# Interception versus prevention in cancer screening: Results from the CRC-MAPS model

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**Abstract #2240**

## BACKGROUND

- Multi-cancer early detection (MCED) tests offer the promise of screening for multiple cancers, even some that are currently unscreened, with a simple and convenient blood test[1]
- However, the first generation of MCED tests are primarily designed to detect cancer (i.e., cancer interception) and not precancerous lesions (i.e., cancer prevention)[2,3]
- Cancers can have longer (e.g., colorectal) or shorter (e.g., ovarian) preclinical phases, with the clinical utility of detecting precancerous lesions varying accordingly[1]
- In colorectal cancer (CRC), detection and removal of adenomas and early-stage CRC significantly reduces CRC incidence and mortality[4]
- The impact of cancer interception versus prevention + interception screening tests on clinical outcomes is unclear, and microsimulation modeling enables systematic examination of different scenarios

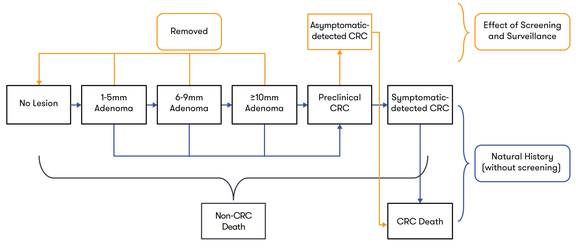
## OBJECTIVE

- This study examines the impact of detecting cancer (interception) versus adenomas and cancer (prevention + interception) on clinical outcomes for a hypothetical CRC screening test or a MCED test that includes CRC

## METHODS

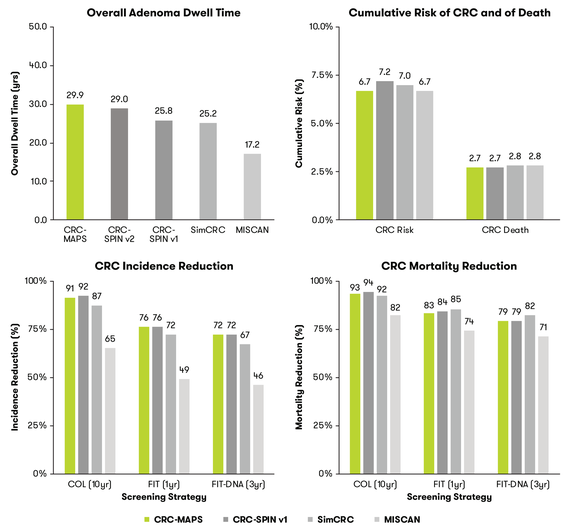
- A semi-Markov microsimulation model of the CRC adenoma-carcinoma pathway was developed and calibrated to autopsy, SEER, and endoscopy data (**Figure 1**)
- The model demonstrated good internal validity, and the model's cumulative lifetime outcomes were consistent with validated CISNET models (**Figure 2**)
- The model also reproduced mortality reduction (MR) estimates observed in the Minnesota FOBT trial[5], a randomized controlled trial from 1993 that can be used for external validation (**Figure 3**)
- This study simulated perfect adherence to a hypothetical annual, blood-based CRC screening test among previously unscreened individuals free of diagnosed CRC
- Outcomes were aggregated from age 40 to death, and individuals were screened from age 45 to 75
- Four scenarios were examined: two cancer interception and two cancer prevention + interception (**Table 1**)
- Threshold analysis was performed to determine the ≥10mm adenoma sensitivity needed for a cancer prevention + interception test (#5) to yield CRC MR equivalent to a near-perfect cancer interception test (#2)

### Figure 1. The CRC-MAPS model schematic



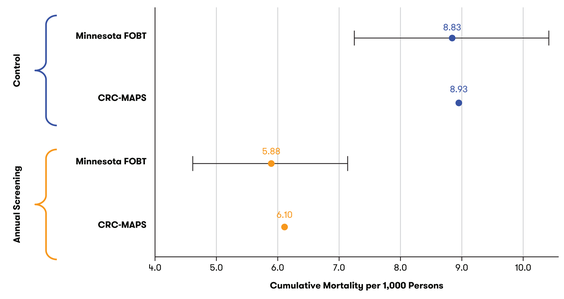

- This model simulates CRC progression through the adenoma-carcinoma pathway and allows for evaluation of different screening strategies

### Figure 2. The CRC-MAPS model demonstrates cross-model validity comparable to CISNET* CRC microsimulation models




*CISNET models include CRC-SPIN, SimCRC, MISCAN[6]
COL= colonoscopy; FIT = fecal immunochemical test

### Figure 3. External validity of the CRC-MAPS model was demonstrated by producing cumulative mortality estimates consistent with a randomized controlled trial[5]



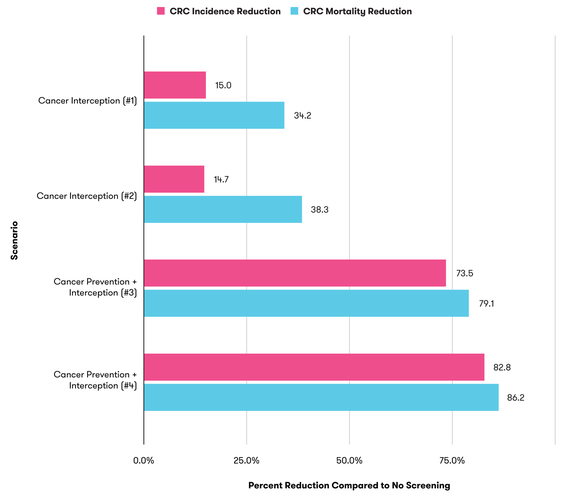

- The CRC-MAPS model was used to simulate the study population characteristics and adherence patterns of the 1993 Minnesota FOBT trial in order to conduct an external validation of the model
- The natural history component of the CRC-MAPS model closely replicated the cumulative 13-year CRC mortality (CRC-MAPS: 8.93 per 1,000; trial: 8.83 per 1,000 [95% CI 7.26-10.40]) of the trial's control arm
- For the annual screening arm, the CRC-MAPS model closely replicated the trial's cumulative 13-year CRC mortality (CRC-MAPS: 6.10 per 1,000; trial: 5.88 per 1,000 [95% CI 4.61-7.15])

### Table 1. Scenarios

| Scenario | Specificity | Adenoma Sensitivity | CRC Sensitivity |
|---|---|---|---|
| 1. Cancer Interception (base-case) | 99% | 1-5mm: 1%<br>6-9mm: 1%<br>≥10mm: 1% | 60% |
| 2. Cancer Interception (near-perfect) | 99% | 1-5mm: 1%<br>6-9mm: 1%<br>≥10mm: 1% | 99% |
| 3. Cancer Prevention (with FIT-like adenoma sensitivity) + Interception | 99% | 1-5mm: 5%<br>6-9mm: 10%<br>≥10mm: 20% | 60% |
| 4. Cancer Prevention (with improved adenoma sensitivity) + Interception | 99% | 1-5mm: 10%<br>6-9mm: 20%<br>≥10mm: 30% | 60% |
| 5. Threshold analysis | 99% | 1-5mm: 1%<br>6-9mm: 1%<br>**≥10mm: Varied** | 60% |

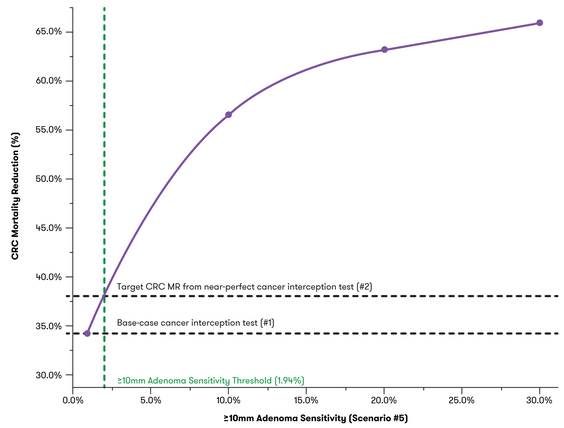
## RESULTS

### Figure 4. The cancer prevention+interception scenarios resulted in more favorable outcomes than the cancer interception scenarios




- The base-case scenario (#1) resulted in 15.0% CRC IR and 34.2% MR compared to 14.7% CRC IR and 38.3% MR for the near-perfect interception scenario (#2)
- Due to increased adenoma detection, the cancer prevention + interception scenarios (#3, #4) resulted in outcomes 2.3-5.6X more favorable than either cancer interception scenario (#1, #2)

### Figure 5. CRC mortality reduction equivalent to a near-perfect cancer interception test is achieved by increasing ≥10mm adenoma sensitivity by only 0.94 percentage points




Base-case cancer intervention test (Scenario #1): 99% specificity; 1% all-size adenoma sensitivity; 60% CRC sensitivity
Near-perfect cancer interception test (Scenario #2): 99% specificity; 1% all-size adenoma sensitivity; 99% CRC sensitivity

- The threshold analysis evaluated the ≥10mm adenoma sensitivity needed for the cancer prevention + interception test (#5) to equal the CRC mortality reduction of a near-perfect cancer interception test (#2)
- CRC MR equivalent to a near-perfect cancer interception test (#2) was achieved in the cancer prevention + interception test (#5) by increasing the ≥10mm adenoma sensitivity from 1% to 1.94%

## CONCLUSION

- This analysis highlights that even small improvements in the detection of precancerous lesions for certain cancers (e.g., adenomas for CRC), which enable cancer prevention, can yield clinical benefits that meaningfully exceed those from cancer interception tests that primarily detect cancer
- This work also suggests that clinical performance requirements may vary by cancer type depending on the clinical utility of detecting precancerous lesions
- Future studies will apply this approach to better understand the clinical utility of MCED tests and explore their benefits and burdens

## REFERENCES

1. Putcha G, Gutierrez A, Skates S. *JCO Precision Oncology*. 2021. doi: 10.1200/PO.20.00488
2. Liu MC, Oxnard GR, Klein EA, et al. 2020. *Ann Oncol*. doi: 10.1016/j.annonc.2020.02.011
3. Lennon AM, Buchanan AH, Kinde I, et al. 2020. *Science*. doi: 10.1126/science.abb9601
4. Gupta S, Lieberman D, Anderson JC, et al. 2020. *Gastroenterology*. doi: 10.1053/j.gastro.2019.10.026
5. Mandel JS, Bond JH, Church TR. *N Engl J Med*. 1993. doi: 10.1056/NEJM199305133281901.
6. Zauber A, et al., AHRQ Publication No. 14-05203-EF02. 2015

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