Blood-Based Colorectal Cancer Testing: State of the Science
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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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
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

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cfDNA blood-based CRC screening test

Genomic Alterations
- Mutations known to be present in CRC

Epigenomic Modifications
- DNA methylation
- DNA fragment size

Integrate these signals to produce an actionable result

RESULTS
- Abnormal Signal Detected
- Normal Signal Detected

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

**Advanced Neoplasia**

- Enrolled Subjects (N = 22,877)
  - Not included in Clinical Validation Cohort (N = 12,619)
  - Clinical Validation Cohort (N = 10,258)
    - Not eligible, No colonoscopy, Invalid coloroscopy, No or invalid cfDNA test result (N = 2,397)
    - Evaluable Individuals (N = 7,861)
      - CRC (N = 65)
      - Advanced precancerous lesions (N = 1,116)
      - Non-advanced precancerous lesion (N = 2,166)
      - Negative for colorectal neoplasia (N = 4,514)

ECLIPSE met co-primary endpoints

CRC Sensitivity
83.1%
(72.2 - 90.3)

Specificity
89.6%
(88.8-90.3)
Promising Early-Stage CRC Sensitivity

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

- **Stage I**
  - Localized: 72.2%
  - Regional: 100%
  - Distant: 100%
  
  * Assumes 5 incompletely staged malignant polyps are Stage I disease (1/5)

- **Stage II**
  - Localized: 100%
  - Regional: 100%
  - Distant: 100%

- **Stage III**
  - Localized: 100%
  - Regional: 100%
  - Distant: 100%

- **Stage IV**
  - Localized: 100%

# Excludes 3 lost to clinical follow-up (2/3)
<table>
<thead>
<tr>
<th>Most advanced finding on Colonoscopy</th>
<th>Positive Results</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced Lesions</td>
<td>1116</td>
<td>147</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(11.3-15.3)</td>
</tr>
<tr>
<td>High Grade Dysplasia</td>
<td>31</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(11.4-39.8)</td>
</tr>
</tbody>
</table>

- No significant differences in APL sensitivity based on key clinical characteristics
- Sensitivity for more advanced pathology trended higher
cfDNA blood-based test: poised to have high impact on CRC screening

<table>
<thead>
<tr>
<th>Test</th>
<th>CRC Sensitivity</th>
<th>Patient Adherence Rate</th>
<th>Effective Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>cfDNA Blood Test</td>
<td>83%</td>
<td>85 - 96%</td>
<td>75 - 80%</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>95%</td>
<td>28 - 42%</td>
<td>27 - 40%</td>
</tr>
<tr>
<td>FIT stool test</td>
<td>74%</td>
<td>43 - 65%</td>
<td>32 - 48%</td>
</tr>
<tr>
<td>Multitarget stool DNA test</td>
<td>92%</td>
<td>48 - 60%</td>
<td>44 - 55%</td>
</tr>
</tbody>
</table>

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

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


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)

**Advanced Adenoma Detection**

**CRC Detection**

AA sensitivity was greater than mSEPT9, the only blood test for CRC screening currently available.

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

• Assay-ctDNA and proteins (Freenome)

Prospective, Blinded, Multi-center Registrational Study (NCT04369053)

- 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

Targeting >25,000 participants: 45-85 years of age, at average risk for CRC and willing to undergo a routine screening colonoscopy

Hybrid traditional and virtual recruitment: Mobile phlebotomy available to all participants and enabling recruitment from every ZIP code in the continental US

Secondary: Sensitivity for advanced adenomas and negative and positive predictive values for CRC detection

Compared to colonoscopy with histopathology as the reference method

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

Proportion detected by CancerSEEK (%)

Ovary Liver Stomach Pancreas Esophagus Colorectum Lung Breast

CSO Accuracy

Accuracy of prediction (%)

Colorectum Ovary Pancreas Breast Upper GI Lung Liver

Cohen, 2018
Next Generation CancerGuard™ MCED test

<table>
<thead>
<tr>
<th>99% Sensitivity, % (95% CI)</th>
<th>Bladder</th>
<th>Breast</th>
<th>Cervical</th>
<th>Colorectal</th>
<th>Esophageal</th>
<th>Liver</th>
<th>Lung</th>
<th>Ovarian</th>
<th>Pancreatic</th>
<th>Prostate</th>
<th>Renal</th>
<th>Stomach</th>
<th>Uterine</th>
<th>All Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDMs</td>
<td>50</td>
<td>64</td>
<td>100</td>
<td>65</td>
<td>100</td>
<td>100</td>
<td>85</td>
<td>75</td>
<td>67</td>
<td>20</td>
<td>45</td>
<td>82</td>
<td>90</td>
<td>68</td>
</tr>
<tr>
<td>(30-70)</td>
<td>(39-84)</td>
<td>(72-100)</td>
<td>(50-79)</td>
<td>(55-65)</td>
<td>(41-93)</td>
<td>(71-93)</td>
<td>(82-75)</td>
<td>(49-81)</td>
<td>(20-51)</td>
<td>(6-26)</td>
<td>(26-66)</td>
<td>(61-93)</td>
<td>(60-74)</td>
<td>(62-74)</td>
</tr>
<tr>
<td>Proteins</td>
<td>20 (8-42)</td>
<td>35 (16-61)</td>
<td>20 (6-51)</td>
<td>26 (15-42)</td>
<td>100 (21-100)</td>
<td>23 (8-50)</td>
<td>73 (56-86)</td>
<td>30 (11-60)</td>
<td>46 (27-65)</td>
<td>10 (3-30)</td>
<td>60</td>
<td>43 (37-83)</td>
<td>60</td>
<td>43</td>
</tr>
<tr>
<td>(30-70)</td>
<td>(39-84)</td>
<td>(72-100)</td>
<td>(50-79)</td>
<td>(55-65)</td>
<td>(41-93)</td>
<td>(71-93)</td>
<td>(82-75)</td>
<td>(49-81)</td>
<td>(20-51)</td>
<td>(6-26)</td>
<td>(26-66)</td>
<td>(61-93)</td>
<td>(60-74)</td>
<td>(62-74)</td>
</tr>
<tr>
<td>MDMs + Proteins</td>
<td>55</td>
<td>64</td>
<td>100</td>
<td>79 (64-89)</td>
<td>100</td>
<td>100</td>
<td>90</td>
<td>88 (53-98)</td>
<td>83 (66-93)</td>
<td>40 (17-69)</td>
<td>45</td>
<td>82 (61-93)</td>
<td>90</td>
<td>75 (69-80)</td>
</tr>
<tr>
<td>(30-70)</td>
<td>(39-84)</td>
<td>(72-100)</td>
<td>(50-79)</td>
<td>(55-65)</td>
<td>(41-93)</td>
<td>(71-93)</td>
<td>(82-75)</td>
<td>(49-81)</td>
<td>(20-51)</td>
<td>(6-26)</td>
<td>(26-66)</td>
<td>(61-93)</td>
<td>(60-74)</td>
<td>(62-74)</td>
</tr>
</tbody>
</table>

Katerov ASCO 2023
Galleri-MCED Assay—mDNA based

The CCGA study
15,254 participants at 142 sites
56% with cancer; 44% without cancer (anticipated enrollment period, ~24 months)

Blood (all) and tissue (cancer only) samples collected

Samples divided among three pre-specified CCGA substudies

CCGA sub-study 1
- Discovery
  - Training, n = 1785
  - Validation, n = 1015
  - Three independent methods evaluated
    1. Targeted sequencing
    2. Whole genome sequencing (copy number variants)
    3. Whole genome bisulfite sequencing (whole genome methylation)
- Whole genome methylation
  - Identified as method to be used for further development

CCGA sub-study 2
- Development of assay and classifier and initial validation
  - Training, n = 3133
  - Validation, n = 1364
  - Plasma ctDNA underwent bisulfite sequencing targeting a panel of >100,000 informative methylation regions. A classifier was developed/validated for cancer detection and CSO
- Targeted methylation
  - Identify key methylation regions
  - Training and validation of the selected and updated targeted methylation assay and classifier

CCGA sub-study 3
- Further refinement of assay and classifier informed by training set
- Large-scale clinical validation
  - n = 5308 participants (cancer = 3237; non-cancer = 2069)
  - n = 4077 confirmed status set (cancer = 2823; non-cancer = 1254)
  - Locked assay and classifier for screening (Galleri™)
    - Validated in independent validation set

Follow-up for 5 years (vitals & cancer status)

Klein, 2021
Galleri-MCED Assay-GI cancer detection

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

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Total N</th>
<th>Sensitivity % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver/Bile-duct</td>
<td>46</td>
<td>93.5 (82.5 - 97.8)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>100</td>
<td>85.0 (76.7 - 90.7)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>135</td>
<td>83.7 (76.8 - 89.0)</td>
</tr>
<tr>
<td>Colon/Rectum*</td>
<td>206</td>
<td>82.0 (76.2 - 88.7)</td>
</tr>
<tr>
<td>Anus</td>
<td>22</td>
<td>81.8 (61.5 - 92.7)</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>17</td>
<td>70.6 (48.9 - 88.7)</td>
</tr>
<tr>
<td>Stomach</td>
<td>30</td>
<td>66.7 (48.8 - 80.8)</td>
</tr>
</tbody>
</table>

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

Positive Blood Test +
N = 134

- No Cancer
  - 108
- Cancer
  - 26
    - Localized
      - 17
    - Advanced
      - 9

PET-CT scan
101

Surgery
3
Minimally Invasive Test
19

B
All cancers identified in the DETECT-A study

- Proportion of cancers first detected by blood testing
- Proportion of cancers first detected by SOC screening
- Proportion of cancers first detected by other means

- Lymphoma (4)
- Thyroid (5)
- Carcinoma of Unknown Primary (1)
- Sarcoma (2)
- Lung (21)
- Breast (27)
- Stomach (3)
- Kidney (2)
- Pancreatic Neuroendocrine (2)
- Bile Duct (1)
- Appendix (1)
- Uterine (15)
- Bladder (1)
- Ovary (7)

Colorectal (3)
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.
Thank You
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

Data source: GLOBOCAN 2020
Map production: IARC

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World Health Organization
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
Don’t think outside the box. Think like there is no box.
Are Blood Tests the Holy Grail?

*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?

Individual Versus Population Benefit

RESOURCES

Sensitivity

Specificity
Early health economic modelling

Typical health economic studies

First clinical use

Coverage and adoption

Early-stage Value Assessment

Mainstream Value Assessment

Decision uncertainty

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


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

Engage subject

Start Here?

Screening Test
(FIT, stool DNA, blood test)

Positive

Diagnostic Procedure (colonoscopy)

Start Here?

Treatment

Rescreen/Surveillance
The multistep screening pathway characteristic of organised screening programs and demonstrating one-step and two-step strategies
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.

Population
(paired testing or parallel cohorts)

- Comparator non-invasive test
  - Neg
  - Pos

- New non-invasive test
  - Pos
  - Neg

Colonoscopy

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.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Goal(s)</th>
<th>Context</th>
<th>Approach and measures</th>
<th>Hurdle for progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Main: Differentiates between CRC and non-neoplastic states? Prescreening cohorts – limited</td>
<td>Distribution of test results in cohorts with and without CRC</td>
<td>• Test result must differ significantly in cancer cases.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Main: Detects early cancer and precursor lesions? Others: Initial positivity threshold? Accuracy relative to comparator? Causes of false positives. Prescreening cohorts - extensive</td>
<td>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.</td>
<td>• Preliminary (although biased) estimates of accuracy are shown to be promising. • ROC analysis identifies a suitable positivity threshold.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>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</td>
<td>Apply test prospectively to a typical unbiased intended-use population. Choose study design appropriate to program goal and jurisdictional context: e.g., colonoscopy all for estimating test accuracy, parallel testing for comparing non-invasive tests and intention-to-screen outcomes.</td>
<td>• 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.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Main: Missed lesions or adverse events? Others: Participation rates over time and retest intervals? Screening population – multiple rounds</td>
<td>Apply the test prospectively to an intended-use screening population over multiple rounds, with careful monitoring of population program outcomes.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A. Design to determine test accuracy where all cases undergo colonoscopy (intention-to-screen cannot be ascertained).

B. Design for estimating intention-to-screen outcomes where accuracy of a new test can be compared with a non-invasive comparator either when colonoscopying 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

Guidelines USPSTF
Regulatory FDA
Payors CMS

The Yellow Brick Road to Market
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.
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

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

The overwhelming whiteness of genetics research is holding back medicine.
ZNA: A Matter of Place and Space

Life Expectancy (Years) at Birth by Neighborhood

- River Forest: 84
- Oak Park: 81
- North Lawndale: 72
- South Lawndale: 82

Western
Division
Chicago
Loop
Loos
Roosevelt
Curran-Chinatown
Ashland

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Association between Improved Colorectal Screening and Racial Disparities

A. Colorectal Cancer Screening

B. Incidence of Early-Stage Colorectal Cancer

C. Incidence of Late-Stage Colorectal Cancer

D. Overall Incidence of Colorectal Cancer (any stage)

E. Death from Colorectal Cancer

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Trends in Colorectal Cancer Incidence Rates

Graph A shows the incidence rates of colorectal cancer by age group from 1980 to 1990, with rates per 100,000 population. Graph B displays the same data but for the year of diagnosis, from 1980 to 1990, also per 100,000 population.
Figure 6.
Median Age: 2000
(For information on confidentiality protection, nonsampling error and
definitions, see www.census.gov/press/2000/das31pdf.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)

Median age by county
- 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

Clinical vs Laboratory assays

Cost of Phase IV Trial
• Don’t have for FIT/Colonoscopy
• Comparison to accepted test adequate?

Meaning of false positives?
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)?
THIS PRESENT MOMENT USED TO BE THE UNIMAGINABLE FUTURE
Thank You