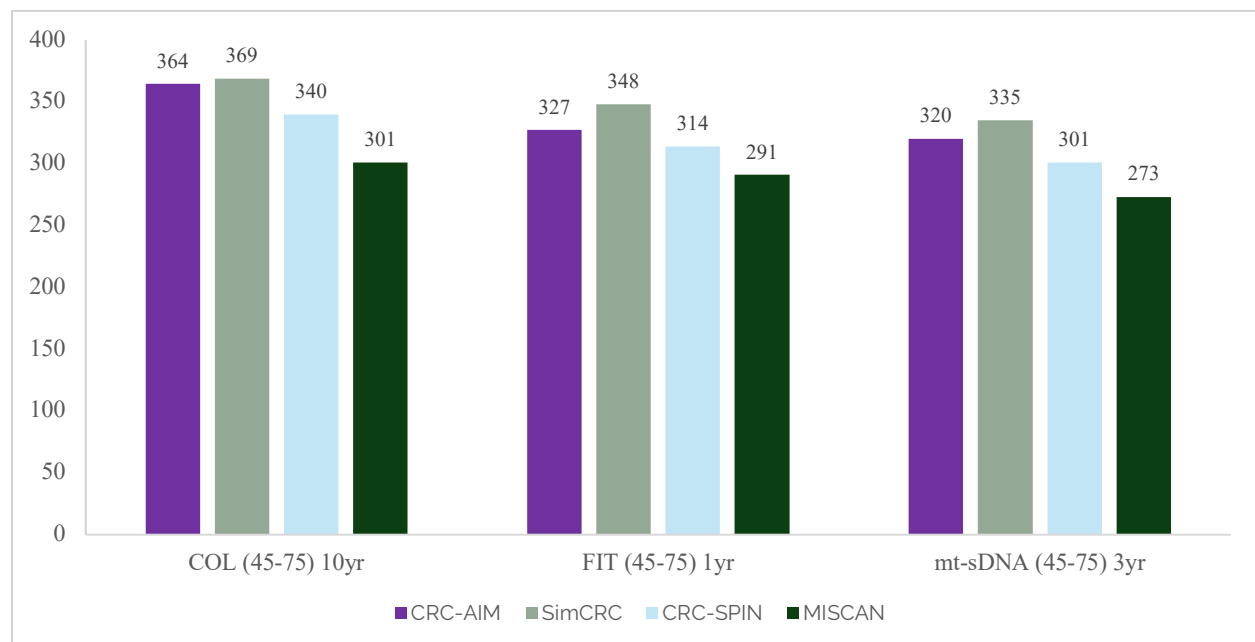## CRC-AIM Screening Cross-model validation

Results from three CISNET models (CRC-SPIN, MISCAN-COLON, and SimCRC), were included in the 2021 USPSTF CRC screening guideline update,[35] and used to cross validate the CRC-AIM model. Model outcomes were compared including life-years gained (LYG) with screening, CRC incidence and deaths (in the presence and absence of screening), and total number of colonoscopies conducted by screening modality. Three screening strategies (at their recommended screening intervals) for individuals aged 45 to 75 years were compared: colonoscopy every 10 years, annual fecal immunochemical test (FIT), and triennial multi-target stool DNA (mt-sDNA) test. Screening test sensitivity for CRC and adenomas (by size) and specificity are provided in Table 9. Sensitivity for stool-tests were calibrated to match the overall non-advanced adenoma sensitivity (consistent with the USPSTF modeling approach).[35] With assumed perfect screening adherence (100%), an incidence rate ratio was applied to reproduce the increasing underlying risk of CRC development after 1970.[34] CRC incidence for adults aged <50 years who are not screening eligible has substantially increased for both men and women in colon and rectum.[34] Previous analysis from USPSTF[35], report an incidence rate ratio set to 1.19. This incidence rate ratio was assumed to be an increase in the baseline log-risk, (β_0) of adenoma and applied through each simulated individual's lifespan.
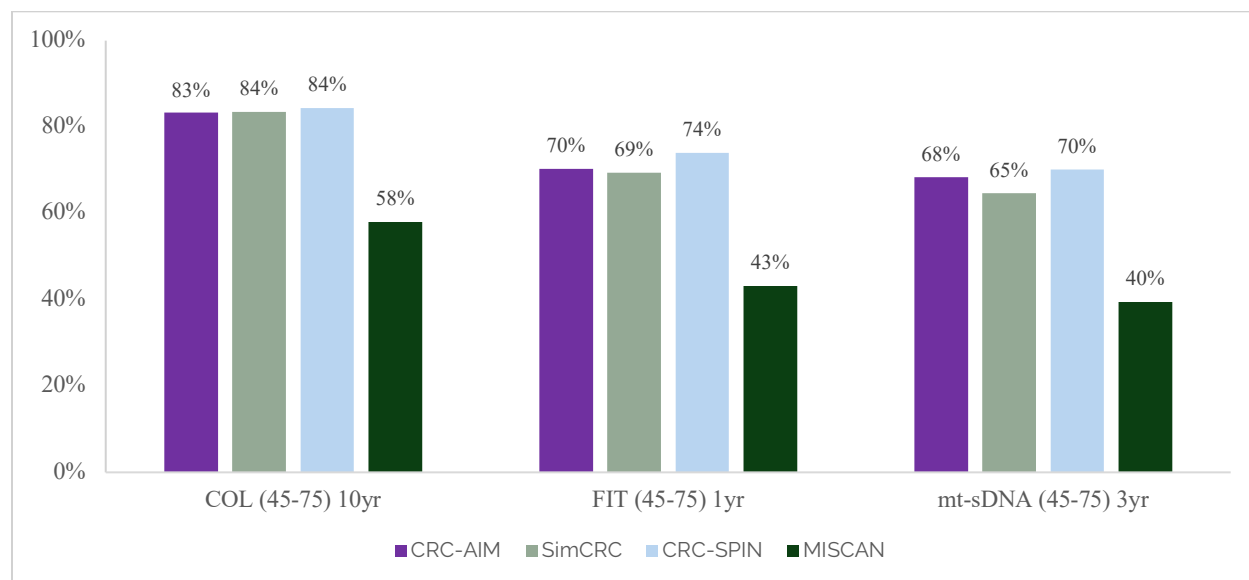
Life-years gained, as well as incidence and mortality reductions associated with colonoscopy, FIT, and mt-sDNA screening strategies (Supplemental Figure 11) and the associated numbers of colonoscopies and stool-based tests (Supplemental Figure 12-Supplemental Figure 15), were estimated by CRC-AIM and compared to CISNET model predictions.

Supplemental Figure 11. CRC-AIM and CISNET[35] estimates of life-years gained from screening by modality (adapted from Vahdat et al.[1])
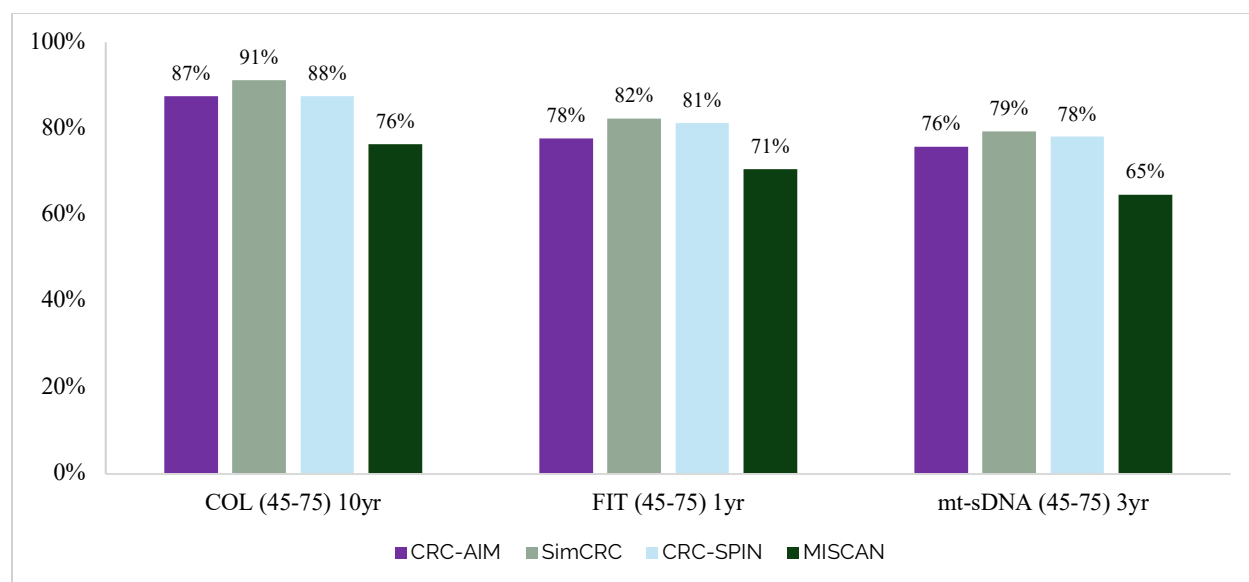
Supplemental Figure 12. CRC-AIM and CISNET estimates of colorectal cancer incidence reduction by screening modality (adapted from Knudsen et al.[35])
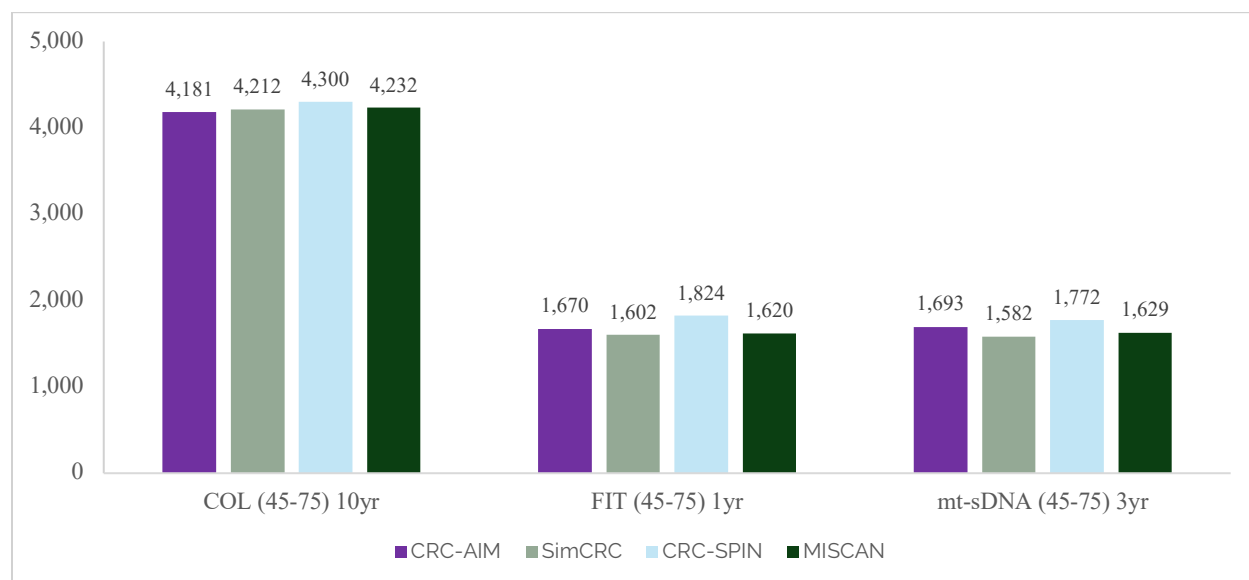
Supplemental Figure 13. CRC-AIM and CISNET estimates of colorectal cancer mortality reduction by screening modality (adapted from Knudsen et al.[35])
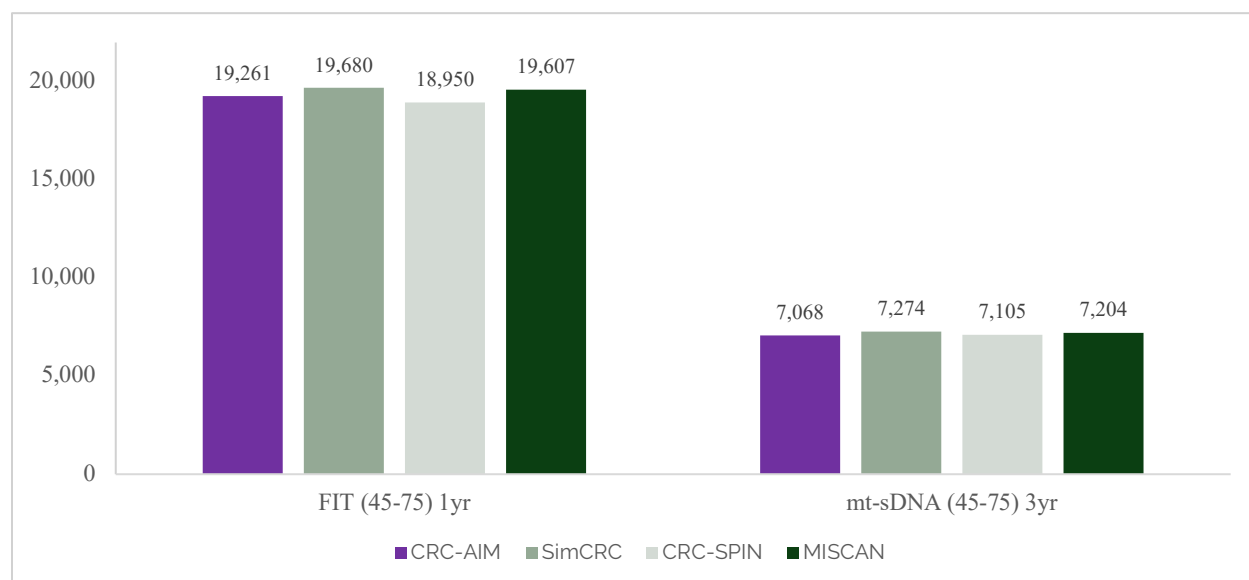
Supplemental Figure 14. CRC-AIM and CISNET estimates of the number of colonoscopies by screening modality (adapted from Knudsen et al.[35])

Supplemental Figure 15. CRC-AIM and CISNET estimates of the number of stool tests by screening modality (adapted from Knudsen et al.[35])