Burden-to-benefit ratios differ by adenoma size: Results from the CRC-MAPS™ model

Girish Putcha[1], Lauren N. Carroll[1], Signe Fransen[1], Ben Wilson[1], Tarun Chandra[2], and Andrew Piscitello[2]

[1]Freenome Holdings, Inc.; [2]EmpiriQA, LLC

BACKGROUND

- Colorectal cancer (CRC) is the third most common cause of cancer-related deaths in the U.S., but 5-year relative survival rates are greater than 90% if the tumor is detected before it spreads[1]
- While adenoma size and histology significantly affect CRC risk, removing all adenomas also carries risks (e.g., risk of complications, burden to patient and healthcare system)[2,3,4]
- As a result, the value of detecting and removing small and medium adenomas is unclear[5,6,7]
- These tradeoffs have important implications for patient care because they inform clinical guideline recommendations for surveillance intervals[2,6]
- Prior work with the CRC-MAPS™ model indicated that improvements in adenoma sensitivity had the largest impact (among test performance characteristics) on CRC incidence reduction (IR) and mortality reduction (MR), with increasing benefits for decreasing adenoma size.[8] However, burden was not quantified.

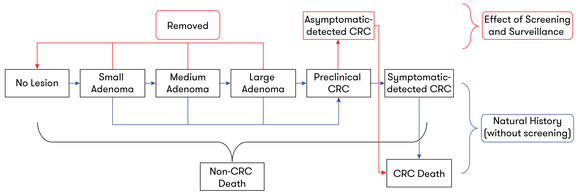
OBJECTIVE

- To examine the tradeoffs between test burden and clinical benefits (i.e., burden-to-benefit ratios) for a hypothetical blood-based test with the CRC Microsimulation of Adenoma Progression and Screening (CRC-MAPS)™ model

METHODS

- A semi-Markov microsimulation model of the 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 existing validated models (**Figures 2, 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 expressed per 1,000 individuals
- Individuals were screened from age 45 to 75
- The base case assumed size-specific adenoma sensitivities (1-5mm: 15%; 6-9mm: 20%; ≥10mm: 30%), 90% CRC sensitivity, and 90% specificity
- Primary outcome measures were the total number of colonoscopies (COL), CRC incidence reduction (IR), and mortality reduction (MR), compared to no screening
- The incremental number of COL per incremental percentage point change in CRC IR or MR (burden-to-benefit ratio) was calculated across changes (+/-5%) to each performance metric

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 with CISNET* CRC microsimulation models

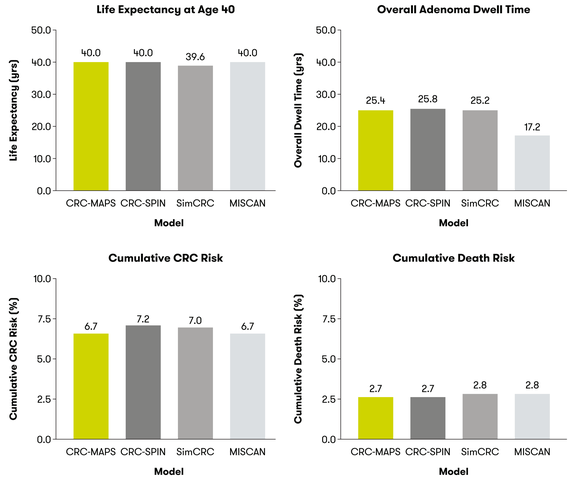
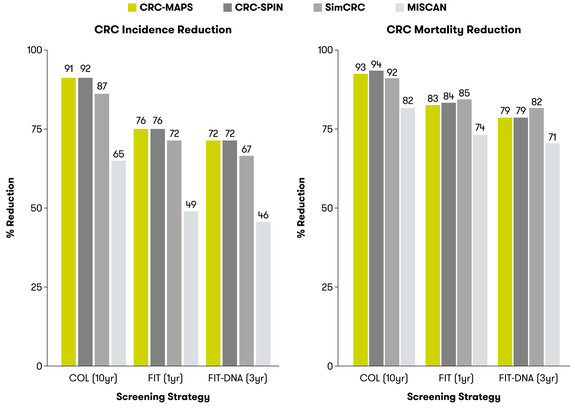


Figure 3. Clinical outcomes for guideline-recommended screening strategies are comparable for the CRC-MAPS™ and CISNET* CRC models



*CISNET CRC models include CRC-SPIN, SimCRC, MISCAN[9]
COL= colonoscopy; FIT = fecal immunochemical test

RESULTS

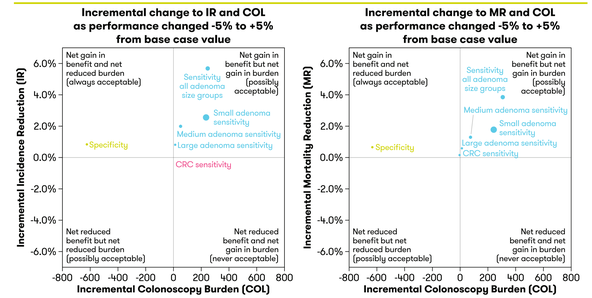
- The base case (size-specific adenoma sensitivities of 15% for 1-5mm, 20% for 6-9mm, and 30% for ≥10mm; 90% CRC sensitivity; and 90% specificity) resulted in 11 CRC cases and 3 CRC deaths, as well as 243 life years gained and 2,824 total colonoscopies per 1,000 individuals, compared to no screening
- The base case also showed an 83.4% and 87.9% reduction in CRC incidence and mortality, respectively, compared to no screening
- Burden-to-benefit ratios differed for each performance metric, with improvements to specificity and ≥10mm adenoma sensitivity resulting in the best tradeoffs for both IR and MR (i.e., lower burden-to-benefit ratios)
- The burden-to-benefit ratios for CRC IR and MR were the least favorable for improvements in 1-5mm adenoma sensitivity and much more favorable for 6-9mm and ≥10mm adenomas
- Increases to specificity greatly reduced the number of total colonoscopies and modestly increased CRC IR and MR, resulting in favorable burden-to-benefit ratios
- The burden-to-benefit ratios for improvements in CRC sensitivity were negligible

Table 1. Improvements in small adenoma detection exhibit 5-7x higher burden-to-benefit ratios than for medium and large adenoma detection

		CRC Incidence Reduction		CRC Mortality Reduction	
Performance Metric (range)	Change in #COL	Change in CRC IR	Burden-to-Benefit	Change in CRC MR	Burden-to-Benefit
Sensitivity for all adenoma size groups[†]	287.3	5.7%	50.0	3.8%	76.0
1-5mm Sensitivity (10% to 20%)	238.8	2.6%	93.3	1.8%	133.1
6-9mm Sensitivity (15% to 25%)	34.5	2.0%	17.0	1.3%	26.9
≥10mm Sensitivity (25% to 35%)	12.3	1.0%	12.6	0.6%	21.5
CRC Sensitivity (85% to 95%)	<< 0.1	-0.01%[‡]	-0.4	0.1%	0.03
Specificity (85% to 95%)	-623.1	0.8%[§]	-764.8	0.8%[§]	-779.9

[†]Sensitivity for all adenoma size groups were simultaneously reduced by 5 percentage points from the base case then increased 5 percentage points from the base case
[‡]Improvements to CRC sensitivity decrease CRC incidence reduction (i.e., result in higher CRC incidence) due to the detection of asymptomatic cases that would otherwise have gone undetected
[§]Improvements to specificity increase CRC incidence reduction (i.e., result in lower CRC incidence) due to fewer unnecessary follow-up colonoscopies, since an individual does not return to screening for 10 years after a colonoscopy-confirmed false positive

Figure 4. Improvements in specificity or adenoma sensitivity demonstrated larger changes in burden-to-benefit ratios than improvements in CRC sensitivity



- Improvements to all adenoma sensitivity and each size-specific adenoma sensitivity resulted in a higher colonoscopy burden but also an increase in both IR and MR; this may be an acceptable tradeoff depending on resource capacity and patient willingness to complete follow-up and surveillance colonoscopies
- For improvements to specificity, the CRC-MAPS model showed an increase in both IR and MR with a lower colonoscopy burden; this is an acceptable outcome since the slight increase in benefits comes with substantially fewer colonoscopies
- Improvements to CRC sensitivity had a negligible impact on colonoscopy burden, IR, and MR

CONCLUSIONS

- This microsimulation study of a hypothetical blood-based CRC screening test provides insights into different burden-to-benefit ratios for small, medium, and large adenomas
- This work underscores meaningful tradeoffs for the detection and removal of different sizes of adenomas, with the greatest burden for increases in small adenoma sensitivity
- The CRC-MAPS model does not simulate serrated lesions because there is currently insufficient natural history data to inform the model; nor does it model adenoma location or multiplicity
- Removal of all adenomas, and presumably non-adenomatous polyps (which were not modeled), may not offer an acceptable tradeoff since any gain in both CRC incidence reduction and mortality reduction comes with a disproportionately greater increase in colonoscopy burden
- Future work with the CRC-MAPS model will continue to explore the impact of adenoma detection and removal on additional outcomes

REFERENCES

1. Siegel et al. *CA Cancer J Clin.* 2021. doi: 10.3322/caac.21654. 2. Gupta et al. *Gastroenterology.* doi: 10.1053/j.gastro.2019.10.026. 3. Kothari et al. *Gastrointest Endosc.* 2019. doi: 10.1016/j.gie.2019.07.033. 4. Peterse et al. *J Natl Cancer Inst.* 2021. doi: 10.1093/jnci/djaa133. 5. Lieberman et al. *Gastroenterology.* 2008. doi: 10.1053/j.gastro.2008.06.083. 6. Dubé et al. *Am J Gastroenterol.* 2021. doi: 10.1038/ajg.2017.360. 7. Pichardt et al. *Gastroenterol Clin North Am.* 2018. doi: 10.1016/j.gtc.2018.04.004. 8. Putcha et al. "Adenoma sensitivity has a greater impact on colorectal cancer (CRC) incidence and mortality reduction than CRC sensitivity or specificity: Results from a novel microsimulation model" presented at Digestive Disease Week; May 21, 2021. 9. Zauber et al. "Estimating the benefits and harms of colorectal cancer screening strategies: A collaborative modeling approach" AHRQ Publication No. 14-05203-EF02. 2015.

Presented at American College of Gastroenterology 2021 Annual Scientific Meeting | Las Vegas, NV | October 22-27, 2021