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Interception versus prevention in cancer screening in a Medicare population: Results from the CRC-MAPS model

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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)[2,10,11]
- 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[3]
- The prevalence of adenomas and asymptomatic CRC increases with age[4], which is especially concerning for a Medicare-aged population since 29% are not up-to-date with screening[5]
- The impact of cancer interception versus prevention + interception screening tests on clinical outcomes is unclear, and microsimulation modeling enables systematic examination of different scenarios

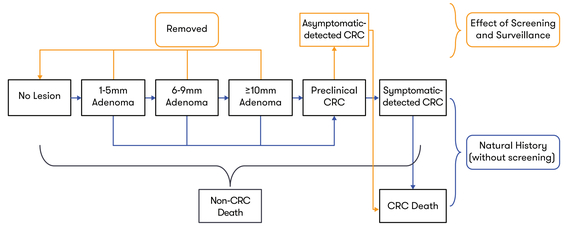
OBJECTIVE

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

METHODS

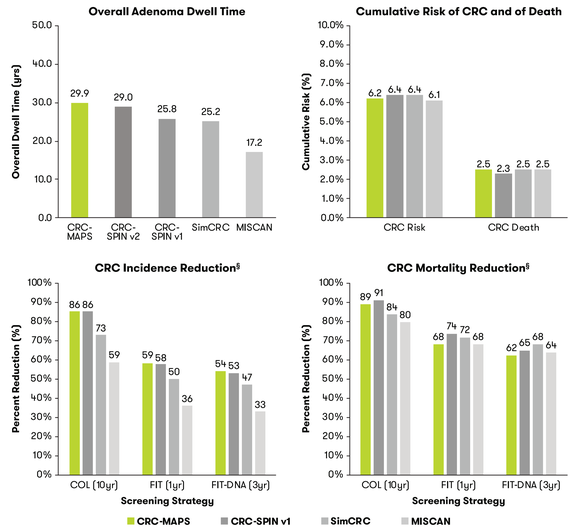
- A semi-Markov microsimulation model of the CRC adenoma-carcinoma pathway was developed in TreeAge and calibrated to autopsy, SEER, and endoscopy data (**Figure 1**)
- The model demonstrated good internal validity, and the model's cumulative lifetime natural history (no screening) and screening outcomes for a cohort of 65-year-olds free of diagnosed CRC were consistent with validated CISNET models[6,7,8] (**Figure 2**)
- The model also reproduced CRC mortality reduction estimates observed in the Minnesota FOBT trial[9], 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 aged ≥65 years free of diagnosed CRC
- Outcomes were aggregated from age 65 to death, and individuals were screened from age 65 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 (scenario #5) to yield CRC mortality reduction (MR) equivalent to a near-perfect cancer interception test (scenario #2)

Figure 1. The CRC-MAPS model schematic



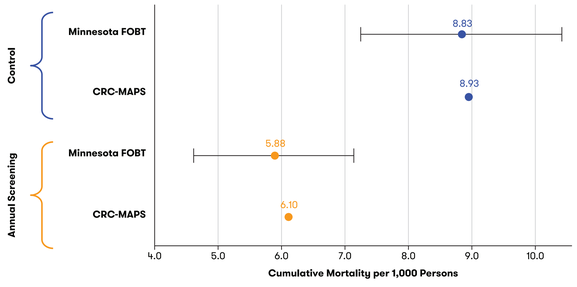
- This model simulates CRC progression through the adenoma-carcinoma pathway and allows for evaluation of different screening strategies

Figure 2. The CRC-MAPS model demonstrates cross-model validity among unscreened 65-year-olds free of diagnosed CRC comparable to CISNET CRC microsimulation models



Source for CRC CISNET models (CRC-SPIN, SimCRC, MISCAN): overall adenoma dwell time[6,7]; Cumulative risk of CRC and of death, CRC incidence reduction and mortality reduction[8]
†Cohort of 1,000 previously unscreened 65-year-old Medicare beneficiaries, screened from 65-75
COL= colonoscopy; FIT = fecal immunochemical test

Figure 3. External validation of the CRC-MAPS model reproduces cumulative mortality estimates observed in the Minnesota FOBT trial[9]



- For external validation of the model, CRC-MAPS was used to simulate the study population characteristics and adherence patterns of the 1993 Minnesota FOBT trial
- 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])

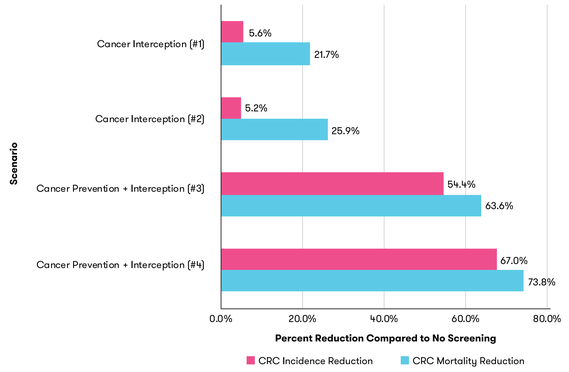
Table 1. Scenarios

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

Values for base-case specificity and CRC sensitivity are based on the reported performance of three MCED tests[2,10,11]

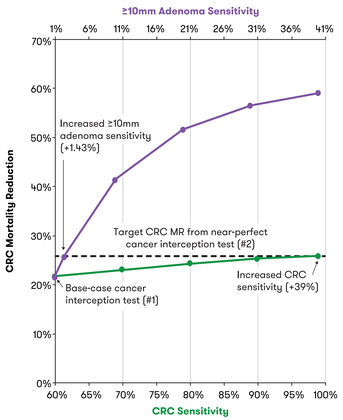
RESULTS

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



- The base-case interception scenario (#1) resulted in 5.6% CRC incidence reduction and 21.7% CRC mortality reduction compared to 5.2% CRC IR and 25.9% MR for the near-perfect interception scenario (#2)
- Due to increased adenoma sensitivity, the cancer prevention + interception scenarios (#3, #4) resulted in outcomes 2.5-12.9X as favorable as either cancer interception scenario (#1, #2)

Figure 5. CRC mortality reduction equivalent to a near-perfect cancer interception test was achieved by increasing ≥10mm adenoma sensitivity by only 1.43 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 2.43%

CONCLUSIONS

- 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
- The benefits from increased adenoma sensitivity are even more important for the unscreened Medicare population due to their higher CRC risk
- 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

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