Elements of Prediction: CRC Screening, New Biomarkers, and Comparative Effectiveness

Carolyn Rutter, PhD, RAND Corporation

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Session 2 - Modeling, Biomarkers and Implementation Science

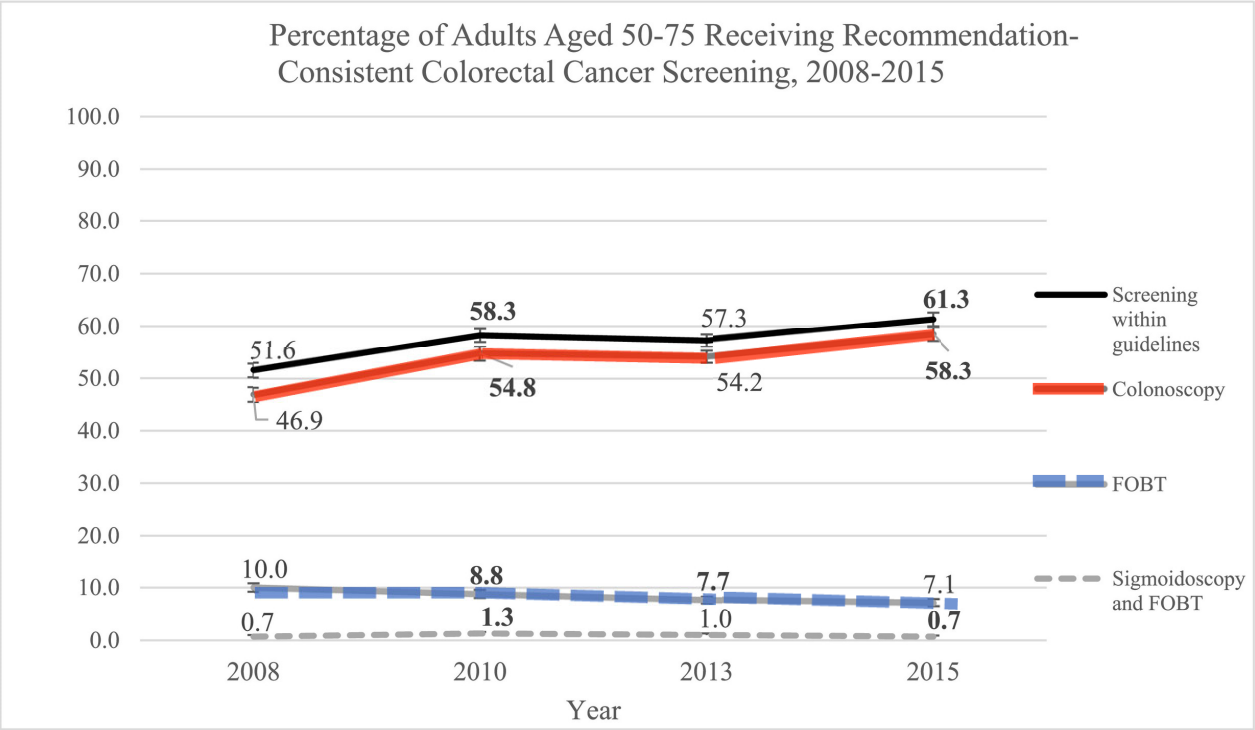
Elements of Prediction:
CRC Screening, New Biomarkers, & Comparative Effectiveness

1. CRC Screening: Context
   - Existing screening modalities & regimens
2. Microsimulation models
   - Model predictions to inform screening guidelines
   - Information needed for modeling
3. Model prediction for a new biomarker
   - Optimal versus realistic assumptions

Existing CRC Screening Modalities

There are many CRC screening modalities

- Colonoscopy is the most common
- FIT is a distant second



de Moor, Janet S., et al. "Colorectal cancer screening in the United States: trends from 2008 to 2015 and variation by health insurance coverage." *Preventive medicine* 112 (2018): 199-206.

Existing CRC Screening Modalities

	FIT: Focused on detection of preclinical CRC and triage to colonoscopy for diagnosis	**Colonoscopy: Focused on detection and removal of both preclinical CRC and precursor lesions**
Pros	Inexpensive, non-invasive, can be done at home	Primary prevention of CRC, longer screening interval
Cons	Requires ongoing patient participation • Annual screening • Follow-up of positive tests	Invasive, requires specialist care, potential adverse events

Both tests have a high patient burden, but the type of burden is different, and this can lead to different patient preferences.

Patients don't especially like either test.

Existing CRC Screening Regimens

	FIT	Colonoscopy
Age to Begin Screening	50 (USPSTF) or 45 (ACS)	
Age to End Screening	75 + shared decision making at older ages	
Screening Interval	Annual	Every 10 years

Other tests have different intervals (e.g., Stool DNA + FIT has a 3-year interval)

Regimens differ for patients with average and elevated risk.

Biomarkers can be used:

- As a screening test, to triage patients to colonoscopy
- As a risk-stratifier, to determine the best screening regimen
  - This may be especially useful for improving our understanding early onset CRC

Adenoma Surveillance

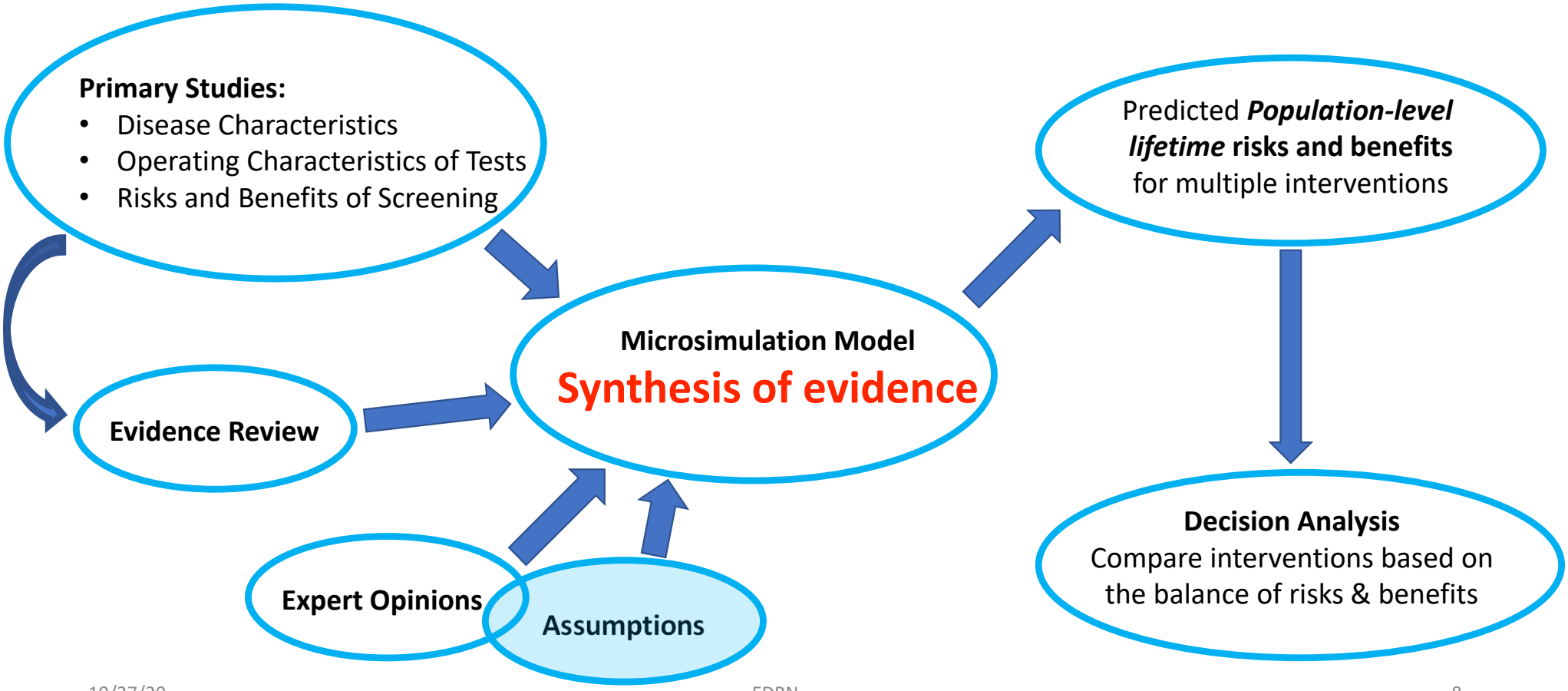
- Risk-based short interval colonoscopy screening
  - Colonoscopy findings that lead to adenoma surveillance:
    3 or more adenomas or at least one advanced adenoma (based on lesion size and histology) or at least one sessile serrated polyp
  - Colonoscopy every 3 to 5 years
  - Currently no clear rules about when to exit surveillance
- Adenomas and sessile serrated polyps are treated as a biomarker

Could biomarkers be used as part of adenoma surveillance?

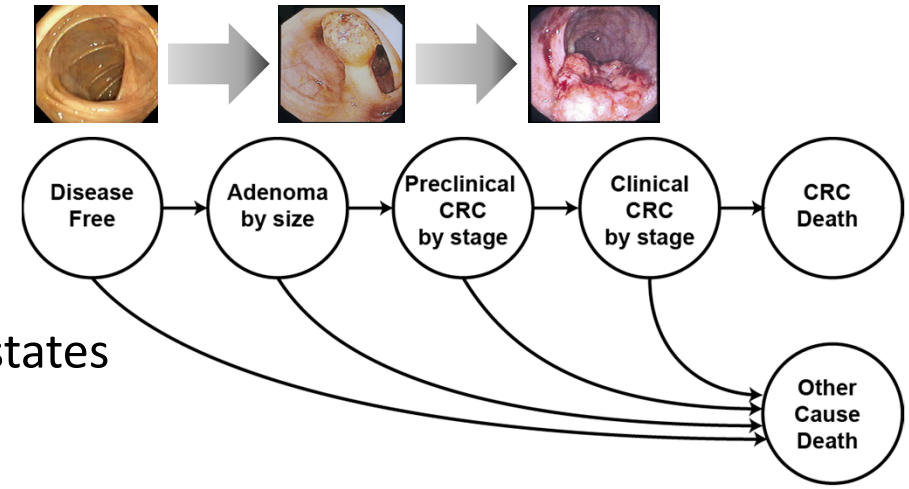
- Referral-based tests are currently not deemed appropriate.
  What would need to be different to enable use of a biomarker?

Microsimulation models

Microsimulation models synthesize available evidence



Microsimulation Models for CRC



Two model components

1. Natural history of CRC
   - Includes key risk factors (age and sex)
   - Simulates transitions between disease states

2. Screening for CRC, based on:
   - **Timing of screening** (when and how often)
   - **Operating characteristics of tests:** sensitivity and specificity for preclinical cancer and precursor lesions, correlation of test over time

Microsimulation Models for CRC

Model Outcomes

Basic:

- Death (CRC, other)
- Complications (colonoscopy only)
- CRC incidence, stage at detection, mode of detection
- False-positive results
- Total tests, Total invasive tests
- Costs

Compared to No Screening

- Life years gained (LYG)
- Quality-Adjusted LYG
- Tests per LGY, Costs per LYG

Compared to Other Regimens

- Incremental cost effectiveness ratios

Microsimulation Models to Inform CRC Screening Guidelines

Models are useful when there are trade-offs between different regimens

- Each regimen is considered in the context of others

Models need to describe between-regimen differences that drive decision making

- Differences in frequency and timing of tests
- Differences in test performance based on health states
  - Example: A company claims their test is better at identifying sessile serrated polyps (SSPs) than existing tests
  - Problem: There are still gaps in the evidence about the SSP process, so model results will be *assumption driven*
- Differences in access / adherence to tests
  - Is there evidence for differential access?

Model prediction for a new biomarker

The value of a new biomarker depends on accuracy, patient burden, and cost relative to existing tests and regimens

- **Accuracy:** If the biomarker is more accurate than existing tests, simulation can be used to identify effective screening regimens
- **Patient burden and costs:** Especially important if the accuracy is similar to – or perhaps somewhat worse than – than existing tests.
- **Patient adherence:** Generally not incorporated in modeling
  - Lack of long-term information means analyses are assumption driven

Adherence is tricky

How we usually simulate screening:

Why?

- Simulating 'realistic' screening is difficult, requiring assumptions about:
  - When to begin screening
  - Intervals between screening
  - Time to follow up
  - When to stop screening – and early cessation
  - Consistency of behaviors within individuals ('adherent' and 'non-adherent' types)

Delays at any point

- Current realistic assumptions, especially involving adherence, are subject to change

Example: Stool DNA+FIT versus FIT

Claim: higher adherence for Stool DNA + FIT

Evidence: None Yet

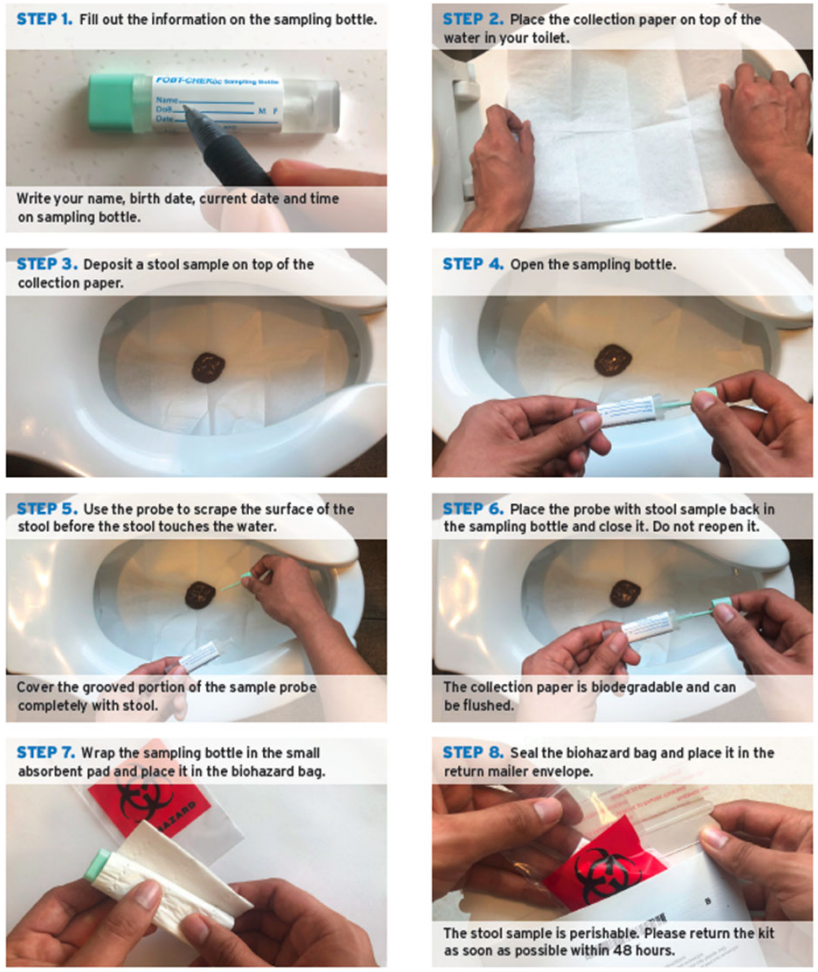
Exact sciences just completed a study

https://clinicaltrials.gov/ct2/show/NCT02419716

How to use your Cologuard kit

1. Receive and unpack your Cologuard kit. Check and use before expiration date.
2. Place your sample container into the toilet bracket.
3. Use your Cologuard kit to collect your sample.
4. Scrape your sample, then fill the sample container with preservative.
5. Using the prepaid UPS label, ship the box back to Exact Sciences Laboratories within 24 hours.

https://www.cologuardtest.com/using-and-returning-your-cologuard-kit



Simulating Realistic Screening

For most simulations, all conditions are optimal. To simulate realistic screening benefit, we would vary:

- **Screening behaviors / adherence**
- **Operating characteristics of tests**
  - Uncertainty in operating characteristics
    - For continuous test, models can be used to examine the impact of different positivity criteria
    - Probabilistic sensitivity analysis can be used to examine the impact of uncertainty
  - Variability in operating characteristics by patient
- **Treatment received / survival after diagnosis**
  - Access to lower quality treatment reduces test effectiveness

Elements of Prediction:
Comparative Effectiveness of a New Biomarker

A validated microsimulation model that incorporates essential elements of the biomarker

Natural History Model

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Natural History Model

+

Screening Model

Biomarker characteristics

Sensitivity & Specificity

Proposed Regimens/Use

Costs

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Natural History Model

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An analytic plan

population(s) simulated

Comparison modalities

Measures of costs and benefits

Biomarker characteristics

- Information needed depends on the questions asked
  - The same level of detail is needed across tests compared.
- Prediction of "realistic" screening effectiveness requires additional information about:

<u>Variability in test characteristics</u>

- Random across individuals
- Systematic variation by
  - lesion characteristics (e.g., size, histology)
  - Individual characteristic (e.g., race, access)
- Correlation over time

<u>Adherence</u>**:**

- Delays in initiation, early cessation
- Delays in repeat screening
- Delays in follow-up of referral tests
- Early cessation
- Consistency of screening behaviors within individuals

Key Takeaways

- Biomarkers have the potential to be used in different ways
  - As a new screening modality, as a risk-stratifier to target screening, for adenoma surveillance
  - As a risk stratifier, biomarkers have the potential to aid our understanding of early onset CRC and racial disparities in CRC incidence and mortalilty
- Microsimulation models are used to predict the comparative effectiveness of different regimens
  - New modalities & regimens are considered in the context of those currently available
  - Models synthesize study results and rely on assumptions to fill in gaps in evidence. Data is important. Say: models can reveal gaps
- Adherence is important, but predicting how adherence is expected to impact screening effectiveness is assumption-driven