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Adenoma detection improves clinical outcomes across adherence scenarios for a CRC screening blood test meeting CMS performance targets: Results from the CRC-MAPS model

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BACKGROUND

- In 2021, the Centers for Medicare and Medicaid Services (CMS) issued a National Coverage Determination (NCD) establishing a specificity (≥90%) and CRC sensitivity (≥74%) required for coverage of an FDA-authorized, triennial, blood-based colorectal cancer (CRC) screening test[1]
- However, CMS did not specify any requirements for adenoma sensitivity[1]
- Detection and removal of adenomas and early-stage CRC significantly reduces CRC incidence and mortality[2,3]
- Prior work with the CRC-MAPS model evaluated burdens and benefits of size-specific adenoma sensitivities, and demonstrated the impact of even modest adenoma sensitivity on clinical outcomes[4,5,6]

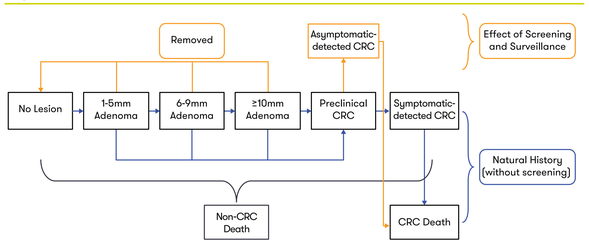
OBJECTIVE

- This study explores the impact of different levels of adenoma sensitivity for a hypothetical triennial blood-based CRC screening test benchmarked to the CMS targets across adherence scenarios, screening stop ages, and test intervals

METHODS

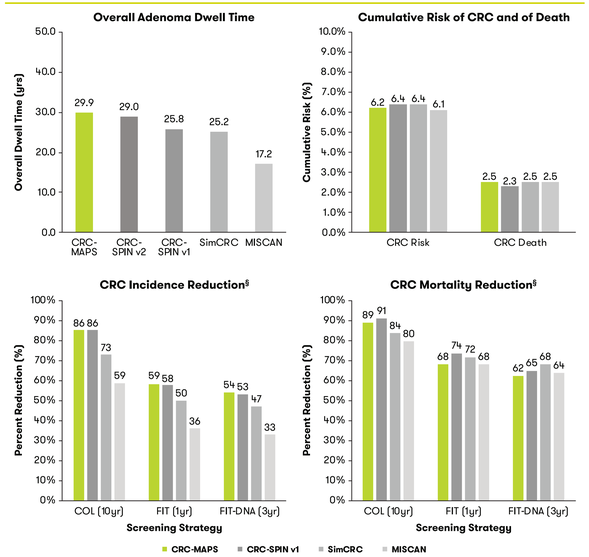
- A semi-Markov microsimulation model of the CRC adenoma-carcinoma pathway was developed in TreeAge and calibrated to autopsy, SEER, and endoscopy data (**Figure 1**)
- The model demonstrated good internal validity, and the model's cumulative lifetime natural history (no screening) and screening outcomes for a cohort of 65-year-olds free of diagnosed CRC were consistent with validated CISNET models[7,8,9] (**Figure 2**)
- The model also reproduced mortality reduction (MR) estimates observed in the Minnesota FOBT trial[10], a randomized controlled trial from 1993 that can be used for external validation (**Figure 3**)
- This study simulated clinical outcomes among previously unscreened individuals aged ≥65 free of diagnosed CRC for two hypothetical triennial CRC screening tests meeting the CMS targets for specificity and CRC sensitivity with different adenoma sensitivities (**Table 1**):
  - Baseline (CMS benchmark): All-size adenoma sensitivity at "noise" = 1 - Specificity
  - Adenoma (CMS benchmark with increased adenoma sensitivity): Size-specific adenoma sensitivities above "noise"
- Perfect and imperfect adherence scenarios were evaluated to reflect ideal and imperfect adherence
- Outcomes were aggregated from age 65 to death, and individuals were screened from age 65 to 85 to reflect CMS coverage guidelines for Medicare beneficiaries in the NCD[1]
- Assuming perfect adherence, a comprehensive analysis of additional test intervals (1yr, 2yr) and screening stop ages (75, 80) was also performed

Figure 1. The CRC-MAPS model schematic



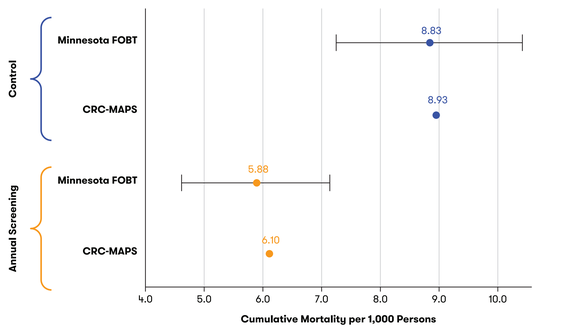
- This model simulates CRC progression through the adenoma-carcinoma pathway and allows for evaluation of different screening strategies

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



Source for CRC CISNET models (CRC-SPIN, SimCRC, MISCAN): overall adenoma dwell time[7]; Cumulative risk of CRC and of death, CRC incidence reduction and mortality reduction[9]
§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[10]



- 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])

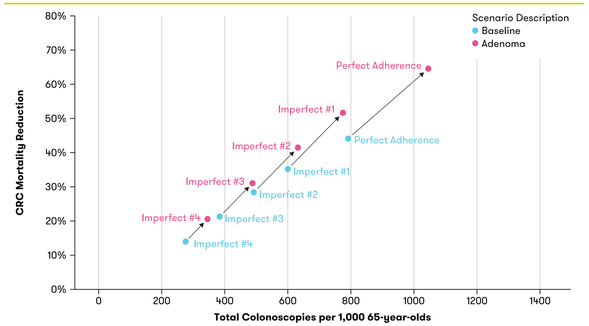
Table 1. Modeling scenarios

Input Parameters	Baseline	Adenoma
Performance		
Specificity[1]	90%	
Adenoma sensitivity	All-size: 1-Specificity = 10%	1-5mm: 15% 6-9mm: 20% ≥10mm: 30%
CRC sensitivity[1]	74%	
Screening interval[1]	Triennial	
Perfect adherence (initial screen participation, diagnostic, and surveillance colonoscopy)	100%	
Imperfect adherence		
Scenario #1:	100% screening, 80% diagnostic, 80% surveillance	
Scenario #2:	80% screening, 80% diagnostic, 80% surveillance	
Scenario #3:	60% screening, 80% diagnostic, 80% surveillance	
Scenario #4:	40% screening, 80% diagnostic, 80% surveillance	

RESULTS

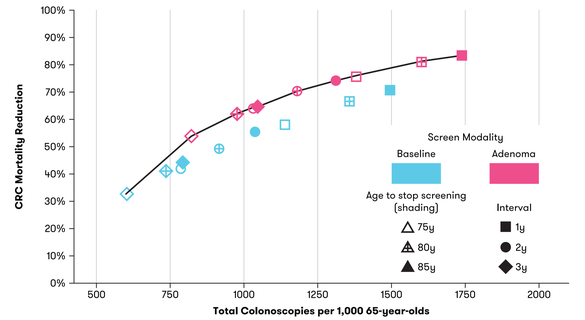
- Perfect adherence to a hypothetical test meeting the CMS benchmark resulted in 794 total colonoscopies and 84.4 life-years gained per previously unscreened 1,000 individuals aged 65 years free of symptomatic CRC compared to an equivalent test with increased adenoma sensitivity, which resulted in 1,048 total colonoscopies and 120.0 life-years gained
- Further, the CMS benchmark test resulted in 28.0% CRC incidence reduction and 43.9% CRC mortality reduction compared to an equivalent test with increased adenoma sensitivity, which resulted in 54.3% CRC incidence reduction and 64.5% CRC mortality reduction

Figure 4. Across adherence scenarios, a CRC screening test with increased adenoma sensitivity yields better outcomes than the CMS benchmark test



- For any given adherence scenario, a test with increased adenoma sensitivity conferred an average increase of 46% in CRC mortality reduction and 28% in colonoscopies relative to a test meeting CMS performance targets
- The difference in CRC mortality reduction for tests with and without increased adenoma sensitivity improved as a function of increasing adherence, favoring a test with increased adenoma sensitivity

Figure 5. All strategies for the CMS benchmark test with increased adenoma sensitivity dominated the CMS benchmark test



- Additional analyses explored the CRC mortality reduction and total colonoscopies per 1,000 individuals aged 65 years resulting from perfect adherence to two hypothetical blood-based CRC tests for different screening stop ages and test intervals
- Across screening stop ages and test intervals, a CMS benchmark test with increased adenoma sensitivity dominated the CMS benchmark test

CONCLUSIONS

- This microsimulation study of hypothetical blood-based CRC screening tests benchmarked to CMS performance targets illustrates the burdens and benefits of adenoma sensitivity for different adherence scenarios
- This analysis indicates that increasing adenoma sensitivity in a blood-based CRC screening test improves CRC incidence and mortality reduction across all adherence scenarios, test intervals, and screening stop ages
- This work also highlights that the impact of higher adherence on clinical outcomes can be further improved by increasing adenoma sensitivity
- Future work will explore the impact of adherence to diagnostic and surveillance colonoscopy on key outcomes

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Presented at Digestive Disease Week (DDW) Annual Meeting | May 20–24, 2022. San Diego, CA, USA