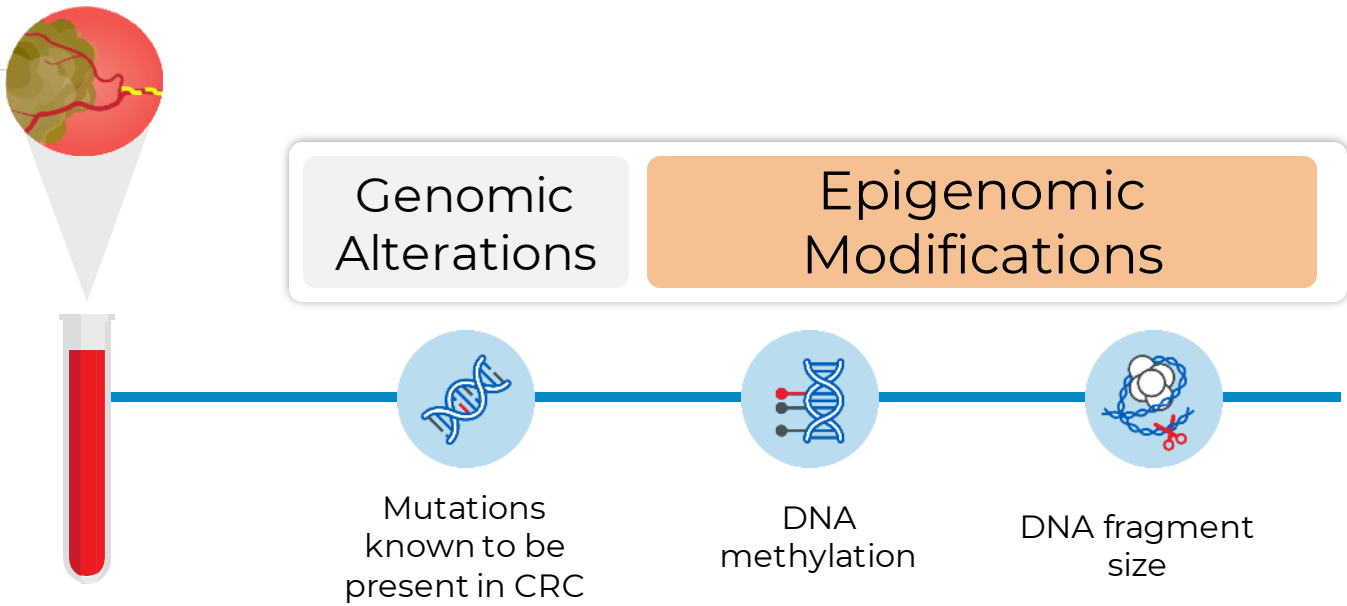
Clinical Validation of a cell-free DNA Blood-based Test for Colorectal Cancer Screening in an Average Risk Population

Daniel C. Chung [1], *Darrell M. Gray II* [2,3], *Joel K. Greenson* [4], *Samir Gupta* [5], *Craig Eagle* [6], *Sylvia Hu* [6], *AmirAli Talasaz* [6], *Rachel B. Issaka* [7,8], *Harminder Singh* [9], *Frank A. Sinicrope* [10], *William M. Grady* [8,11]

1. Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 2. Gray Area Strategies LLC, Owings Mills, MD 3. Association of Black Gastroenterologists and Hepatologists, New York, NY 4. Department of Pathology at Michigan Medicine, Ann Arbor, MI 5. University of California San Diego, San Diego, CA 6. Guardant Health, Palo Alto, CA 7. Clinical Research & Public Health Sciences Divisions, Fred Hutchinson Cancer Center, Seattle Washington 8. Division of Gastroenterology, University of Washington School of Medicine, Seattle Washington 9. Departments of Internal Medicine and Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba & Cancer Care Manitoba Research Institute, Winnipeg, Manitoba, Canada 10. Mayo Clinic and Mayo Alix School of Medicine, Rochester, MN 11. Translational Science and Therapeutics and Public Health Sciences Division, Fred Hutchinson Cancer Center, Seattle, WA

cfDNA blood-based CRC screening test





Integrate these signals to produce an **actionable result**

RESULTS

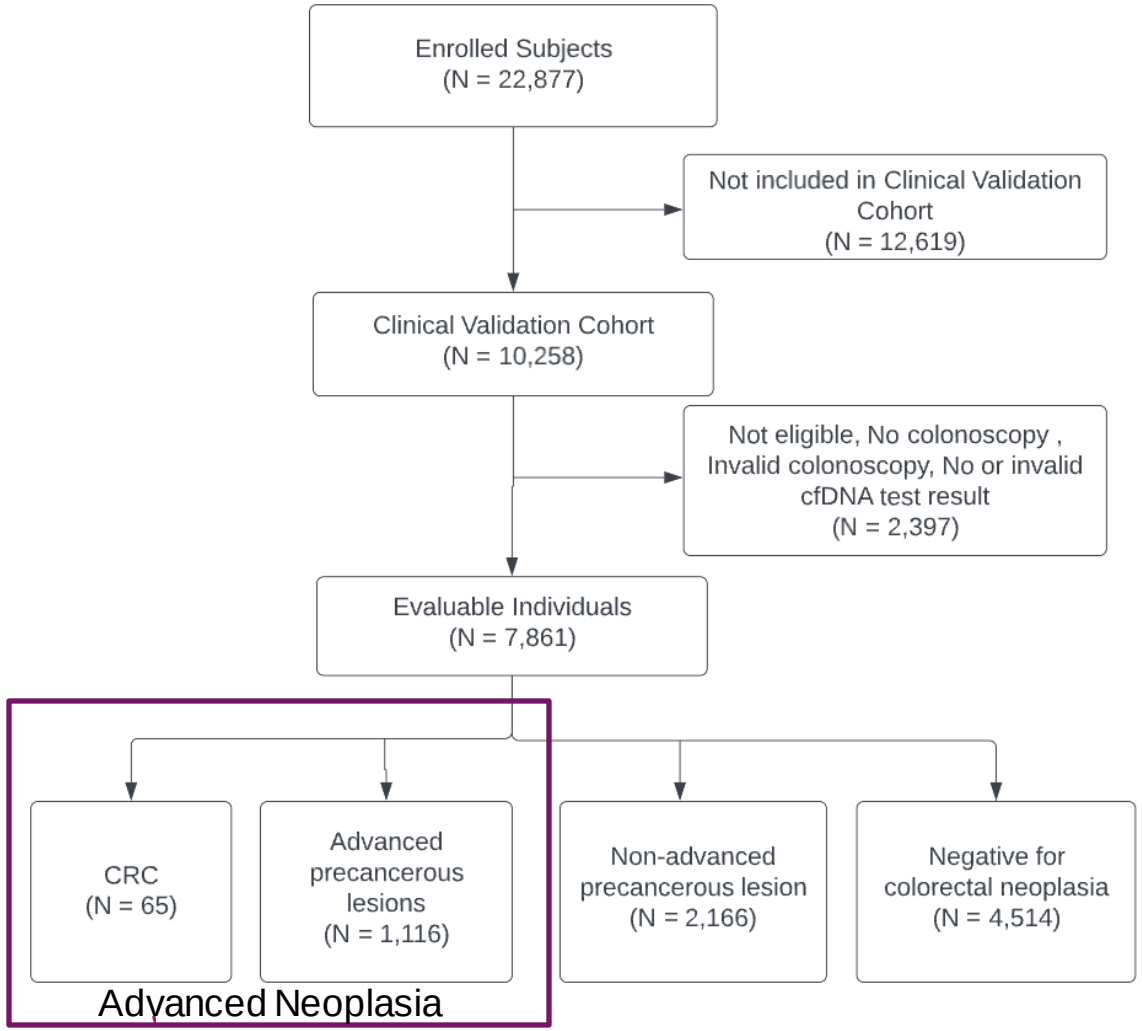
Abnormal Signal Detected

Normal Signal Detected

Chung, et al. Digestive Diseases Week 2023. Abstract #913e

5) D'Auria, et al. 2022. Journal of Clinical Oncology supplement

Enrolled Participants



Colonoscopy Outcome	Histopathology Definition
CRC	CRC
Advanced Precancerous Lesion	Carcinoma in situ High Grade Dysplasia Villous architecture >25% Tubular Adenoma > 10mm Sessile Serrated Lesion > 10mm
Non-advanced precancerous lesion	Adenoma and sessile serrated lesion < 10mm
Negative for colorectal neoplasia	Negative colonoscopy Hyperplastic polyps

Chung, *et al*. Digestive Diseases Week 2023. Abstract #913e

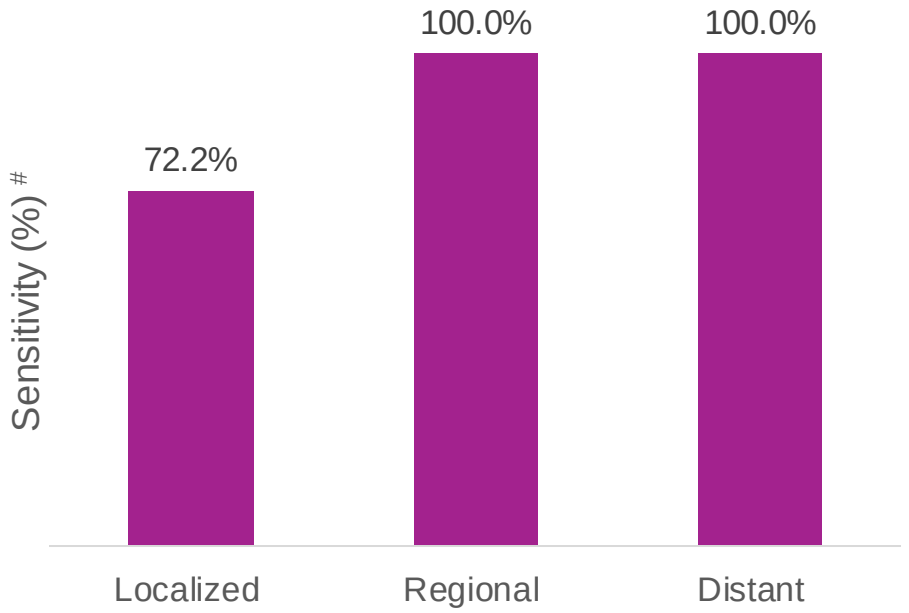
ECLIPSE met co-primary endpoints

CRC Sensitivity	Specificity
83.1% (72.2 - 90.3)	89.6% (88.8-90.3)

Chung, *et al*. Digestive Diseases Week 2023. Abstract #913e

Promising Early-Stage CRC Sensitivity

Overall CRC Sensitivity: 83.1% | Stage I – III Sensitivity : 80%



Excludes 3 lost to clinical follow-up (2 / 3)

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

Stage I*	Stage II	Stage III	Stage IV
54.5% (12/22)	100% (14/14)	100% (16/16)	100% (10/10)

Advanced Precancerous Lesion Detection

Sensitivity for more advanced pathology trended higher

Most advanced finding on Colonoscopy		Positive Results	Sensitivity
Advanced Lesions	1116	147	13.2% (11.3-15.3)
High Grade Dysplasia	31	7	22.6% (11.4-39.8)

- No significant differences in APL sensitivity based on key clinical characteristics
- Sensitivity for more advanced pathology trended higher

Chung, *et al*. Digestive Diseases Week 2023. Abstract #913e

cfDNA blood-based test: poised to have high impact on CRC screening

	CRC Sensitivity[6,7]	Patient Adherence Rate[8-13]	Effective Sensitivity
cfDNA Blood Test	83%	85 - 96%	75 - 80%
Colonoscopy	95%	28 - 42%	27 - 40%
FIT stool test	74%	43 - 65%	32 - 48%
Multitarget stool DNA test	92%	48 - 60%	44 - 55%

Screening programs require consideration of clinical effectiveness: Performance of the test under real world conditions[14]

The cfDNA blood-based test is a highly effective CRC screening option

6) Imperiale, et al. 2014. NEJM; 7) Knudsen, et al. 2021. JAMA; 8) Lin JS, et al. 2021. Agency for Healthcare Research and Quality; 9) Bretthauer, et al. 2022. NEJM; 10) Forsberg, et al. 2022. Lancet Gastroenterol Hepatol; 11) Quintero, et al. 2012. NEJM.; 12) Jensen, et al. 2016. Ann Intern Med; 13) Bakker, et al. 2011. Endoscopy; 14) Singal, et al. 2014. Clin Transl Gastroenterol

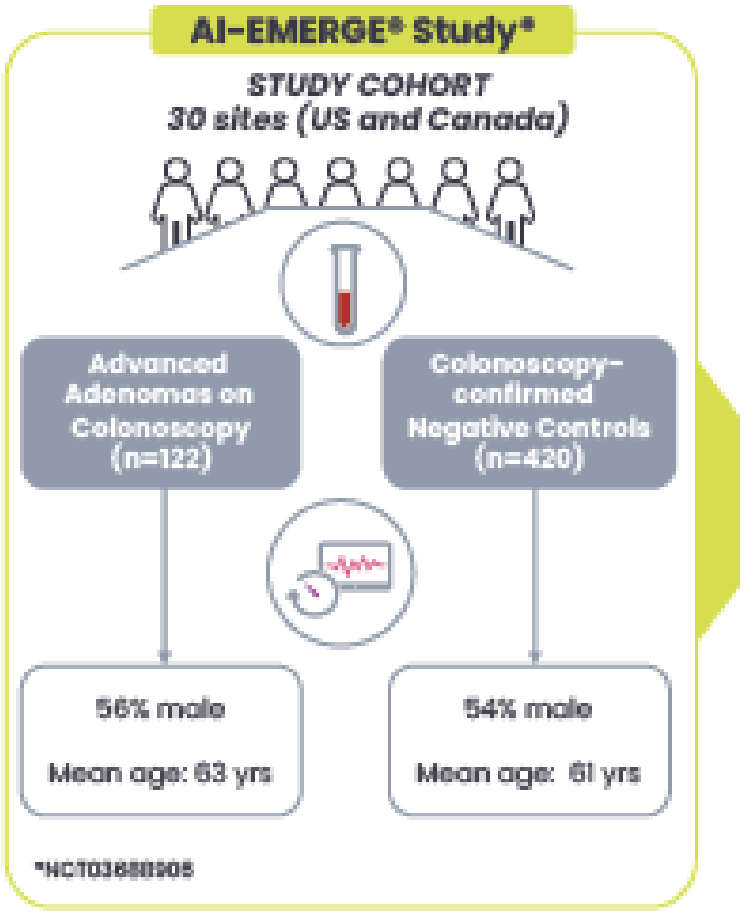
Chung, *et al*. Digestive Diseases Week 2023. Abstract #913e

Conclusions

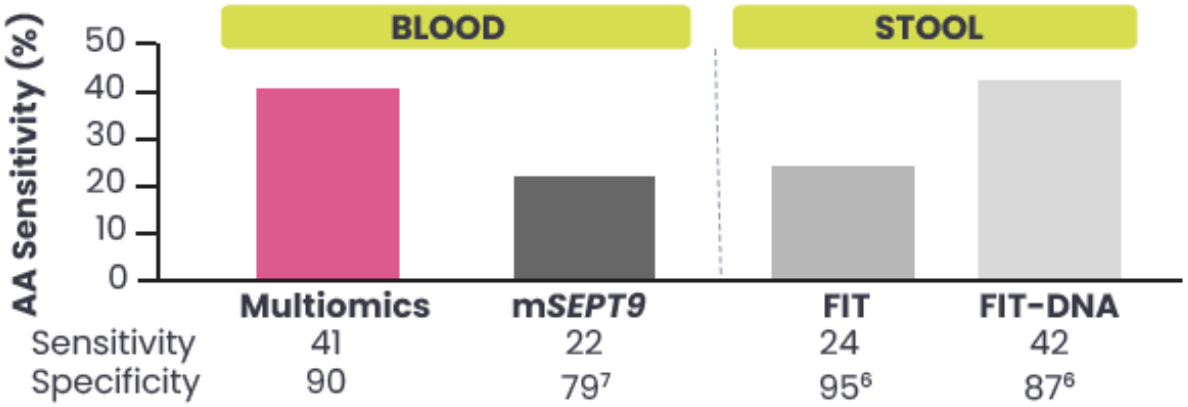
- This cfDNA blood-based test demonstrates **83% sensitivity, 90% specificity** in average-risk CRC screening, including clinically relevant early-stage performance
- The ECLIPSE study diversity is reflective of the demographics of the intended use population in the US
- This cfDNA assay is the **first blood-based test with performance comparable to current guideline-recommended non-invasive options for CRC detection**
- Combined with improved adherence with blood-based diagnostics, this blood-based testing strategy has the potential to have a significant impact on CRC screening in the population

ctDNA+ protein blood CRC assay

- Assay-ctDNA and proteins (Freenome)



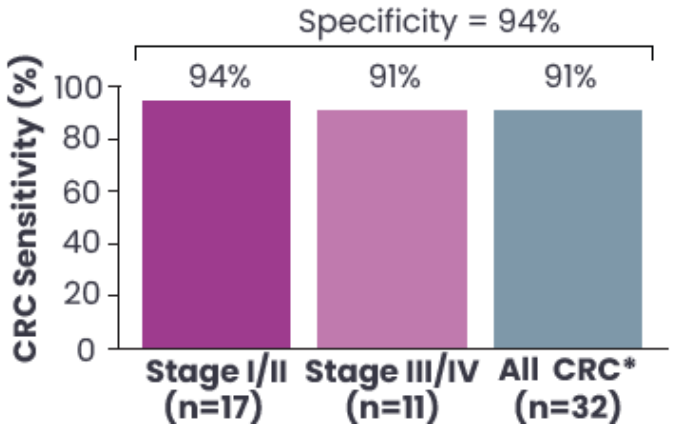
Adv Adenoma Detection



AA sensitivity was greater than m*SEPT9*, the only blood test for CRC screening currently available

AA sensitivity was much higher than FIT and comparable to FIT-DNA

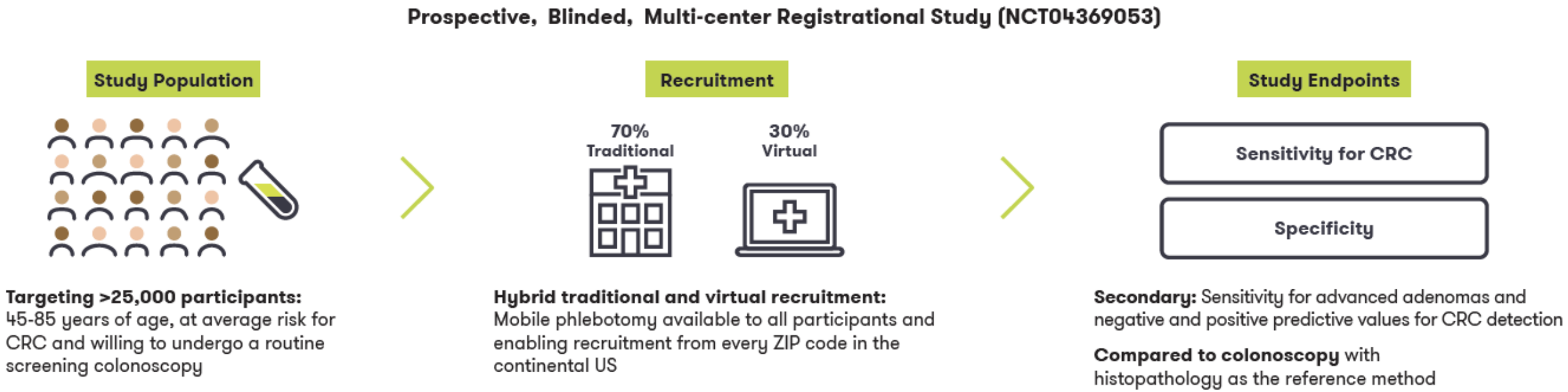
CRC Detection



Lin, 2021

PREEMPT TRIAL

- Assay-ctDNA and proteins (Freenome)



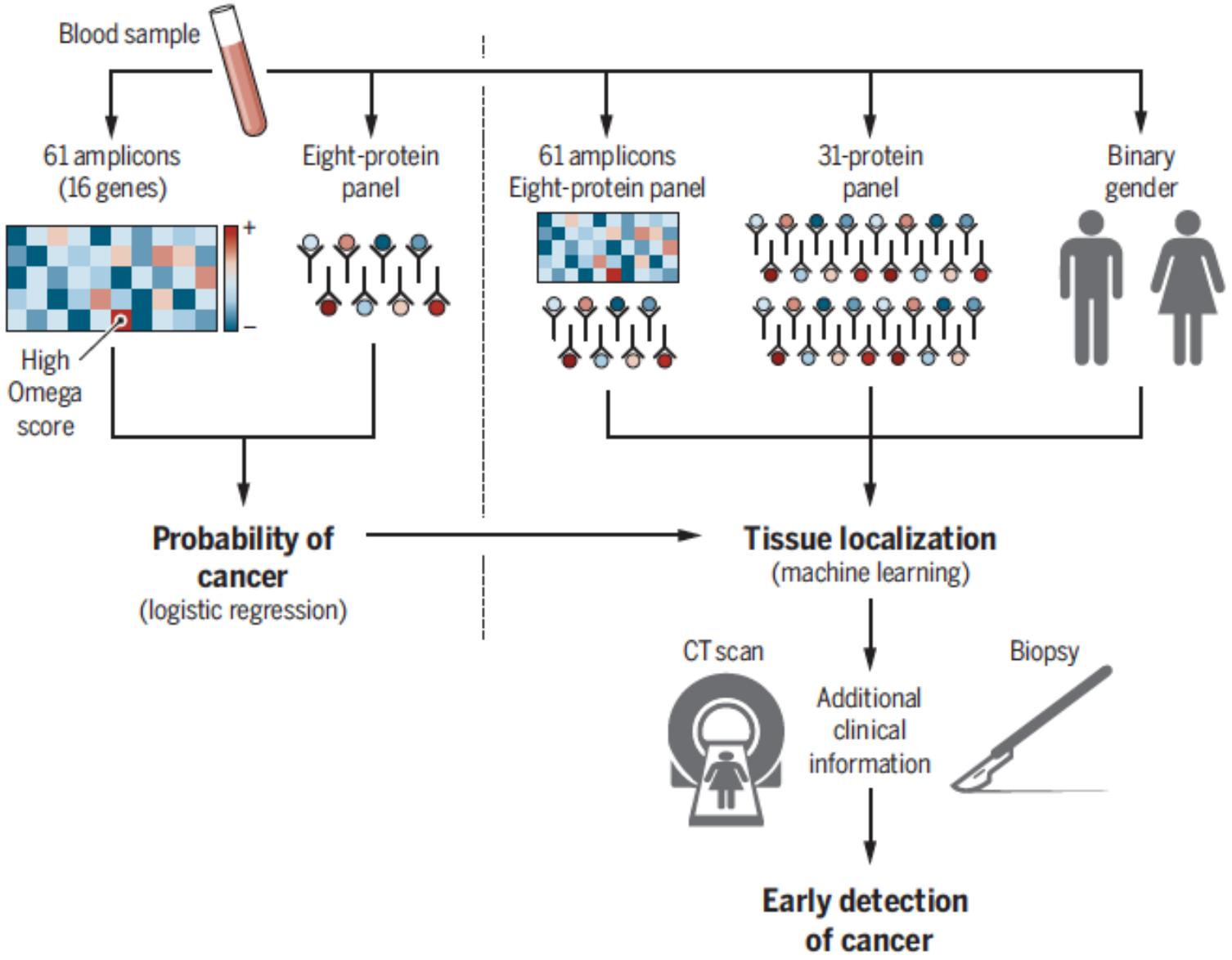
-N=49170 subjects enrolled between May 2020 and March 2022 (at the time of the Jan 26, 2023 snapshot).
-Ethnic diversity well represented in enrolled study population

Putcha, 2022
Shaukut 2023

Multi-Cancer Early Detection Tests (MCED)

- CancerGuard™ (CancerSEEK)
  - Thrive/Exact Sciences
- Galleri™
  - Grail/Illumina
- MCED test-”anchor” indications
  - Guardant Health, Freenome, etc
- Other companies with MCED tests in development:
  - Foundation Medicine, AnchorDx, Burning Rock Biotech, GENECAST, Singlera Genomics, Laboratory for Advanced Medicine

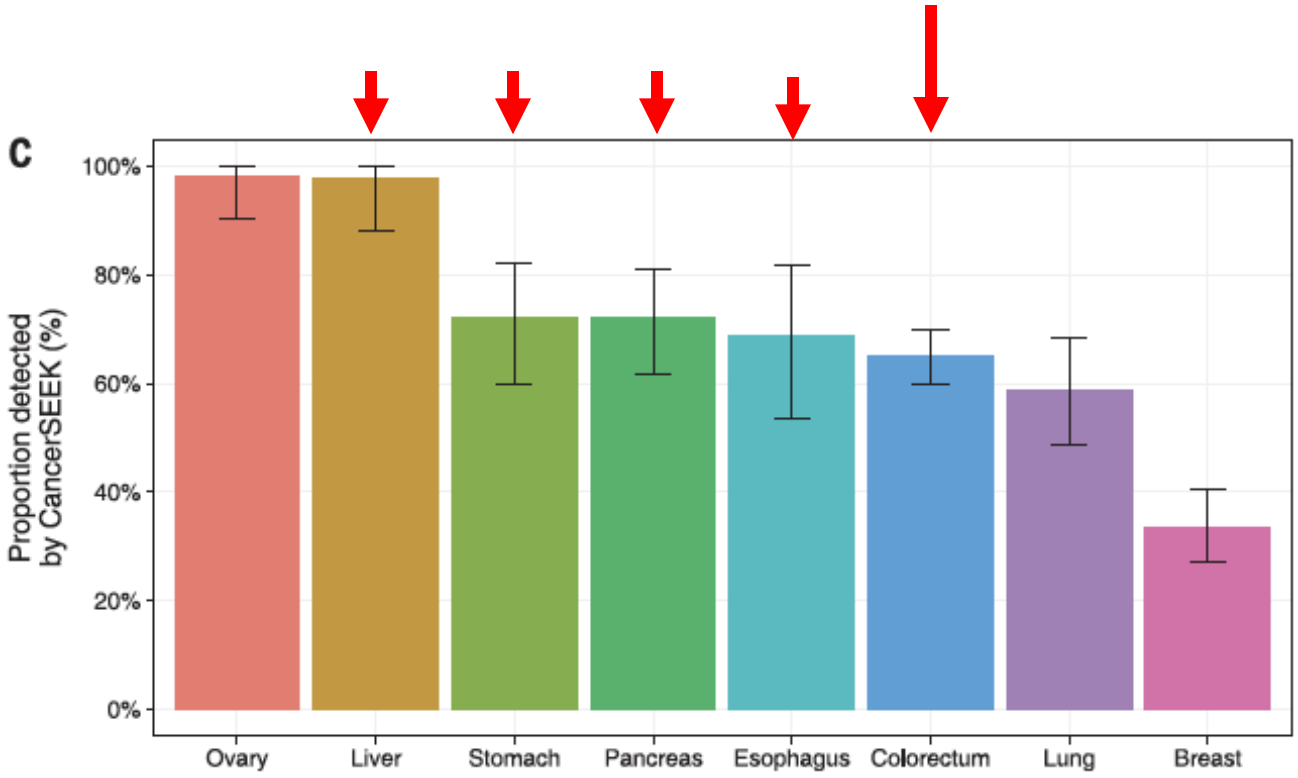
CancerSEEK-MCED Assay



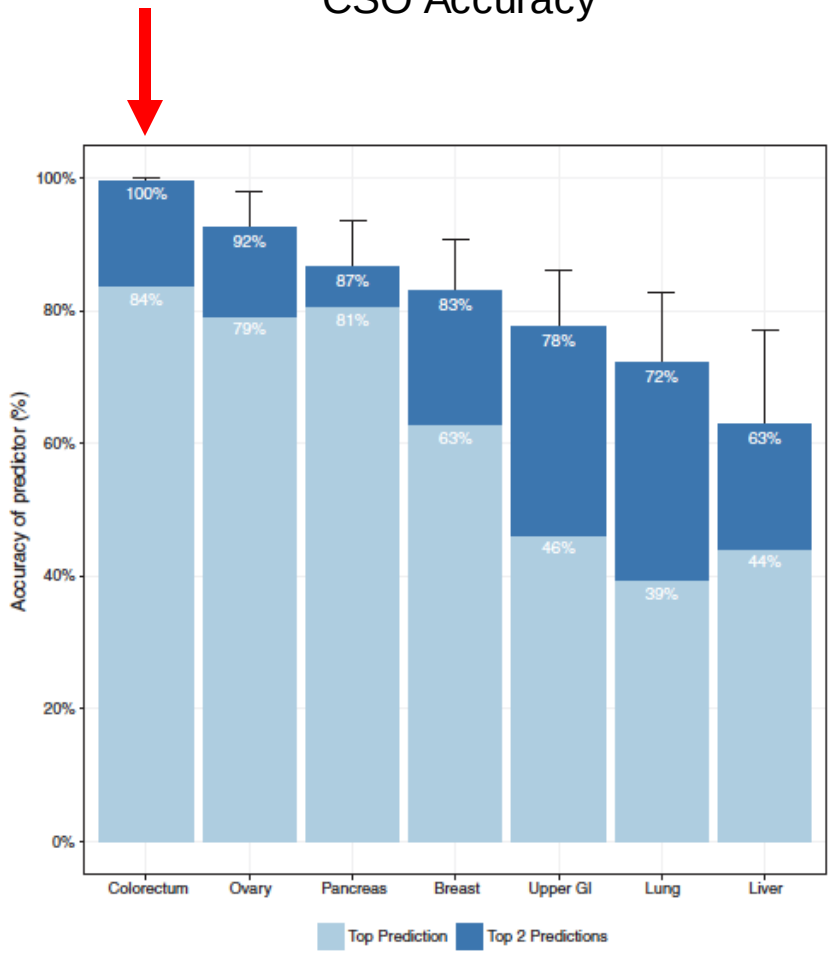
Cohen, 2018

CancerSEEK-MCED Assay

Sensitivity



CSO Accuracy



Cohen, 2018

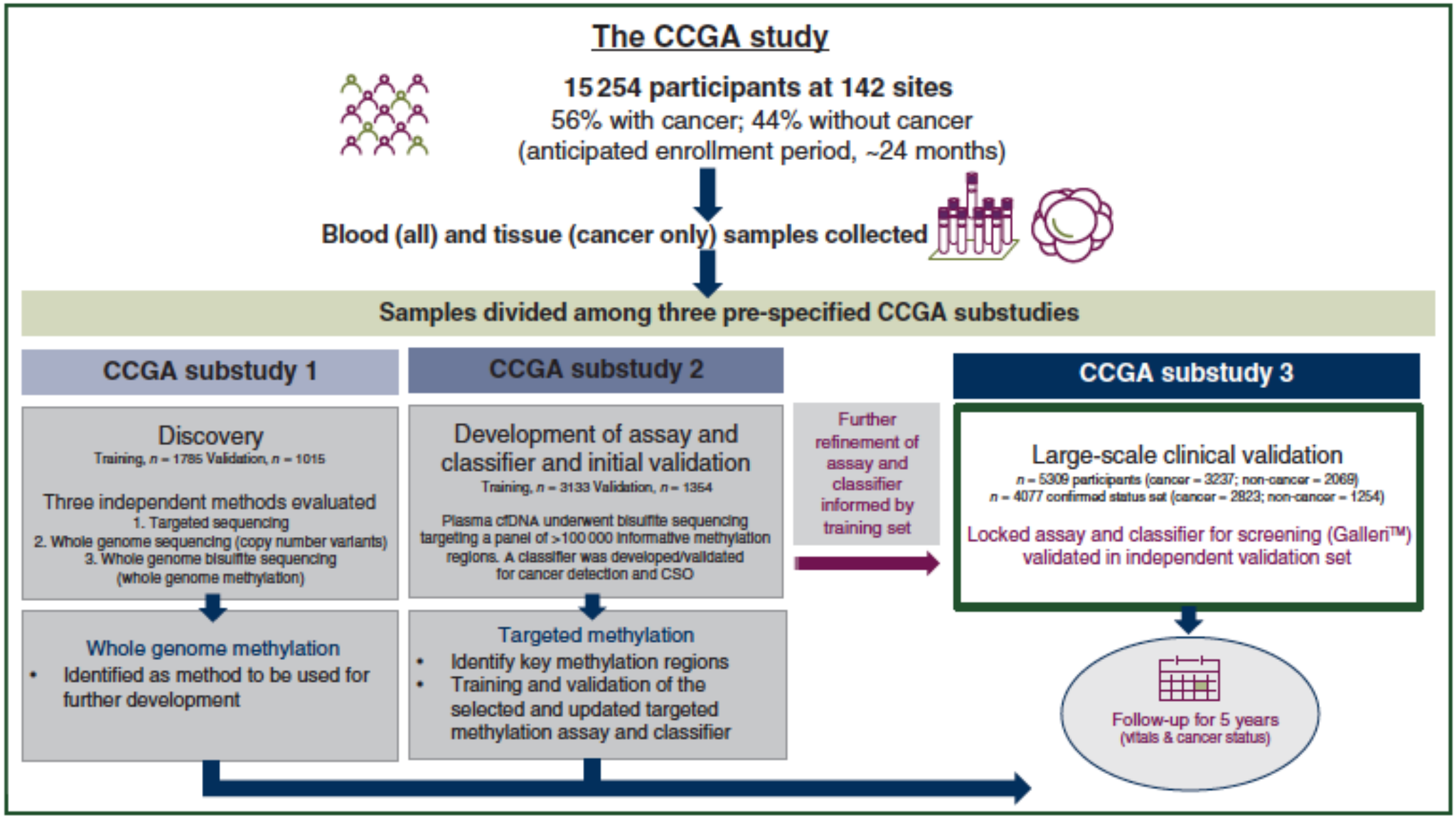
Next Generation CancerGuard™ MCED test

Sensitivity, % (95% CI).

99% Specificity	Bladder	Breast	Cervical	Colorectal	Esophageal	Liver	Lung	Ovarian	Pancreatic	Prostate	Renal	Stomach	Uterine	All Cancers
MDMs	50 (30-70)	64 (39-84)	100 (72-100)	65 (50-79)	100 (21-100)	62 (36-82)	85 (71-93)	75 (41-93)	67 (49-81)	20 (6-51)	45 (26-66)	82 (61-93)	90 (60-98)	68 (62-74)
Proteins	20 (8-42)	35 (16-61)	20 (6-51)	26 (15-42)	100 (21-100)	23 (8-50)	68 (52-80)	100 (68-100)	73 (56-86)	30 (11-60)	10 (3-30)	46 (27-65)	60 (31-83)	43 (37-50)
MDMs + Proteins	55 (30-70)	64 (39-84)	100 (72-100)	79 (64-89)	100 (21-100)	62 (36-82)	90 (77-96)	88 (53-98)	83 (66-93)	40 (17-69)	45 (26-66)	82 (61-93)	90 (60-98)	75 (69-80)
	Stage II	Stage III	Stage IV	Stage N/A										
MDMs	54 (42-66)	62 (49-73)	81 (70-89)	76 (62-86)										
Proteins	25 (16-37)	24 (15-37)	68 (56-78)	54 (40-68)										
MDMs + Proteins	62 (50-73)	67 (54-78)	87 (77-93)	83 (69-91)										

Katerov ASCO 2023

Galleri-MCED Assay—mDNA based



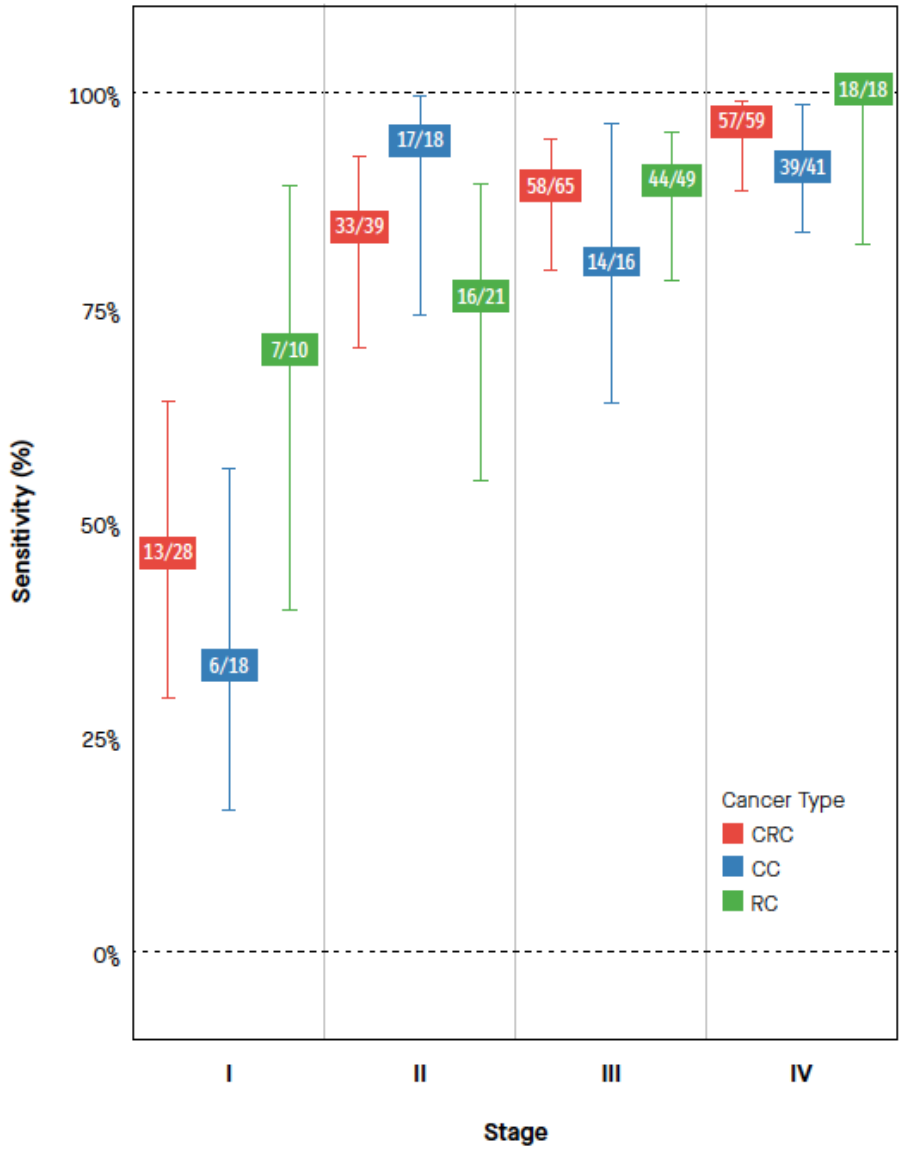
Klein, 2021

Galleri-MCED Assay-GI cancer detection

Table 1. The MCED Test Detected Multiple GI Cancers (All Stages) in CCGA3.

Cancer Type	Total N	Sensitivity % (95% CI)
Liver/Bile-duct	46	93.5 (82.5 - 97.8)
Esophagus	100	85.0 (76.7 - 90.7)
Pancreas	135	83.7 (76.6 - 89.0)
Colon/Rectum*	206	82.0 (76.2 - 86.7)
Anus	22	81.8 (61.5 - 92.7)
Gallbladder	17	70.6 (46.9 - 86.7)
Stomach	30	66.7 (48.8 - 80.8)

Colorectal Cancer

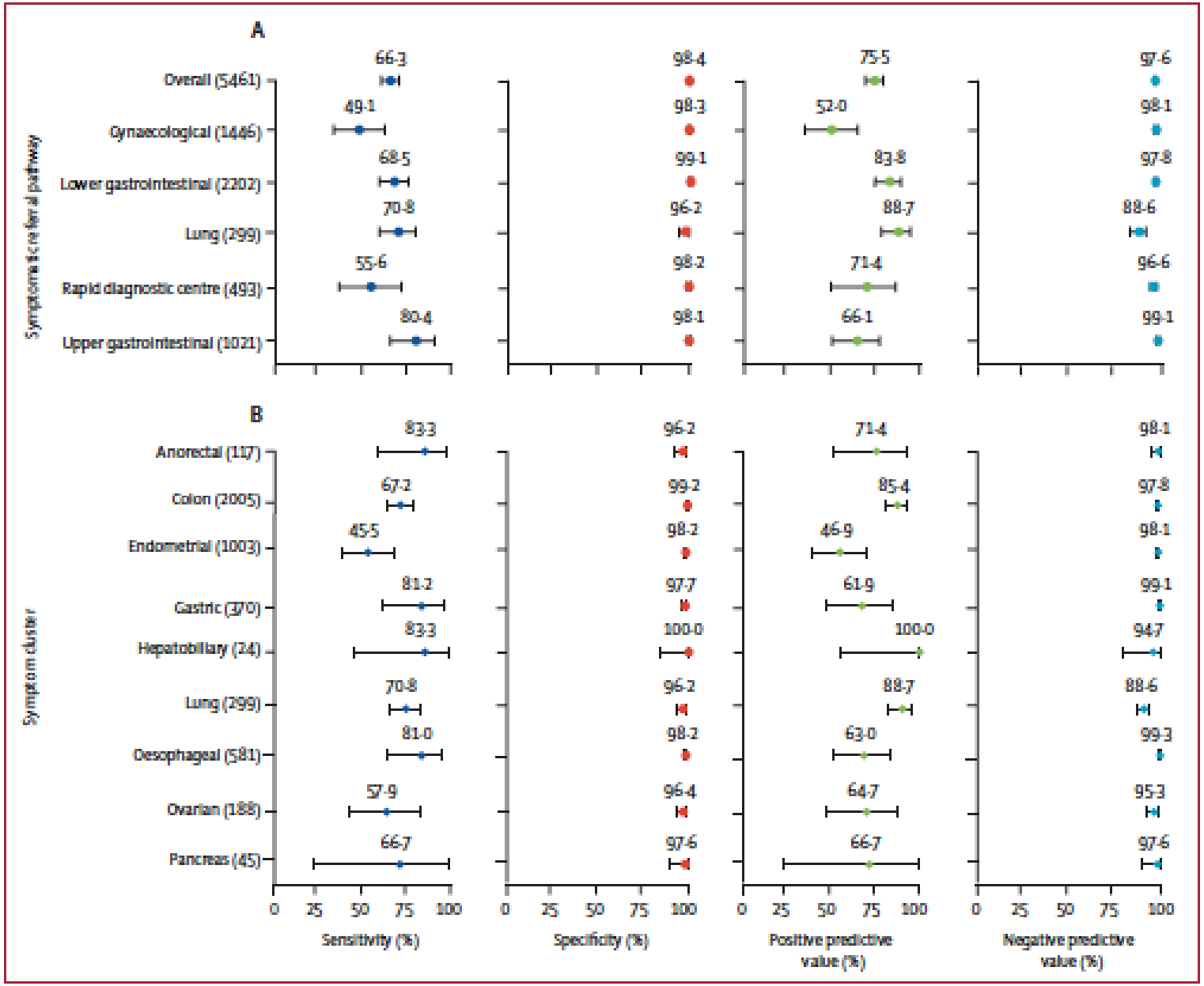


Margolis 2023

Galleri-MCED Assay-GI cancer detection

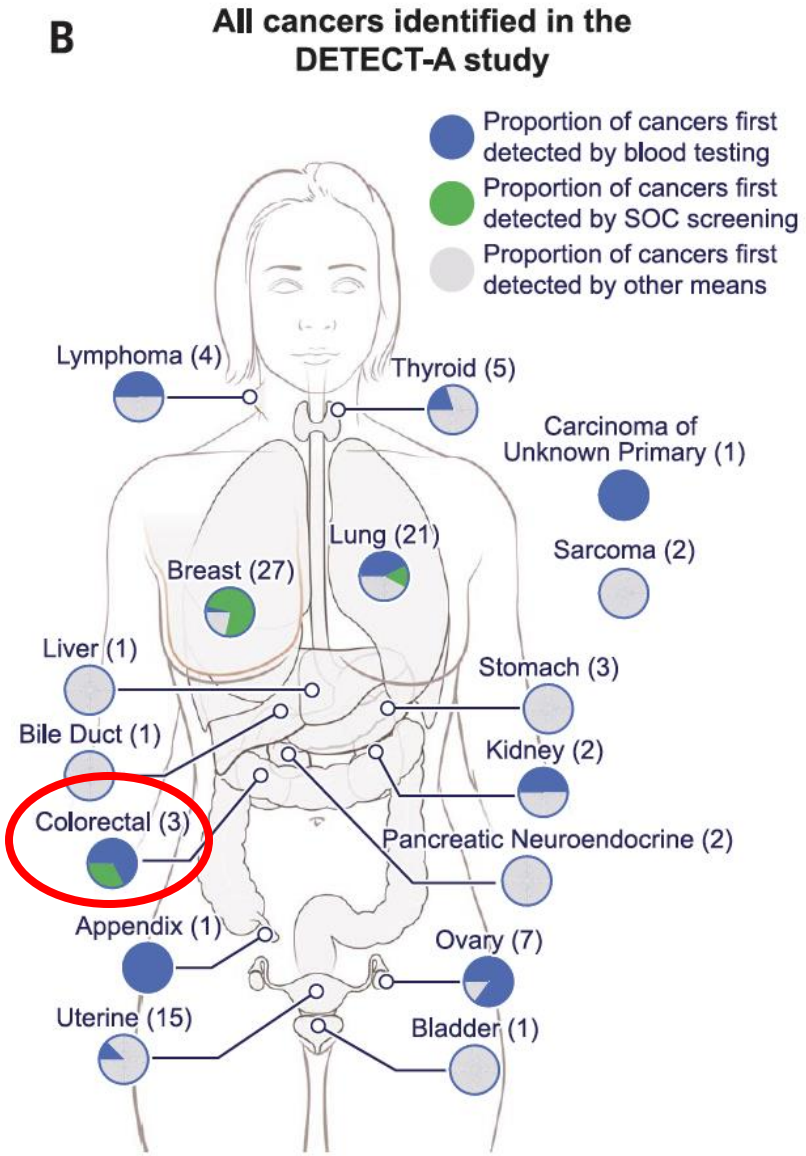
Symptomatic Colorectal Cancer

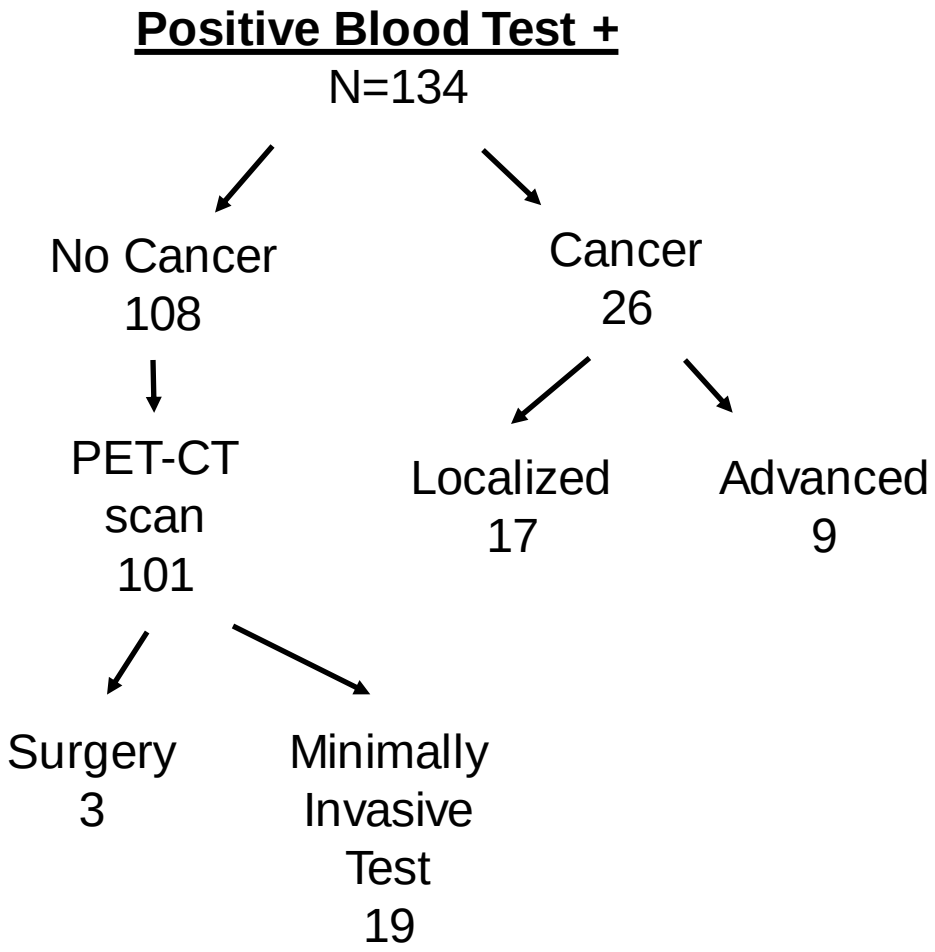
Symptomatic Colorectal Cancer



Nicholson SYMPLFY study 2023

Value of MCED tests beyond Standard of Care screening and Potential for Harm





Total Number of Subjects= 9911

Lennon 2020

Clinical Utility of MCED tests

- **Potential impact and unresolved issues**
  - Potential to revolutionize cancer screening-convenience, multiple cancers with one test, screening of non-standard of care cancers
  - Issues for discussion
    - Cost effectiveness
    - Effectiveness of screening for “unscreened” cancers
      - Overdiagnosis
      - Unknown impact on cancer related mortality
    - Harms caused by unnecessary procedures and diagnostic tests
    - Patient and care provider anxiety
    - How to best evaluate MCED tests in the near-term

Conclusions

- ctDNA CRC screening assays appear to have sensitivity for CRC similar to other noninvasive CRC screening tests

- Current versions of ctDNA CRC screening tests will likely have lower sensitivity for colon adenomas and serrated polyps than stool based tests or colonoscopy.

- ctDNA based MCED assays and CRC screening
  - Technical performance of the assays is promising but more data is needed to determine role in CRC screening.
  - It is unclear how to best evaluate the performance of MCED tests

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Thank You

nccrt.org @NCCRTnews #80inEveryCommunity

Colorectal Cancer Screening in a Changing World: Implications for Screening At-Risk Populations

Robert S. Bresalier, MD
Professor, Department of Gastroenterology, Hepatology & Nutrition
Division of Internal Medicine
University of Texas MD Anderson Cancer Center

Colorectal Cancer Screening in a Changing World: Implications for Screening At-Risk Populations

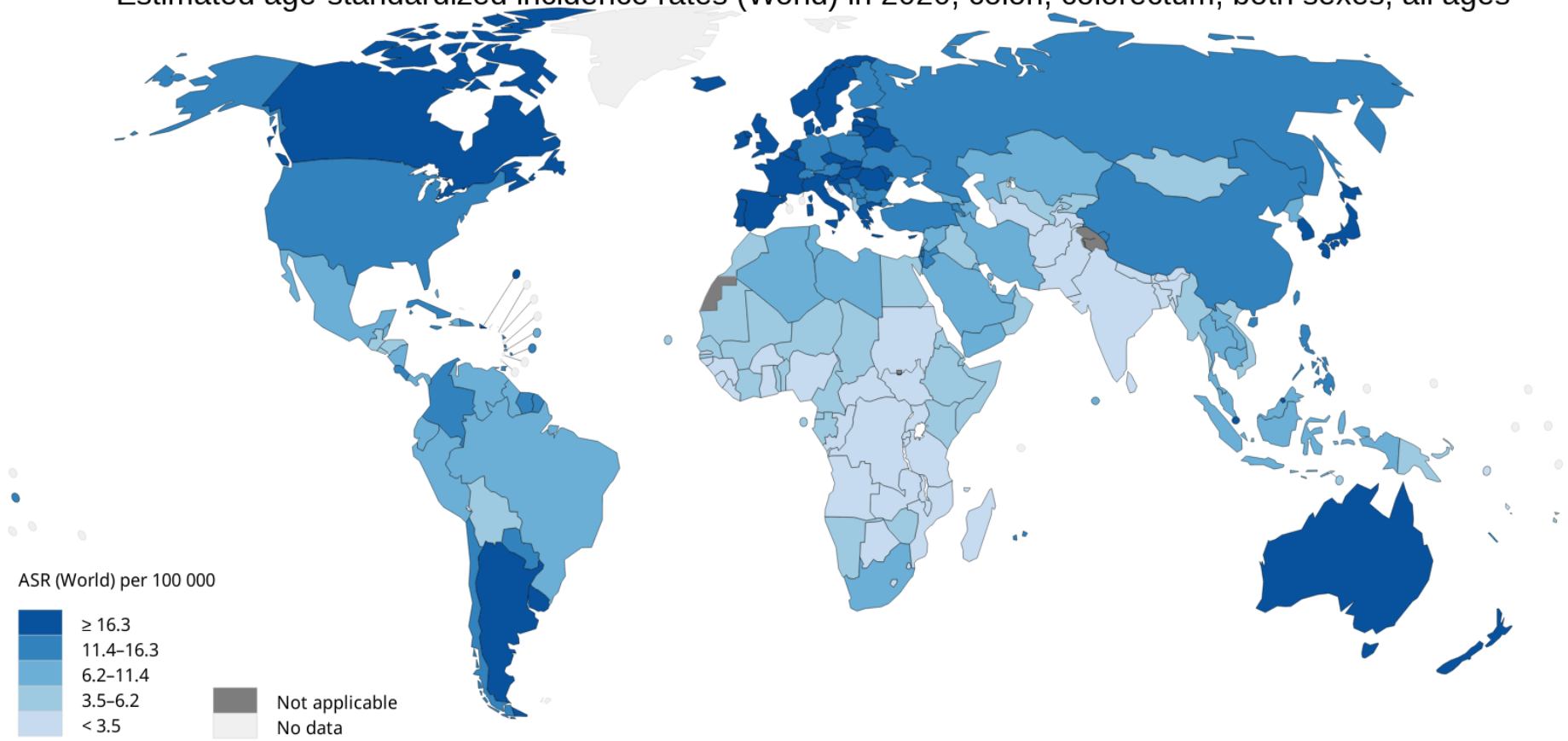
An efficient strategy for evaluating new non-invasive screening tests for colorectal cancer: The guiding principles

Robert S. Bresalier, M.D.

Professor of Medicine and Distinguished Professor in Gastrointestinal Oncology
University of Texas MD Anderson Cancer Center

Colorectal Cancer is a Global Disease

Estimated age-standardized incidence rates (World) in 2020, colon, colorectum, both sexes, all ages



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Data source: GLOBOCAN 2020
Map production: IARC
(http://gco.iarc.fr/today)
World Health Organization

World Health Organization

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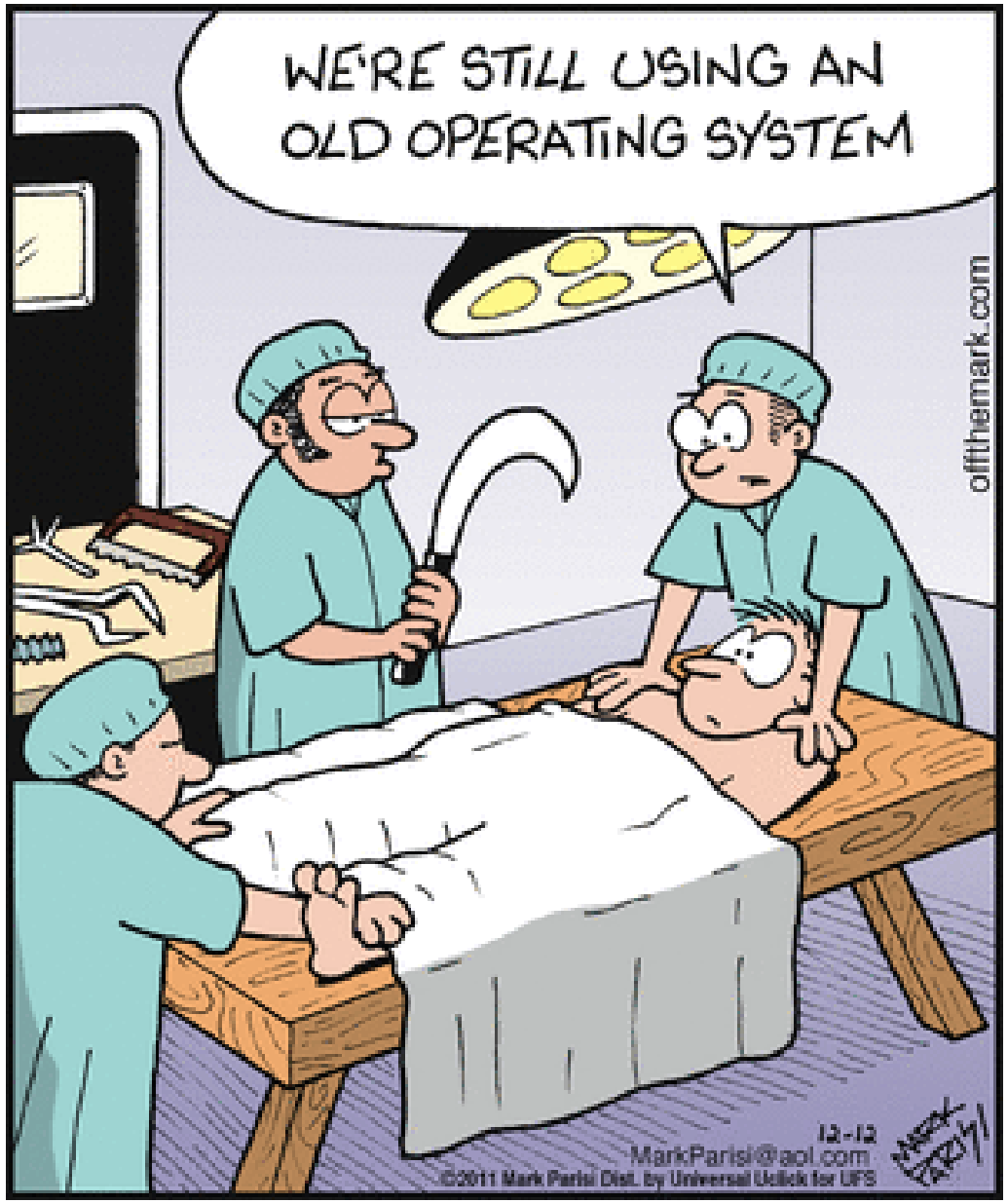
Overcoming multiple barriers to screening will require

- Efficient use of multiple screening modalities
- **Continued development of noninvasive screening tests**
- Improved personal risk assessment to best risk-stratify patients
- Development of organized screening programs to achieve targeted screening rates and reductions in CRC morbidity and mortality


WE'RE STILL USING AN OLD OPERATING SYSTEM
offthemark.com
12-12
MarkParisi@aol.com
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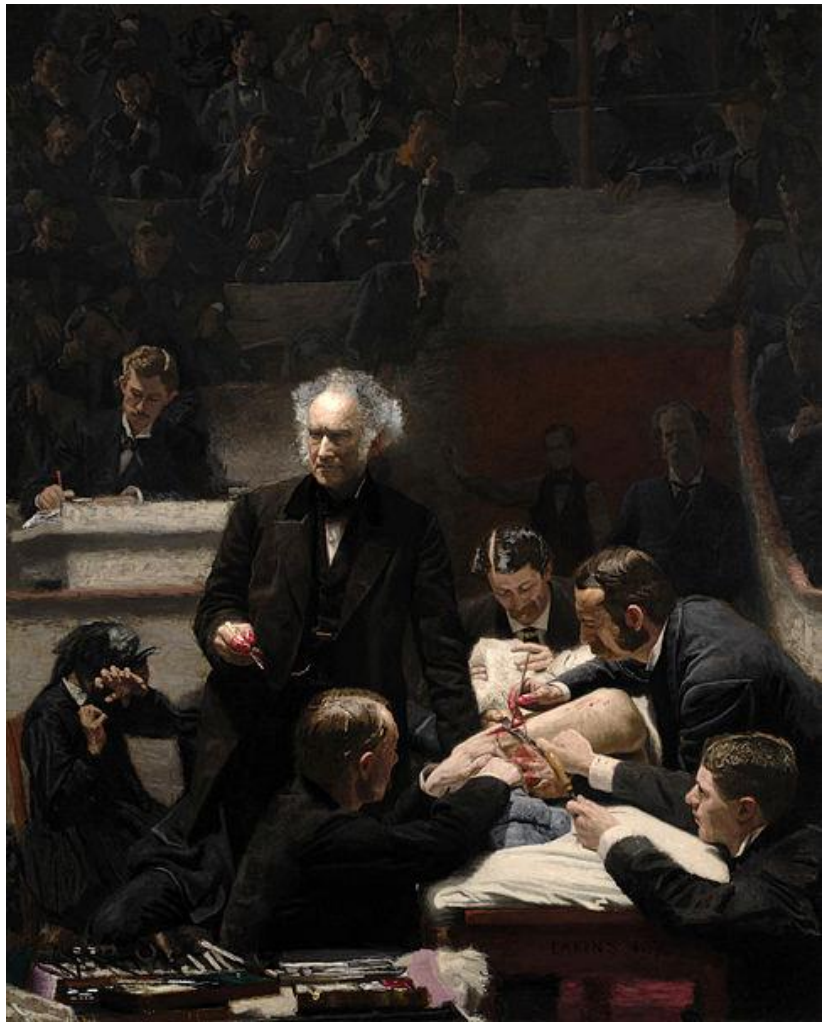
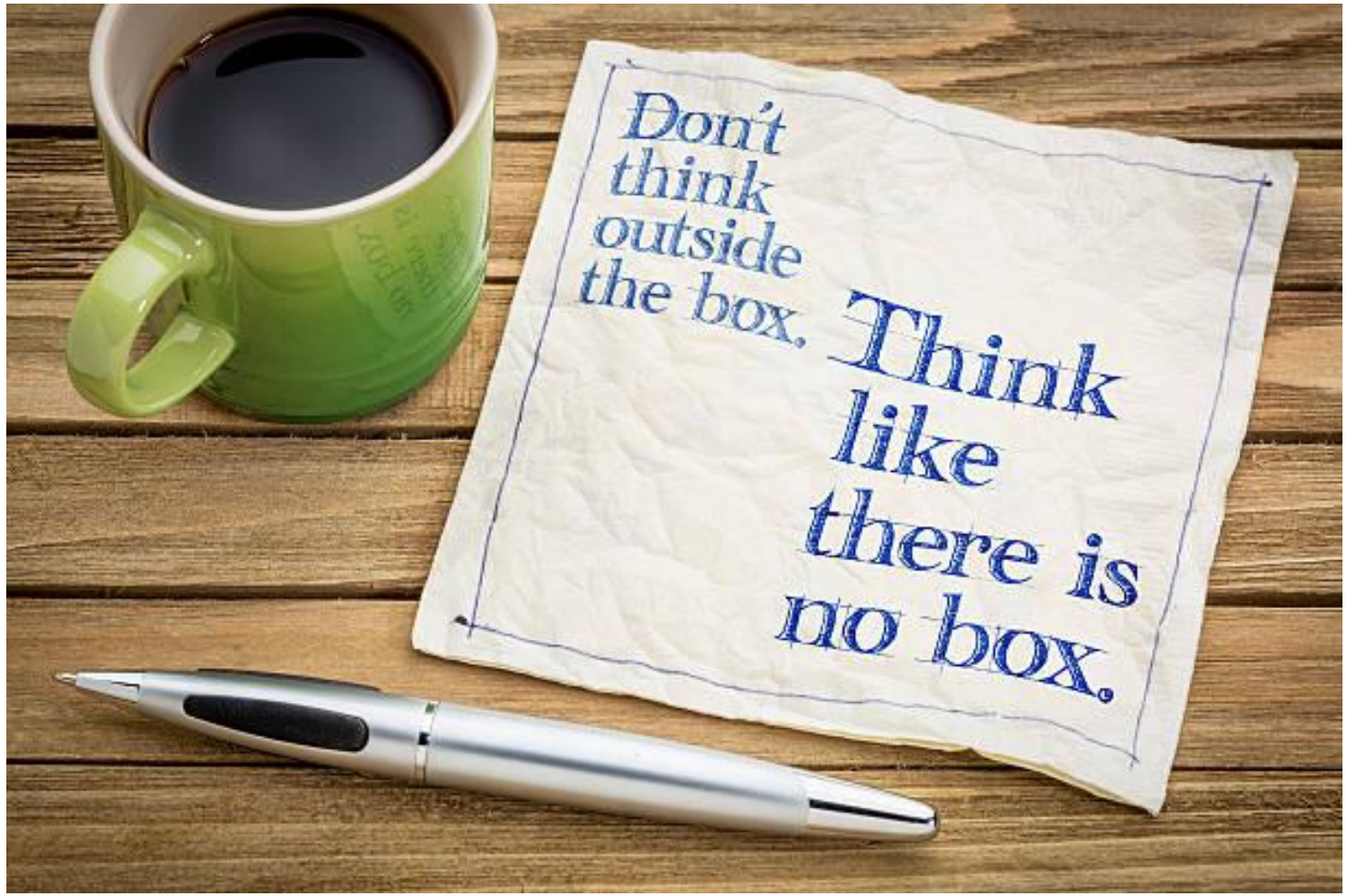
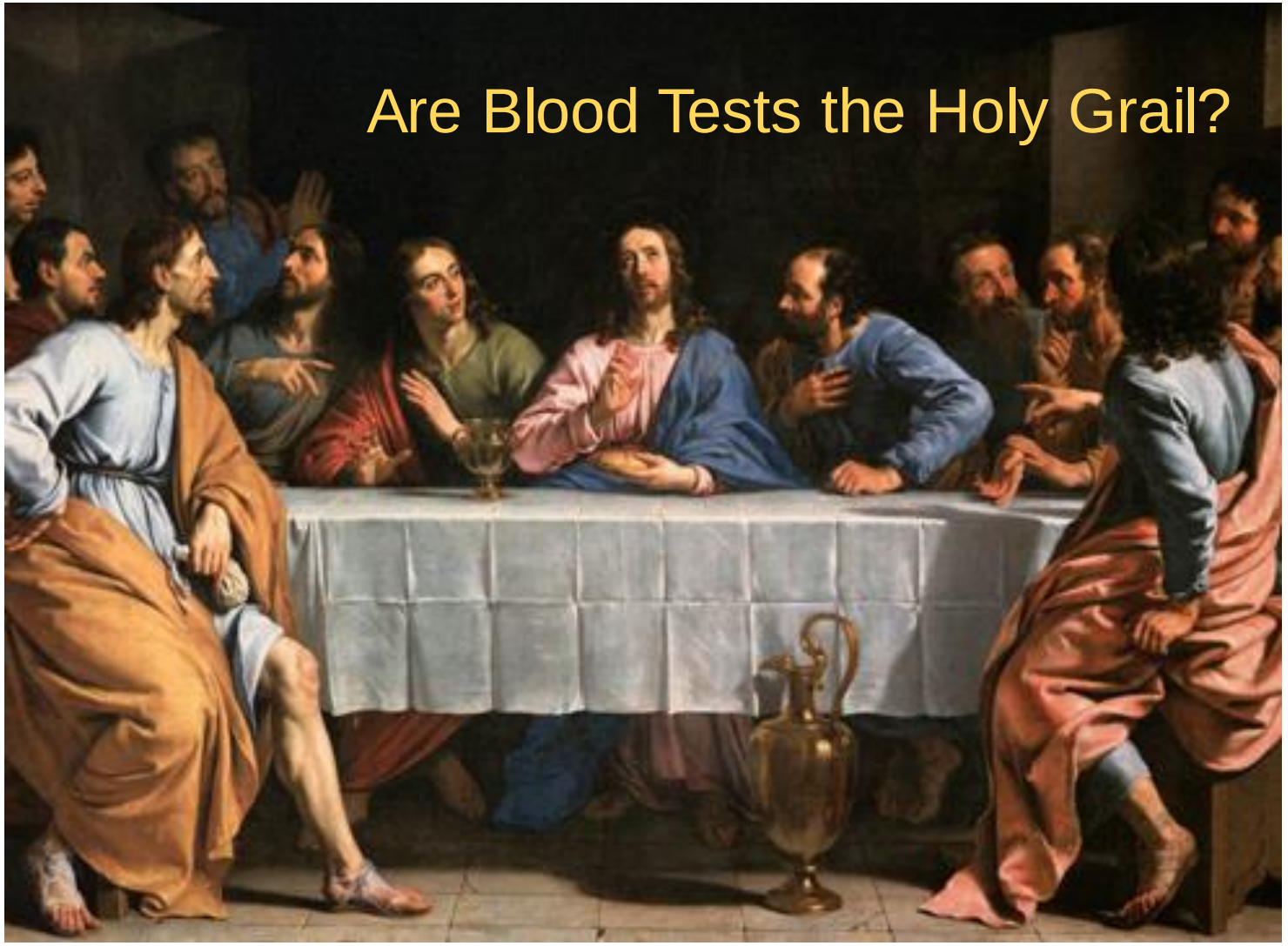



Don't think outside the box.
Think like there is no box.



It's all about context

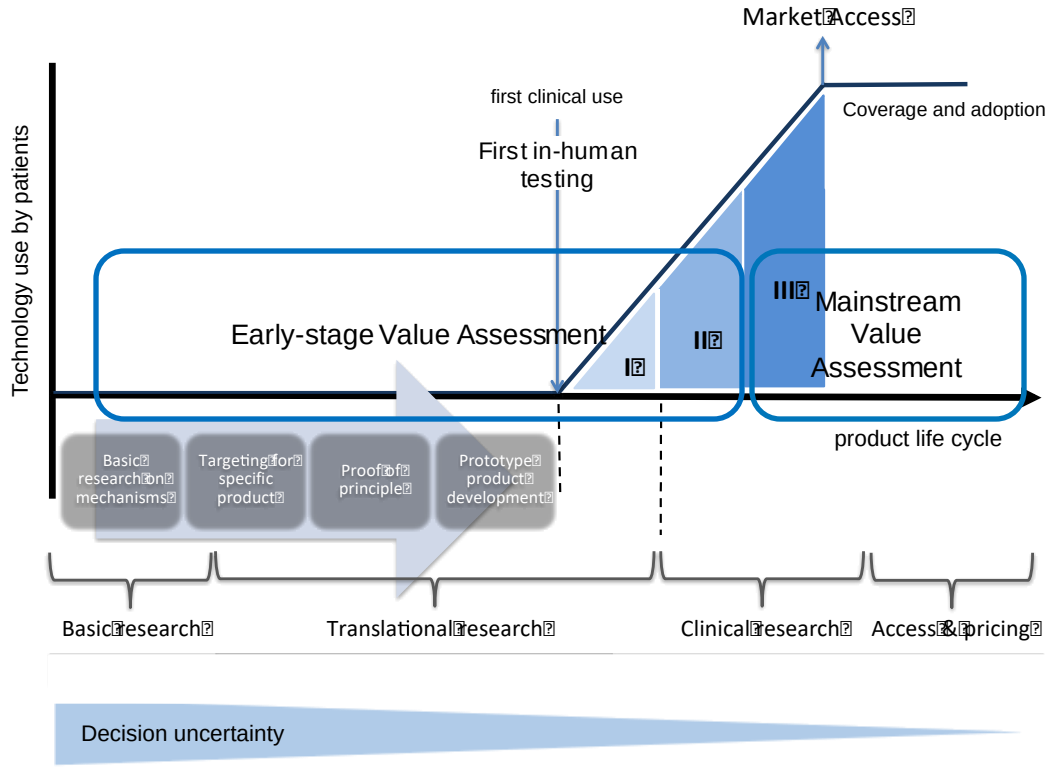
- What do we want to detect?
- In what clinical setting?
- How good is "good enough" (where do we set the bar) ?

Colorectal Cancer Screening
How Good Should a Test Be?

Sensitivity

Specificity

Individual Versus Population Benefit



IJzerman & Steuten, Applied Health Econ Health Policy 2011

Colorectal cancer is a global disease, and a “one size fits all” approach to CRC screening may not be relevant. Guiding Principles, however, are necessary and should be universal. The epidemiology of CRC will undoubtedly change over time which may alter the composition of intended use populations. **We present a framework that allows a dynamic process that has broad application.** This process is not bound by any one specific test.

WEO

The voice of world endoscopy

An efficient strategy for evaluating new non-invasive screening tests for colorectal cancer: The guiding principles

Bresalier* R.S., Senore*, C., Young*, G.P., Allison, J., Benamouzig, R, Benton, S., Bossuyt, P.M., Caro, L., Carvalho, B., Chiu, H.M., Coupe, V.M.H., de Klaver, W., de Klerk, C.M., Dekker, E., Dolwani, S., Fraser, C.G., Grady, W.M., Guittet, L., Gupta, S., Halloran, S.P., Haug, U., Hoff, G., Itzkowitz, S.H., Kortlever, T.L., Koulauzidis, A., Ladabaum, U., Lauby-Secretan, B., Leja, M., Levin, B., Levin, T.R., Macrae, F., Meijer, G.A., Melson, J., O'Morain, C., Parry, S., Rabeneck, L., Ransohoff, D.F., Saenz, R., Saito, H., Sanduleanu, S., Schoen, R.E., Selby, K., Singh, H., Steele, R.J.C., Sung, J.J.Y., Symonds, E., Winawer, S.J. (Members of the WEO CRC Screening New Test Evaluation Expert Working Group)

Gut 2023;72:1904-1918

- **Glaser and Delphi** approaches adapted to be undertaken by a combination of webinars and voting via virtual platforms due to the constraints of the COVID-19 pandemic (in-person discussion during DDW 2022)
- The membership consisted of experts (gastroenterologists, endoscopists, gastrointestinal surgeons, public health physicians, epidemiologists, clinical biochemists and tumor biologists) with knowledge or experience in practice or research relevant to screening for CRC. **Forty-seven experts** were involved.
- A series of specific questions (each of which was a draft principle to be critiqued) was initially expanded from the original eight to ten and then, after the first consensus round of voting, further increased to 12. The **12 principles** were progressively redrafted in response to specific feedback: webinars, conference seminars addressing specific issues and semi-structured discussions were held, and members voted and commented on each principle using a spreadsheet. After four rounds of voting, the consensus goal of **>80% agreement** (agree or strongly agree on a 5-point scale) was achieved for all 12 principles.
- The **explanatory text** for each principle was developed from the feedback received during the consensus process and from the extensive comments received during the consultation of experts and industry representatives. Multiple drafts of the explanatory text were circulated to the expert panel over a period of six months, and feedback has been incorporated into the final manuscript.

Topics Addressed in Each of the Principles Established by the Consensus Process

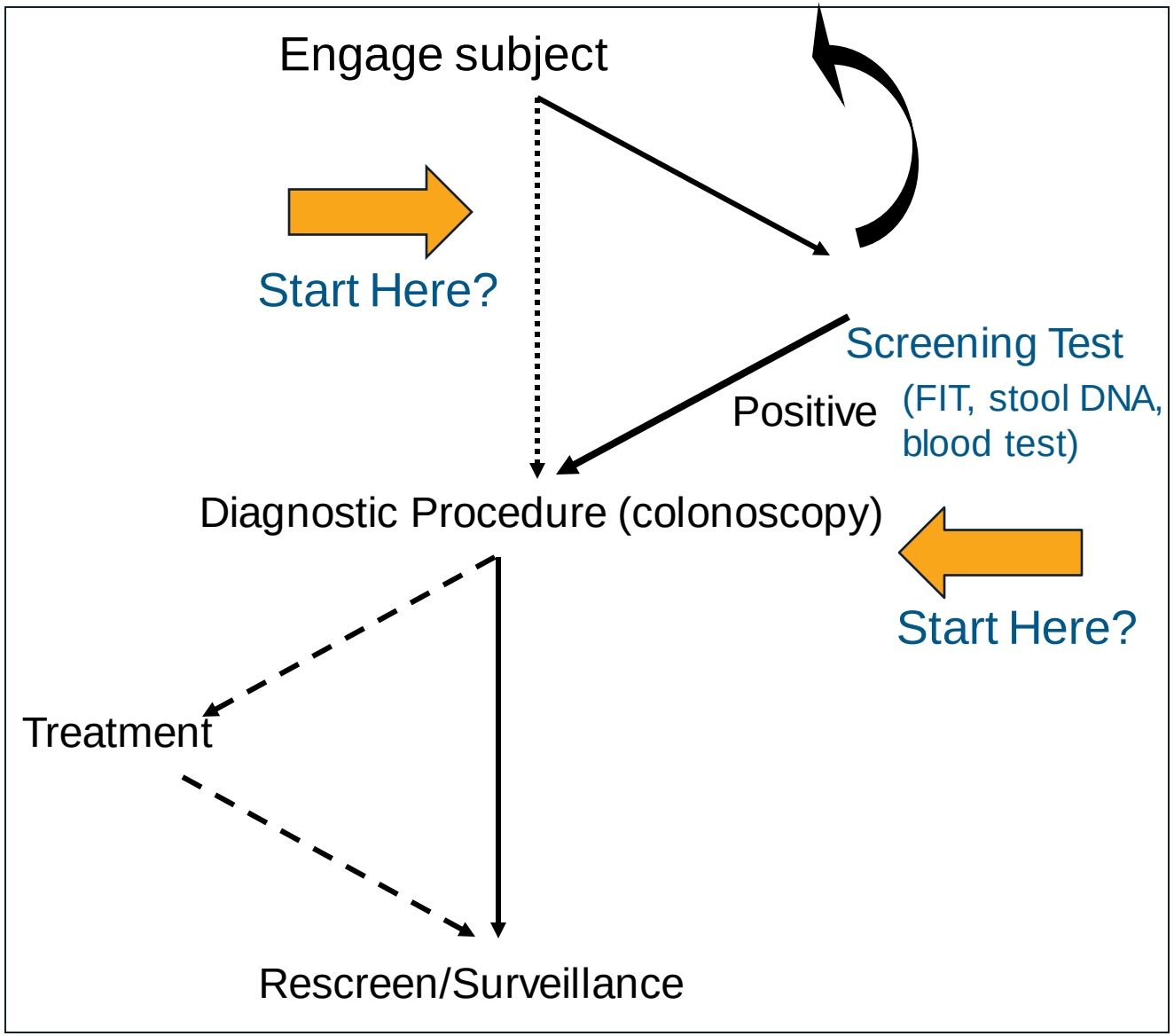
Principle Number	Topic
1	Desired outcomes of CRC screening
2	Screening is a multi-step process
3	A screening test identifies individuals with an increased likelihood of CRC and/or advanced precursor lesions
4	Nature of precursor lesions most important to detect
5	New biomarkers might detect lesions with a different natural history
6	Outcomes to be estimated in a screening population
7	Expectations of a new non-invasive test
8	An adjustable test positivity threshold accommodates different program goals
9	Predicting value by paired comparison to a proven non-invasive test
10	Evaluation proceeds through increasingly complex phases
11	Accuracy required for evaluation in a screening population
12	Analytic specifications, standards, and performance

A rigorous and efficient four-phased approach is proposed

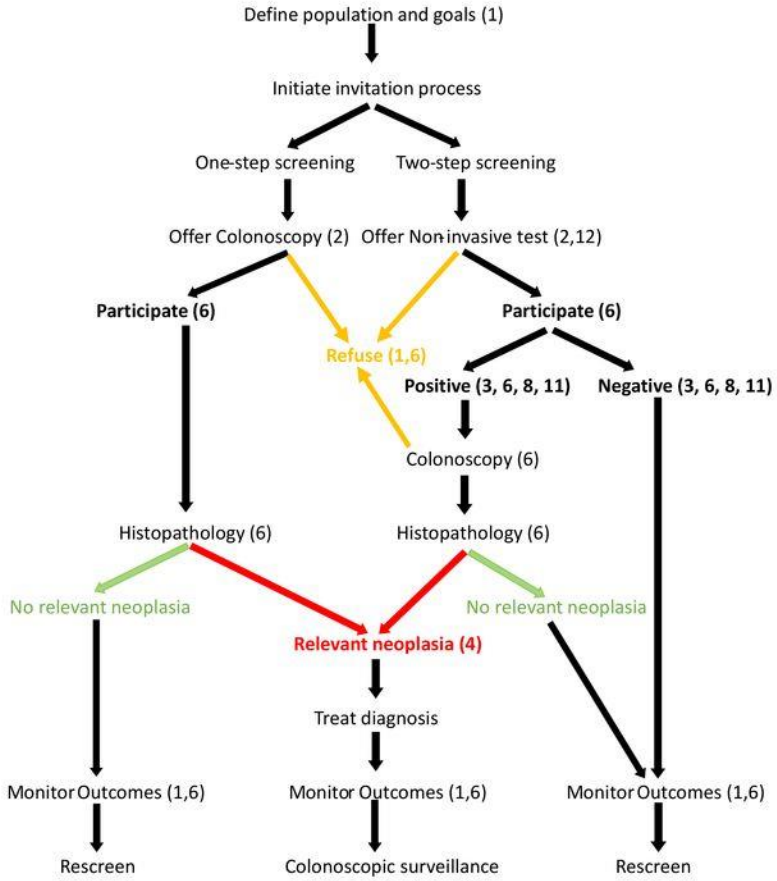
- Commencing with small studies to assess the test's ability to discriminate between CRC and non-cancer states (Phase 1)
- Followed by prospective estimation of accuracy across the continuum of neoplastic lesions in neoplasia-enriched populations (Phase 2).
- If these phases show promise, a provisional test-positivity threshold is set before evaluation in a typical screening population.
- Phase 3 prospective studies in a single screening round determine intention-to-screen program outcomes.
- Phase 4 studies involve evaluation over repeated screening rounds with monitoring for missed lesions.

Phase 3 and 4 findings will provide the real-world data required to model test impact on CRC mortality and incidence.

One-Step Versus Two-Step Screening



The multistep screening pathway characteristic of organised screening programs and demonstrating one-step and two-step strategies



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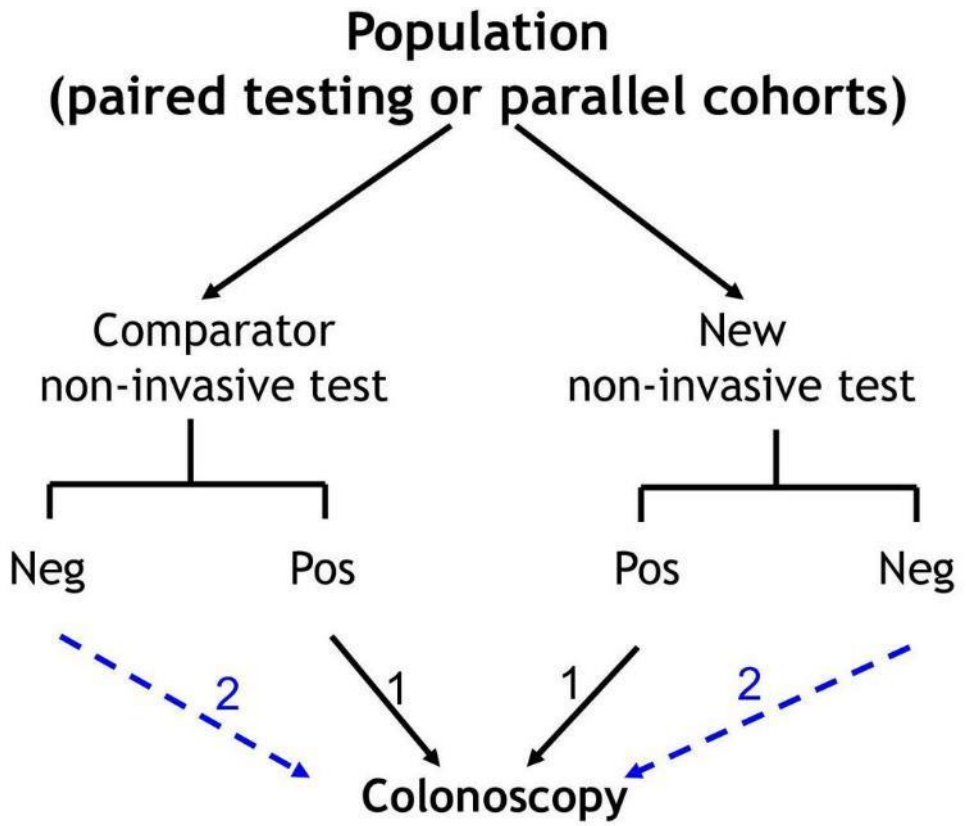
Diagrammatic outline of a trial design appropriate for comparing non-invasive tests in the initial phases of test evaluation. Prediction value by paired comparison with a proven non-invasive test



1 For comparing true-positive and false-positive fractions.
2 For comparing sensitivity and specificity (depending on biases due to population selection).

Paired testing is conducted in a single cohort where an individual does both the new and comparator test, whereas parallel testing is where study participants are randomized to one or the other test.

Goals, context and approach for each phase of evaluation, together with the hurdle identifying justification to advance to the next phase.

Phase	Goal(s)	Context	Approach and measures	Hurdle for progression
1	**Main:** Differentiates between CRC and non-neoplastic states?	Prescreening cohorts – limited	Distribution of test results in cohorts with and without CRC	• Test result must differ significantly in cancer cases.
2	**Main:** Detects early cancer and precursor lesions? **Others:** Initial positivity threshold? Accuracy relative to comparator? Causes of false positives.	Prescreening cohorts - extensive	Distribution of test results in cohorts with CRC relevant precursor lesions, other colorectal diagnoses and no disease. Parallel or paired testing of new and comparator tests will be informative.	• Preliminary (although biased) estimates of accuracy are shown to be promising. • ROC analysis identifies a suitable positivity threshold.
3	**Main:** Test accuracy in a typical screening evaluation? Test acceptance? **Others:** Test failure rate? Other variables for modelling effectiveness and cost-effectiveness.	Screening populations – single round	Apply test prospectively to a typical unbiased intended-use population. Choose study design appropriate to program goal and jurisdictional context: e.g., colonoscope all for estimating test accuracy, parallel testing for comparing non-invasive tests and intention-to-screen outcomes.	• A significant improvement in some aspect of screening. • Non-inferior in accuracy to a comparator test, OR • Accuracy likely delivers benefit. • Feasible colonoscopy workload. • Modeled effectiveness and cost-effectiveness are satisfactory.
4	**Main:** Missed lesions or adverse events? **Others:** Participation rates over time and retest intervals?	Screening population – multiple rounds	Apply the test prospectively to an intended-use screening population over multiple rounds, with careful monitoring of population program outcomes.	

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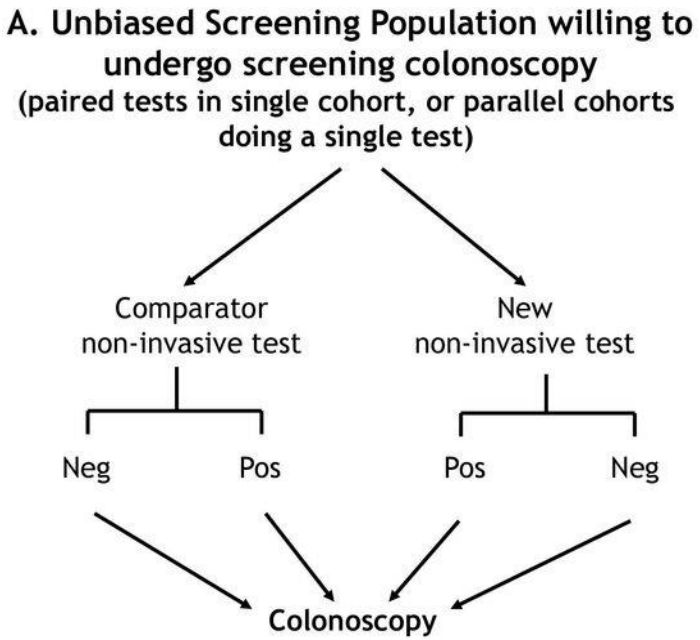
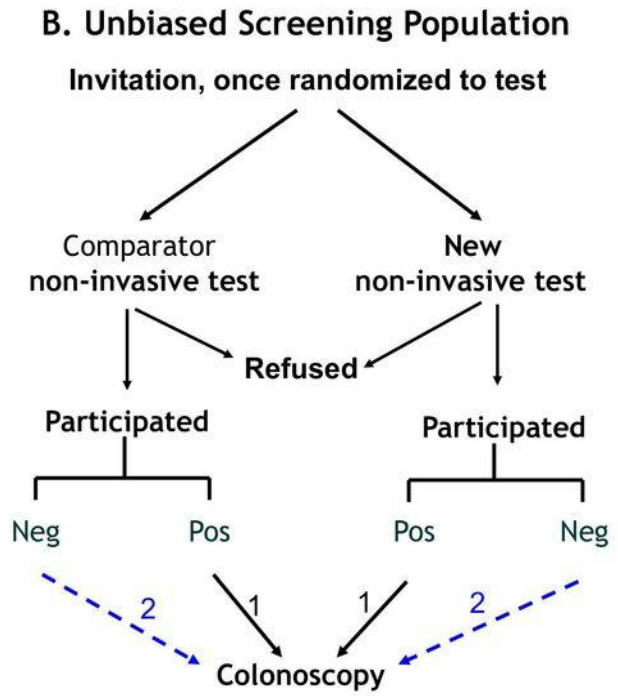
Study design frameworks applicable to phase III studies.



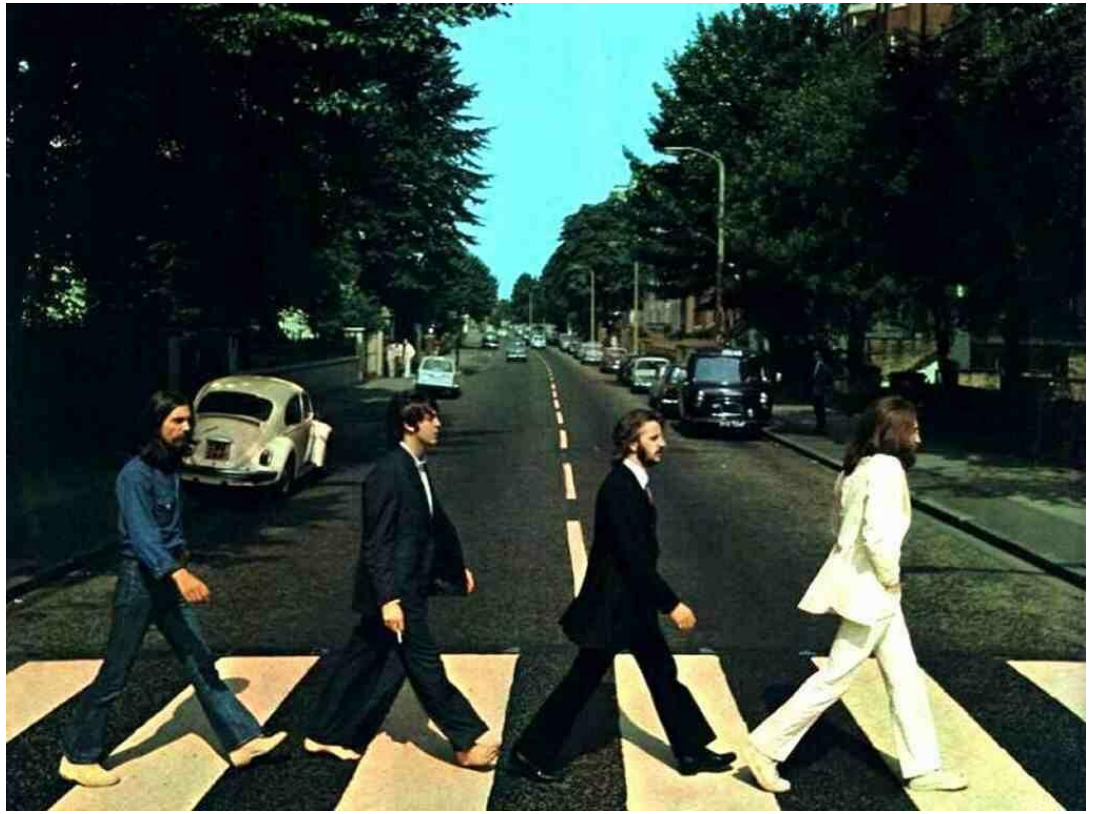
A. Design to determine test accuracy where all cases undergo colonoscopy (intention-to-screen cannot be ascertained).



1 For comparing test true-positive and false-positive proportions.
2 For additionally comparing sensitivity and specificity.

B. Design for estimating intention-to-screen outcomes where accuracy of a new test can be compared with a non-invasive comparator either when colonoscoping only test positive individuals (compare true-positive and false-positive fractions) or all participants (sensitivity and specificity)

The Long and Winding Road



This Little Piggy
Went to Market

?

The Yellow
Brick Road
to Market

Guidelines USPSTF

Regulatory FDA

Payors CMS

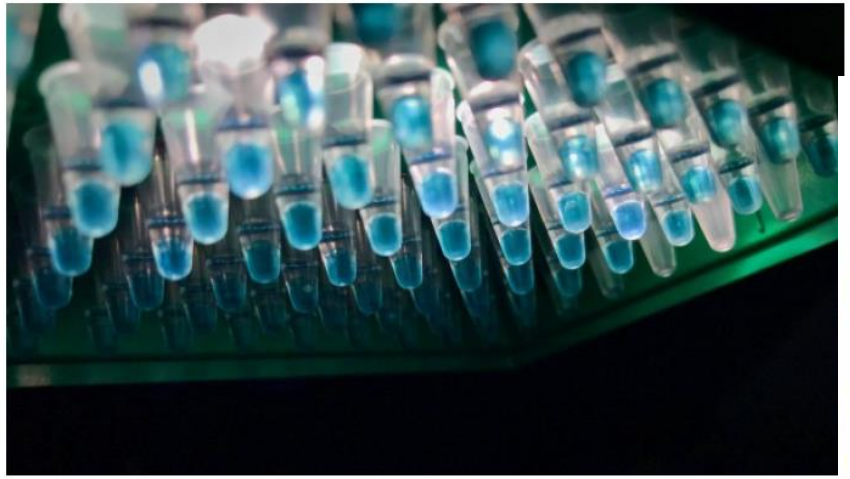
One Size May Not Fit All

Pivotal Evaluation of the Accuracy of a Biomarker Used for Classification or Prediction: Standards for Study Design

Clinical Context

- **Clinical Application**
- Define the target population and clinical setting intended for use of the biomarker.
- Define subject inclusion and/or exclusion criteria and process for enrollment.
- Define the setting for specimen collection.
- Ensure adequate generality in the population studied.

- **Outcome**
- Define the outcome of interest.
- Specify procedures for ascertaining and measuring the outcome.



COLOR GENOMICS

Rewriting Life

White-people-only DNA tests show how unequal science has become

Companies are selling disease-risk tests that only work in people of European ancestry. They hope to fix that soon.

by Antonio Regalado October 18, 2018

The Guardian

Genetics research 'biased towards studying white Europeans'

Ethnic minorities set to miss out on medical benefits of research, scientist warns

Hannah Devlin *Science correspondent*

Mon 8 Oct 2018 01.00 EDT

Christina Animashaun/Vox

Genetics has learned a ton — mostly about white people. That's a problem.

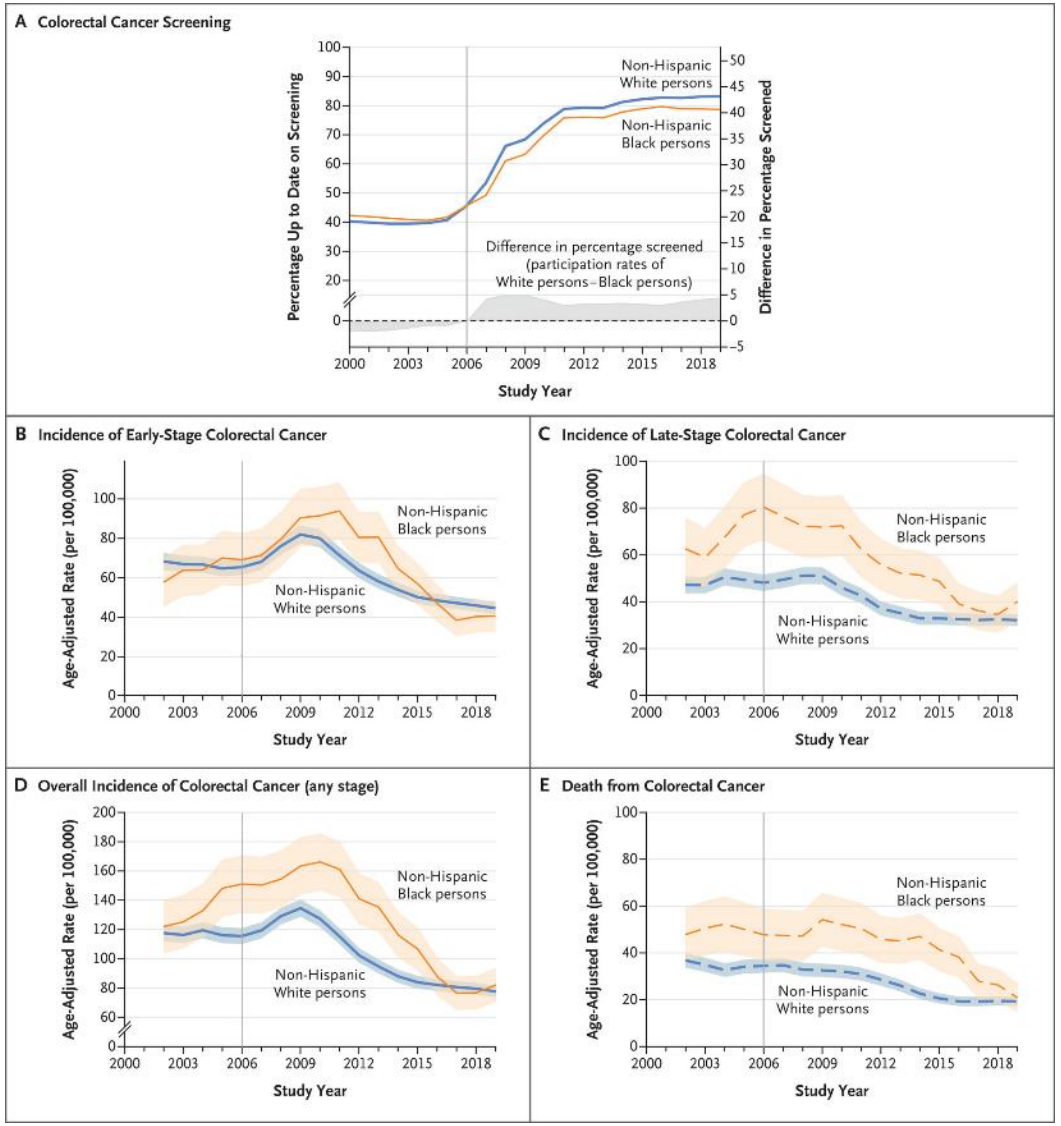
The overwhelming whiteness of genetics research is holding back medicine.

Robert A. Winn M.D.

ZNA: A Matter of Place and Space

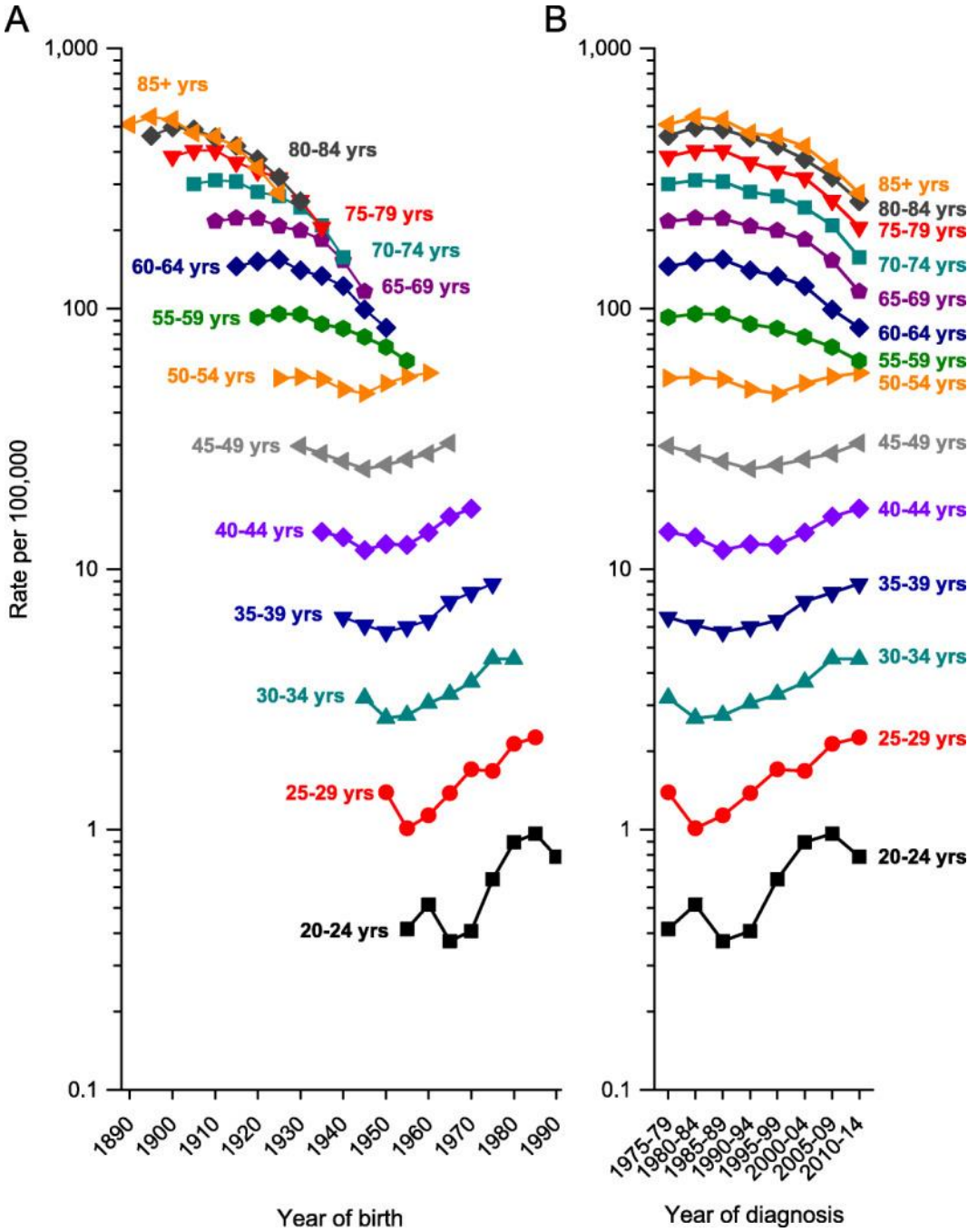
MASSEY CANCER CENTER VCU

Association between Improved Colorectal Screening and Racial Disparities



N Engl J Med 2022;386-8

Trends in Colorectal Cancer Incidence Rates



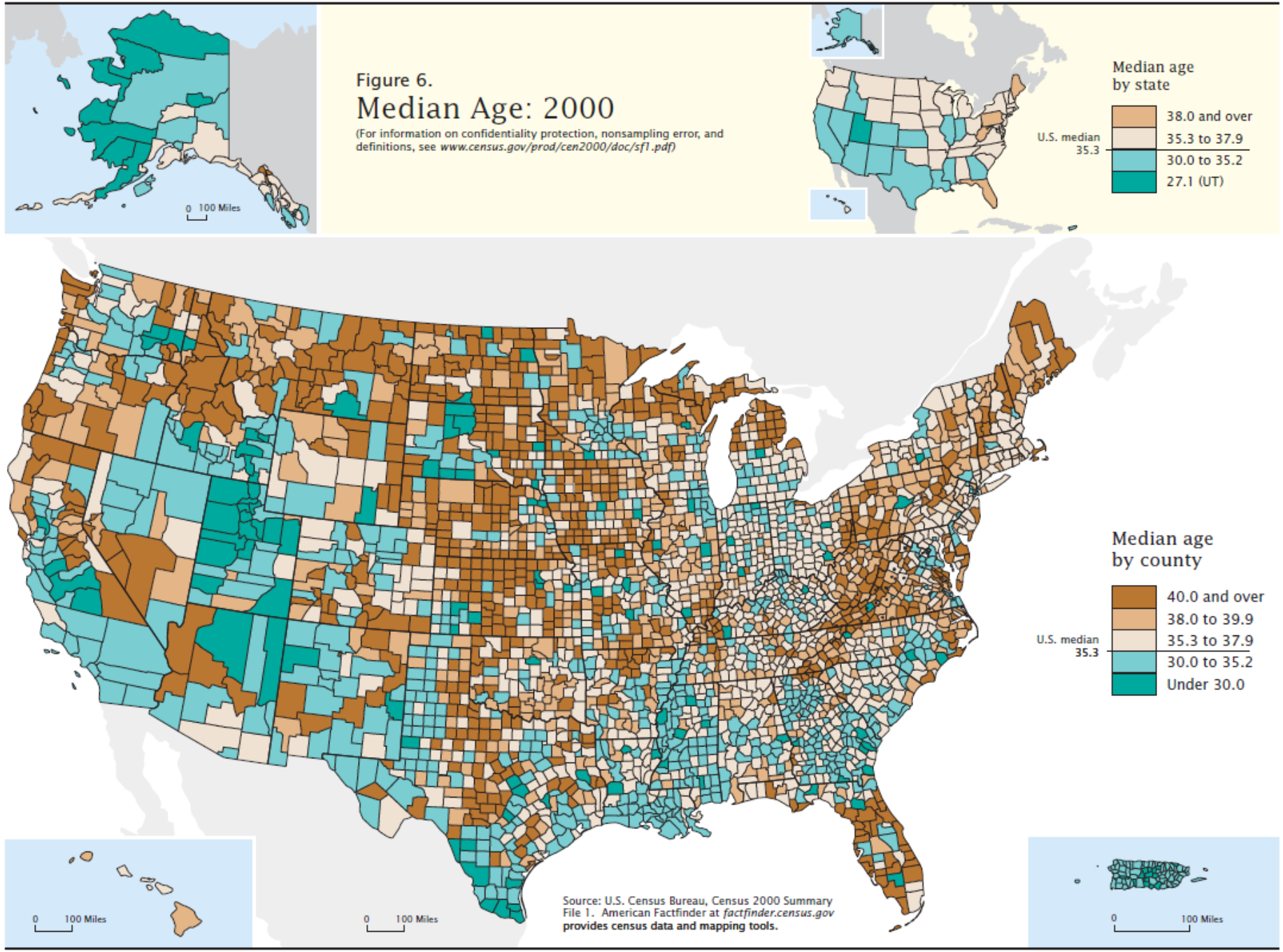


Figure 6.
Median Age: 2000
(For information on confidentiality protection, nonsampling error, and definitions, see www.census.gov/prod/cen2000/doc/sf1.pdf)
Median age by state
U.S. median 35.3
38.0 and over
35.3 to 37.9
30.0 to 35.2
27.1 (UT)
0 100 Miles
Median age by county
U.S. median 35.3
40.0 and over
38.0 to 39.9
35.3 to 37.9
30.0 to 35.2
Under 30.0
Source: U.S. Census Bureau, Census 2000 Summary File 1. American Factfinder at factfinder.census.gov provides census data and mapping tools.

Non-Invasive Tests for CRC Conclusions

- *What is the goal?- Depends on where/who you are*
- *Where does the field stand now?*

  -Lots of promising markers that need further testing
- ***What are the biggest challenges?***

  -Low sensitivity for early lesions, resources, acceptability (versus colonoscopy), long duration (and cost) from bench to bedside
- *What are the bright spots?*

  -Technology, targeted resources
- *What can we legitimately expect?*

  -As good or incrementally better than FIT, or perhaps FIT-DNA, **but** not as good as colonoscopy (we need to accept this) 

Biggest Challenges?

Lack of sensitivity for early CRCs and Advanced Adenomas

- Depends on point of view (how good is “good enough” ?)

Availability of samples and funding for Phase II/III studies

- EDRN- http://edrn.nci.nih.gov/resources/sample-reference-sets/edrn-pre-validation-reference-set-specimen-sharing-guidelines

Clinical vs Laboratory assays

Cost of Phase IV Trial

- Don’t have for FIT/Colonoscopy
- Comparison to accepted test adequate?

Meaning of false positives?

aga

To Be Determined

- How do we combine markers (and different types of markers)?
- What is the optimal (or at least acceptable) combination of sensitivity and specificity?

  ↑ Sensitivity vs ↓ Spec
- How do we report results? (quantitative vs qualitative measures)
- Intervals-How often do we screen?
- Will markers be generalizable to different molecular sub-types?
- Where does compliance factor in?

  Efficacy = Acceptability X Accuracy
- **ARE MARKERS/SCREENING TESTS VALIDATED FOR AVERAGE-RISK OLDER INDIVIDUALS RELEVANT TO EOCRC (and which subgroups)?**

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TAR HEELS
CAROLINA


THIS PRESENT
MOMENT
USED TO BE
THE UNIMAGINABLE
FUTURE

American Cancer Society | NATIONAL COLORECTAL CANCER ROUNDTABLE

Thank You

nccrt.org @NCCRTnews #80inEveryCommunity