# Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a microsimulation modelling study

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## ABSTRACT

### OBJECTIVE
To estimate benefits and harms of different colorectal cancer screening strategies, stratified by (baseline) 15-year colorectal cancer risk.

### DESIGN
Microsimulation modelling study using MIcrosimulation SCreening ANalysis-Colon (MISCAN-Colon).

### SETTING
A parallel guideline committee (*BMJ* Rapid Recommendations) defined the time frame and screening interventions, including selection of outcome measures.

### POPULATION
Norwegian men and women aged 50-79 years with varying 15-year colorectal cancer risk (1-7%).

### COMPARISONS
Four screening strategies were compared with no screening: biennial or annual faecal immunochemical test (FIT) or single sigmoidoscopy or colonoscopy at 100% adherence.

### MAIN OUTCOME MEASURES
Colorectal cancer mortality and incidence, burdens, and harms over 15 years of follow-up. The certainty of the evidence was assessed using the GRADE approach.

### RESULTS
Over 15 years of follow-up, screening individuals aged 50-79 at 3% risk of colorectal cancer with annual FIT or single colonoscopy reduced colorectal cancer mortality by 6 per 1000 individuals. Single sigmoidoscopy and biennial FIT reduced it by 5 per 1000 individuals. Colonoscopy, sigmoidoscopy, and annual FIT reduced colorectal cancer incidence by 10, 8, and 4 per 1000 individuals, respectively. The estimated incidence reduction for biennial FIT was 1 per 1000 individuals. Serious harms were estimated to be between 3 per 1000 (biennial FIT) and 5 per 1000 individuals (colonoscopy); harms increased with older age. The absolute benefits of screening increased with increasing colorectal cancer risk, while harms were less affected by baseline risk. Results were sensitive to the setting defined by the guideline panel. Because of uncertainty associated with modelling assumptions, we applied a GRADE rating of low certainty evidence to all estimates.

### CONCLUSIONS
Over a 15 year period, all screening strategies may reduce colorectal cancer mortality to a similar extent. Colonoscopy and sigmoidoscopy may also reduce colorectal cancer incidence, while FIT shows a smaller incidence reduction. Harms are rare and of similar magnitude for all screening strategies.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Randomised trials with 15 or more years of follow-up have shown that sigmoidoscopy and guaiac faecal occult blood test (gFOBT) screening reduce colorectal cancer mortality

Colonoscopy and faecal immunochemical test (FIT) are increasingly used for colorectal cancer screening, but there are no published data from randomised trials on the relative effectiveness of the different screening strategies

Although risks and benefits differ across individuals, there is limited evidence for individualised screening recommendations. Basing screening on individual cancer risk, determined in large part by age and sex, may be desirable

## WHAT THIS STUDY ADDS

This modelling study found that, over a 15 year period, colorectal cancer mortality reduction may be very similar with a single colonoscopy or sigmoidoscopy, or annual or biennial FIT. Colonoscopy and sigmoidoscopy may result in similar reductions in colorectal cancer incidence, while the effect of FIT on incidence may be smaller or absent

At a baseline cancer risk of 3%, MISCAN-Colon estimates for 1000 individuals over 15 years are:

- Colorectal cancer deaths prevented: colonoscopy 6, sigmoidoscopy 5, annual FIT 6, biennial FIT 5

- Colorectal cancer cases prevented: colonoscopy 10, sigmoidoscopy 8, annual FIT 4, biennial FIT 1

- Harms were similar across screening strategies, with serious colonoscopic complications of <5 per 1000 at highest risk levels

Screening benefits and harms may increase as risk of colorectal cancer increases; benefits more so than harms

## Introduction

Colorectal cancer is a public health issue, with an estimated 1.4 million new cases and 700 000 deaths worldwide in 2018.[1] Screening is intended to reduce colorectal cancer incidence and mortality, and its effectiveness has been demonstrated in randomised controlled trials of guaiac faecal occult blood testing (gFOBT) and sigmoidoscopy.[2-11] Colonoscopy is likely to be at least as effective as sigmoidoscopy since it reaches the whole large bowel, whereas sigmoidoscopy reaches only the distal part of the large bowel. Faecal immunochemical testing (FIT) is likely to be at least as effective as gFOBT, since both tests detect blood in stools, and FIT demonstrates higher sensitivity and specificity.[12] However, because of the lack of published evidence from randomised trials for colonoscopy and

FIT screening, it is not known if they are more effective than gFOBT and sigmoidoscopy.[13]

Despite its benefits, colorectal cancer screening can be burdensome, and colonoscopy is associated with rare but serious complications. In addition, screening performance depends on the baseline risk of cancer for individuals. Few studies and guidelines have incorporated how baseline risk affects the balance between benefits, burden, and harms of screening in the past.

To elucidate these issues, we undertook micro-simulation modelling as part of the *BMJ* Rapid Recommendations project, a collaborative effort from the MAGIC research and innovation programme (www. magicproject.org) and *The BMJ*. The aim of the Rapid Recommendations is to respond to new, potentially practice changing, evidence and provide trustworthy practice guidelines in a timely manner. The *BMJ* Rapid Recommendations project for colorectal cancer screening was triggered by recent updates from three large randomised trials on sigmoidoscopy screening with follow-up data of 15 years or longer.[3 5 14] In light of this new evidence, we addressed the potential benefits and harms of colorectal cancer screening with annual or biennial FIT or a single sigmoidoscopy or colonoscopy in the time frame of 15 years. This work informed the parallel guideline published in a multilayered electronic format on bmj.com and MAGICapp. Box 1 shows the articles and evidence linked to this Rapid Recommendation.

### Methods
At the request of the guideline panel (Helsingen et al[15]), we applied the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model to simulate 15 years of follow-up of population cohorts aged 50-79 years. We estimated the benefits, burden, and harms of the following four screening strategies: annual FIT, biennial FIT, a single sigmoidoscopy, and a single colonoscopy. We compared the four screening strategies with each other and with no screening. We performed the analyses stratified by different levels of baseline colorectal cancer risk. Additionally, we determined screening benefits for men and women separately, and screening harms for different age groups, as requested by the panel.

### MISCAN-Colon model
MISCAN-Colon is a well established microsimulation model for colorectal cancer.[17 18] In brief, MISCAN-Colon simulates life histories of a large group of individuals from birth to death. In addition, the model simulates the development of colorectal cancer through the adenoma carcinoma sequence. As each simulated person ages, one or more adenomas may develop. These adenomas can progress in size increasing from small (≤5 mm) to medium (6–9 mm) to large (≥10 mm). Some adenomas can develop into preclinical cancer, which may progress through cancer stages I to IV. At any time during the development of the disease, the process may be interrupted because a person dies of other causes. With screening, colorectal cancer may either be prevented (by the detection and removal of adenomas) or detected at an earlier stage with a more favourable prognosis. In this way, colorectal cancer incidence and/or colorectal cancer mortality may be reduced. The model also estimates harms associated with screening.

The quantification and model assumptions are described in detail in appendix 1. In brief, the age-specific prevalence and multiplicity distribution of adenomas (the distribution of the individual number of adenomas across the population) were calibrated using autopsy studies.[19-29] The duration of preclinical colorectal cancer (sojourn time) and the adenoma dwell-time (the duration of progression of adenomas) were calibrated using rates of interval cancers (cancers that are diagnosed between screening tests) and surveillance detected cancers (found during surveillance) in randomised gFOBT and sigmoidoscopy trials.[8 30-35]

For this study, we developed a MISCAN-Colon model version calibrated to the sex-, age-, stage-, and localisation-specific colorectal cancer incidence and survival as observed in Norway during the timeframe of the NORCCAP trial (1999-2011) (appendix 2 (fig 1)), using data provided by the Norwegian Cancer Registry.[36] Life expectancy was based on sex-specific lifetables for 2007, the middle of the NORCCAP trial period, from Statistics Norway.[37] We validated this model using the results of one of the trigger publications: 15-year follow-up data from the Norwegian Colorectal Cancer Prevention (NORCCAP) trial.[5] The validation methods and results are described in appendix 3.

### Simulated cohorts
We simulated seven population cohorts consisting of men and women aged 50-79 years with a 15-year colorectal cancer risk varying from 1% to 7%, using the same Norwegian sex-specific MISCAN-Colon versions as we used for the validation. The age-specific onset of adenomas in MISCAN-Colon for all ages was adjusted to match the 15-year colorectal cancer risk in the seven cohorts. The modelled risk levels were chosen to cover the majority of individuals under consideration for this study (healthy people aged 50 to 79 years), but still with a manageable number of risk levels. We used the range of risk levels found when applying the QCancer risk prediction model to the UK Biobank cohort as guidance.[38] The simulated risk levels from 1% to 7% cover approximately 90% of the colorectal cancer risk levels found in the UK Biobank cohort (personal communication UK Biobank researcher Juliet Usher-Smith). We confirmed that the chosen risk levels also cover the range of risk levels observed in the general population, by comparing the risk levels with the 15 year colorectal cancer risk ranges found in two large population based cancer databases.[39 40] Data from the UK Biobank were also used to validate the QCancer prediction model for colorectal cancer. The QCancer Calculator is an open-access online tool that aims to predict individual colorectal cancer risk

Box 1: Linked resources for this BMJ Rapid Recommendations cluster

- Helsingen LM, Vandvik PO, Jodal HC, et al. Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a clinical practice guideline. *BMJ* 2019;367:l5515.15
  - Summary of the results from the Rapid Recommendation process
- Jodal HC, Helsingen LM, Anderson JC, et al. Colorectal cancer screening with faecal testing, sigmoidoscopy or colonoscopy: a systematic review and network meta-analysis. *BMJ Open* 2019;0:e032773.16
  - Review of all available trials that assessed colorectal cancer screening
- Buskermolen M, Cenin DR, Helsingen LM, et al. Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a microsimulation modelling study. *BMJ* 2019;367:l5383.
  - Modelling study of different modalities for colorectal cancer screening
- MAGICApp (http://magicproject.org/190220dist)
  - Expanded version of the results with evidence summaries and decision aids for use on all devices

based on risk factors such as medical history, lifestyle factors, and ethnicity.[41] Individuals may predict their 15-year colorectal cancer risk with this calculator (https://qcancer.org/15yr/colorectal/index.php). Subsequently, they may use this predicted colorectal cancer risk to look up the best risk-matching MISCAN-Colon predictions of screening outcomes, to get a personal estimate of the magnitude of benefits and harms of colorectal cancer screening. The clinical practice guideline presents relevant details.[15]

### Screening strategies

For each cohort, we assessed four colorectal cancer screening strategies during a 15-year period: biennial FIT, annual FIT, a single sigmoidoscopy, and colonoscopy. All strategies were compared with no screening. For FIT, we chose a cut-off of $20\,\mu g\,Hb/g$ faeces since this is used in many screening programmes.[42] We assumed that individuals with a positive FIT result and those with at least one adenoma (of any size) diagnosed at sigmoidoscopy screening were referred for colonoscopy.

Sensitivity and specificity of the screening tests were based on diagnostic test accuracy studies (table 1).[43 47] Age-specific risks for complications associated with colonoscopy were derived from SEER-Medicare data (table 1).[45 48 49] Only complications requiring hospital admission within 30 days after the colonoscopy were taken into account. Only colonoscopies with polypectomies were considered to cause adverse effects. We included colorectal perforations and bleedings, other gastrointestinal adverse events, cardiovascular adverse events, and mortality related to screening procedure. The number of complications was calculated by multiplying the number of colonoscopies with polypectomies by each complication risk. The simulated cohorts were assumed to have no prior screening.

We simulated surveillance consistent with European Society of Gastrointestinal Endoscopy Guidelines.[50] Individuals with low risk findings (fewer than three low risk adenomas (<10 mm diameter) at primary screening) did not receive any surveillance, whereas individuals with high risk findings were offered surveillance with colonoscopy after three years, and thereafter colonoscopies repeated at intervals of three to five years depending on the findings.

As our aim is to provide individuals who are considering screening with estimates of the possible benefits and harms of participation, we assumed 100% adherence to screening, follow-up and surveillance for all analyses.

### Outcomes

We distinguished the three screening-related outcome groups for the 15-year follow-up time frame chosen by the *BMJ* Rapid Recommendation guideline panel: benefits of screening, screening harms, and screening burden. For benefits of screening, we present model-predicted colorectal cancer incidence and mortality, and all-cause mortality reduction. For screening burden, we present the number of screening tests, number of individuals with at least one colonoscopy (including screening colonoscopies), and number of individuals with at least two colonoscopies (for example, individuals with at least one surveillance colonoscopy). For screening harms, we present risk of screening related colorectal perforations and bleedings, other gastrointestinal adverse events, cardiovascular adverse events, and mortality related to screening procedure.

### Sensitivity analyses

As a one-way sensitivity analysis, we assessed results stratified by age and sex; and we assessed outcomes with lifetime follow-up instead of a 15-year follow-up.

### Certainty of evidence

We used the GRADE approach to address the certainty of the evidence.[51] GRADE has not yet produced detailed guidance for assessing certainty of evidence in modelling studies. To make our assessment, we considered uncertainty associated with key inputs into the model.

### Guideline panel and patient involvement

According to the *BMJ* Rapid Recommendations process, a multiprofessional guideline panel that included three patients who have experienced colorectal cancer screening provided oversight to the study and identified the population and outcomes of interest.

### Results

The Rapid Recommendation panel suggests against screening if the risk is below a 15-year colorectal cancer risk of 3% and suggests screening if the risk is above 3%.[15] For simplification, we only describe the estimates for individuals with the 3% risk level. Estimates for all other risk levels are provided in table 2 and figure 1.

### Benefits of screening

MISCAN-Colon predicted that all screening strategies reduced colorectal cancer incidence and mortality

across all colorectal cancer risk groups (fig 1a and b, table 2). Colonoscopy showed the largest reduction in colorectal cancer mortality, but the differences between the screening strategies were small and the reduction may be similar for all strategies. For instance, the model predicted that, at 3% risk without

screening, colorectal cancer mortality was nine deaths per 1000 individuals. There were six per 1000 fewer colorectal cancer deaths with colonoscopy and annual FIT (approximately 60% reduction) and five per 1000 fewer deaths with sigmoidoscopy and biennial FIT (approximately 50% reduction).

### Table 1 | Key modelling assumptions used in study

| Input parameter | Base-case assumption | References |
|---|---|---|
| **Demography** | | |
| All-cause mortality | Norwegian lifetables 2007 | Statistics Norway |
| **Natural course of cancer** | | |
| Adenoma onset | Age dependent (non-homogeneous Poisson) | * |
| Adenoma progression: | | |
|   State transitions | Age dependent | * |
|   State duration (years, total) | Exp(λ=130) | * |
| Cancer progression (preclinical): | | |
|   Stage transitions | Age-dependent | * |
|   Stage durations (years) | Exp (λ=2.5) | * |
| Colorectal cancer incidence (without exposure to screening) | Age-, stage-, and location-dependent | Norwegian Cancer Registry |
| Colorectal cancer stage distribution | Age- and location-dependent | Norwegian Cancer Registry |
| Colorectal cancer survival | Age-, stage-, and location-dependent | Norwegian Cancer Registry |
| **Colonoscopy quality** | | |
| Sensitivity (%)†: | | |
|   Adenomas 0-5 mm | 75% | * |
|   Adenomas 6-9 mm | 85% | *, van Rijn et al[43] |
|   Adenomas ≥10 mm | 95% | *, van Rijn et al[43] |
|   Malignant neoplasia | 95% | * |
| Specificity (%) | 100% | |
| Complete colonoscopy examination (%)‡ | Men 93.5%, women 85.2% | Holme et al[44] |
| Complication rates (%)§: | | |
|   With polypectomy | Age dependent (50-79 years) | van Hees et al[45] |
|     Perforations and bleeding | 0.2-0.9 | |
|     Other GI adverse events | 0.2-0.8 | |
|     Cardiovascular events | 0.1-0.7 | |
|     Screening procedure related mortality | 0.008-0.04 | |
|   Without polypectomy§ | - | |
| **Sigmoidoscopy quality** | | |
| Sensitivity (%)†: | | |
|   Adenomas 0-5 mm | 75% | * |
|   Adenomas 6-9 mm | 85% | *, van Rijn et al[43] |
|   Adenomas ≥10 mm | 95% | *, van Rijn et al[43] |
|   Malignant neoplasia | 95% | * |
| Specificity (%)¶ | 98.2% | Buskermolen et al[46] |
| Complete examination (%)** | Men 93.2%, women 83.8% | Holme et al[44] |
| **Faecel immunochemical test (FIT) quality** | | |
| Sensitivity (%)†: | | Imperiale et al[47] |
|   Adenomas 0-5 mm | 0 | |
|   Adenomas 6-9 mm | 11.4 | |
|   Adenomas ≥10 mm | 15.9 | |
|   Malignant neoplasia: | | |
|     Short before clinical detection | 88.6 | |
|     Long before clinical detection | 62.6 | |
| Specificity (%)¶ | 97.6 | |

Poisson=Poisson distribution; Exp=exponential distribution. GI=gastrointestinal.
*More details available in appendix 1.
†Sensitivity was defined as the probability of detecting an adenoma that was present at the time of test.
‡Colonoscopy was considered complete if the caecum was reached. In the incomplete examinations, the endpoint was assumed to be distributed uniformly over the colon/rectum.
§We assumed that colonoscopy without polypectomy was not associated with a higher risk of complications. The risk of complications for polypectomy was assumed to increase exponentially with age. Perforation and bleeding concerned adverse events requiring blood transfusions; other GI adverse events included paralytic ileus, nausea, vomiting and dehydration, abdominal pain; and cardiovascular adverse events included myocardial infarction or angina, arrhythmias, congestive heart failure, cardiac or respiratory arrest, or syncope, hypotension, or shock. The screening procedure related mortality was derived from estimates of the incidence of perforation and case-fatality for perforation.[45 48 49]
¶The lack of specificity indicates how many of the tests that did not detect adenomatous lesions resulted in a referral for follow-up colonoscopy. The MISCAN-Colon model is a natural history microsimulation model simulating onset of adenomas in some individuals, that may progress to colorectal cancer in some cases. The model does not explicitly simulate the presence of blood in stool. To simulate FIT screening, we rather use estimates of per-person sensitivity and specificity by disease status based on a study by Imperiale et al. with a cut-off of 20 µg of haemoglobin per g of faeces.[47] We fitted per-lesion sensitivity and per-person specificity of the model to the per-person sensitivity and specificity estimates found in the study. In the model, the probability for a person to test positive depends on the lack of specificity and the per-lesion sensitivity for the lesions present in that individual.
**Flexible sigmoidoscopy was considered complete if the junction of the sigmoid/colon descendens was reached. In the incomplete examinations, the endpoint was assumed to be distributed uniformly over the rectosigmoid.

Table 2 | Predictions of benefits and harms of screening for individuals aged 50-79 years at varying levels of colorectal cancer risk. All outcomes are given per 1000 screened individuals over 15 years and compared to a scenario with no screening.

| Screening strategy | Colorectal cancer | | | | All-cause mortality reduction (%) | No of screening tests | No of individuals with ≥1 colonoscopy | No of individuals with ≥2 colonoscopies | Risk of complications | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Incidence reduction (%) | No of cases prevented | Mortality reduction (%) | No of deaths prevented | | | | | Perforation and bleeding | Other GI events | Cardio-vascular events | Screen procedure related mortality |
| **1% colorectal cancer risk without screening (10 cases per 1000, with risk of dying of colorectal cancer of 0.3% (3 per 1000))** | | | | | | | | | | | | |
| Biennial FIT | 8 | 1 | 53 | 2 | 0.4 | 5441 | 160 | 26 | 0.3 | 0.3 | 0.3 | 0.02 |
| Annual FIT | 18 | 2 | 62 | 2 | 0.5 | 9464 | 254 | 31 | 0.4 | 0.4 | 0.3 | 0.02 |
| Single sigmoidoscopy | 29 | 3 | 57 | 2 | 0.4 | 1000 | 82 | 28 | 0.4 | 0.4 | 0.3 | 0.02 |
| Single colonoscopy | 35 | 3 | 66 | 2 | 0.5 | 1000 | 1000 | 33 | 0.5 | 0.5 | 0.4 | 0.03 |
| **2% colorectal cancer risk without screening (20 cases per 1000, with risk of dying of colorectal cancer of 0.6% (6 per 1000))** | | | | | | | | | | | | |
| Biennial FIT | 6 | 1 | 51 | 3 | 0.8 | 5288 | 203 | 54 | 0.7 | 0.7 | 0.5 | 0.04 |
| Annual FIT | 16 | 3 | 60 | 4 | 0.9 | 9091 | 300 | 66 | 0.9 | 0.9 | 0.6 | 0.05 |
| Single sigmoidoscopy | 28 | 6 | 54 | 3 | 0.8 | 1000 | 159 | 57 | 0.8 | 0.8 | 0.6 | 0.05 |
| Single colonoscopy | 34 | 7 | 64 | 4 | 0.9 | 1000 | 1000 | 68 | 1.1 | 1.1 | 0.8 | 0.07 |
| **3% colorectal cancer risk without screening (30 cases per 1000, with risk of dying of colorectal cancer of 0.9% (9 per 1000))** | | | | | | | | | | | | |
| Biennial FIT | 5 | 1 | 50 | 5 | 1.1 | 5134 | 246 | 83 | 1.1 | 1 | 0.8 | 0.06 |
| Annual FIT | 15 | 4 | 59 | 6 | 1.3 | 8715 | 347 | 101 | 1.3 | 1.3 | 1 | 0.08 |
| Single sigmoidoscopy | 27 | 8 | 52 | 5 | 1.1 | 1000 | 237 | 86 | 1.3 | 1.2 | 0.9 | 0.07 |
| Single colonoscopy | 34 | 10 | 63 | 6 | 1.4 | 1000 | 1000 | 105 | 1.7 | 1.7 | 1.2 | 0.1 |
| **4% colorectal cancer risk without screening (40 cases per 1000, with risk of dying of colorectal cancer of 1.2% (12 per 1000))** | | | | | | | | | | | | |
| Biennial FIT | 4 | 2 | 49 | 6 | 1.5 | 4980 | 288 | 112 | 1.4 | 1.4 | 1.1 | 0.09 |
| Annual FIT | 15 | 6 | 59 | 7 | 1.8 | 8346 | 391 | 138 | 1.8 | 1.7 | 1.3 | 0.11 |
| Single sigmoidoscopy | 27 | 11 | 52 | 6 | 1.5 | 1000 | 312 | 119 | 1.7 | 1.7 | 1.2 | 0.1 |
| Single colonoscopy | 34 | 14 | 63 | 8 | 1.8 | 1000 | 1000 | 144 | 2.3 | 2.3 | 1.7 | 0.14 |
| **5% colorectal cancer risk without screening (50 cases per 1000, with risk of dying of colorectal cancer of 1.6% (16 per 1000))** | | | | | | | | | | | | |
| Biennial FIT | 4 | 2 | 49 | 8 | 1.8 | 4834 | 328 | 142 | 1.8 | 1.8 | 1.3 | 0.11 |
| Annual FIT | 15 | 7 | 59 | 9 | 2.2 | 7996 | 433 | 175 | 2.2 | 2.2 | 1.6 | 0.13 |
| Single sigmoidoscopy | 27 | 14 | 52 | 8 | 1.8 | 1000 | 382 | 153 | 2.2 | 2.1 | 1.6 | 0.13 |
| Single colonoscopy | 34 | 17 | 63 | 10 | 2.4 | 1000 | 1000 | 184 | 2.9 | 2.8 | 2.1 | 0.17 |
| **6% colorectal cancer risk without screening (60 cases per 1000, with risk of dying of colorectal cancer of 1.9% (19 per 1000))** | | | | | | | | | | | | |
| Biennial FIT | 5 | 3 | 50 | 9 | 2.2 | 4694 | 365 | 171 | 2.2 | 2.1 | 1.6 | 0.13 |
| Annual FIT | 15 | 9 | 59 | 11 | 2.6 | 7664 | 472 | 211 | 2.7 | 2.6 | 2 | 0.16 |
| Single sigmoidoscopy | 28 | 17 | 53 | 10 | 2.2 | 1000 | 446 | 189 | 2.7 | 2.6 | 1.9 | 0.16 |
| Single colonoscopy | 34 | 21 | 64 | 12 | 2.8 | 1000 | 1000 | 226 | 3.5 | 3.4 | 2.5 | 0.2 |
| **7% colorectal cancer risk without screening (70 cases per 1000, with risk of dying of colorectal cancer of 2.2% (22 per 1000))** | | | | | | | | | | | | |
| Biennial FIT | 5 | 4 | 50 | 11 | 2.6 | 4558 | 401 | 201 | 2.6 | 2.5 | 1.9 | 0.15 |
| Annual FIT | 16 | 11 | 59 | 13 | 3.0 | 7346 | 509 | 247 | 3.1 | 3.1 | 2.3 | 0.18 |
| Single sigmoidoscopy | 29 | 20 | 54 | 12 | 2.6 | 1000 | 505 | 228 | 3.2 | 3.1 | 2.3 | 0.19 |
| Single colonoscopy | 35 | 24 | 64 | 14 | 3.2 | 1000 | 1000 | 268 | 4 | 3.9 | 2.9 | 0.24 |

FIT=faecal immunochemical test.

Colonoscopy may be the most effective strategy in reducing colorectal cancer incidence, followed by sigmoidoscopy (fig 1b, table 2). Colonoscopy was estimated to reduce colorectal cancer incidence by 10 colorectal cancer cases and sigmoidoscopy by eight per 1000 individuals (approximately 30% reduction); annual FIT had four and biennial FIT had one incident cancer cases per 1000 screened (approximately 10% and 5% reduction).

The estimated relative effects were similar across the different levels of baseline risk (1% to 7% over 15 years) for both colorectal cancer incidence and mortality, resulting in larger absolute effects for colorectal cancer incidence and mortality for individuals with higher risk. The model assumes that prevented colorectal cancer deaths lead to a corresponding reduction in all-cause mortality. At 3% risk, the estimated relative reduction in all-cause mortality was around 1.5% (table 2), corresponding to a reduction of five per 1000 individuals (all-cause mortality reduced from 328 to 323).
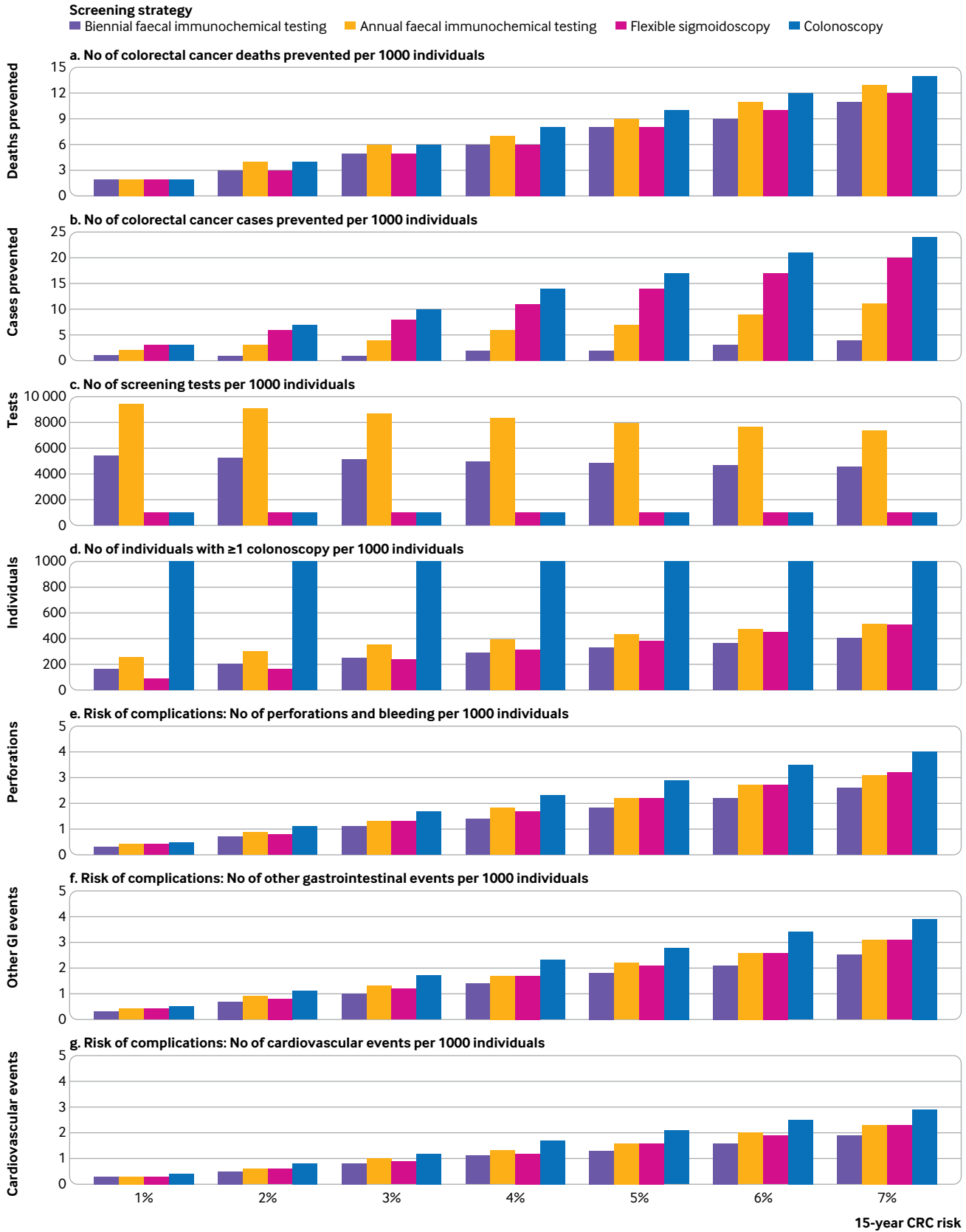
**Screening strategy**

- Biennial faecal immunochemical testing
- Annual faecal immunochemical testing
- Flexible sigmoidoscopy
- Colonoscopy



**a. No of colorectal cancer deaths prevented per 1000 individuals**

**b. No of colorectal cancer cases prevented per 1000 individuals**

**c. No of screening tests per 1000 individuals**

**d. No of individuals with ≥1 colonoscopy per 1000 individuals**

**e. Risk of complications: No of perforations and bleeding per 1000 individuals**

**f. Risk of complications: No of other gastrointestinal events per 1000 individuals**

**g. Risk of complications: No of cardiovascular events per 1000 individuals**

15-year CRC risk

Fig 1 | MISCAN-Colon predictions of colorectal cancer mortality and incidence reduction, screen tests, colonoscopies and complications per 1000 individuals, using biennial or annual faecal immunochemical test (FIT), flexible sigmoidoscopy, or colonoscopy. Results are stratified by colorectal cancer risk. Individuals were followed-up for 15 years

### Screening burden

The two FIT strategies required the most screening tests (fig 1c, table 2). The number of FIT rounds for the simulated cohort depended on the age of the individual at the first screening and the screening interval. Individuals ≤65 years old at cohort entry received seven rounds with biennial FIT and 15 rounds with annual FIT. However, many individuals received fewer screening rounds: individuals >65 years at cohort entry because they stopped screening after age 79; individuals who died within 15 years of follow-up; individuals who tested FIT positive and were referred for a colonoscopy and therefore received screening according to the surveillance guidelines. For individuals with a 3% colorectal cancer risk, we predicted that approximately 8700 tests were required with annual FIT screening, and 5100 with biennial FIT screening. Colonoscopy screening resulted in the highest number of individuals receiving at least one colonoscopy, since all individuals received colonoscopy as a screening test (fig 1d, table 2). The number of individuals with at least two colonoscopies (that is, individuals with at least one surveillance colonoscopy) was highest for colonoscopy regardless of colorectal cancer risk (table 2).

### Screening harms

The risk of screening related mortality, colorectal perforations and bleedings, other serious gastrointestinal adverse events, or cardiovascular adverse events was proportional to the number of required colonoscopies (fig 1e-g). In the 3% colorectal cancer risk group, the predicted overall complication risk was lowest with biennial FIT screening (2.9 per 1000) and highest with colonoscopy screening (4.6 per 1000) (table 2).

### Sensitivity analyses

The model predicted similar reductions in cancer incidence and mortality for the screening tests for men and women for all levels of 15-year baseline risk of colorectal cancer, except for sigmoidoscopy, for which the model predicted that women may benefit slightly less than men (appendix 4 (tables 1-12, fig 1)).

When results were stratified by age, annual FIT was more effective in reducing colorectal cancer mortality than a single colonoscopy in younger individuals (50-59 years old). In older individuals (75-79 years), colonoscopy and sigmoidoscopy were more effective. In addition, the estimated risk of complications increased more with age for the colonoscopy and sigmoidoscopy screening strategies than for the FIT strategies, although the increase in risk in absolute numbers was small (appendix 4 (tables 1-12. fig 2)). For example, at 3% colorectal cancer risk, a single colonoscopy strategy resulted in colorectal perforations and bleedings of 1.6 per 1000 in men aged 50-54 years and 3.4 per 1000 in men aged 75-79 years.

When we considered lifetime follow-up, the model predicted larger absolute reductions in colorectal cancer incidence and mortality for all screening strategies (appendix 5 (figs 1 and 2)), and less differences between annual FIT and colonoscopy. At younger ages (50-64 years) the model predicted that annual FIT was more effective at reducing colorectal cancer incidence and mortality than a single colonoscopy, although the difference was small. For example, annual FIT screening prevented 43 lifetime colorectal cancer cases in those aged 50-54 compared with 37 prevented cases with a single colonoscopy.

### Certainty of evidence

We noted appreciable uncertainty associated with the following model inputs: (a) all colorectal cancers develop through adenomas; (b) differences in colorectal cancer risk are caused by differences in adenoma incidence; and (c) adenoma dwell time. There is no high certainty data to inform the model regarding these model inputs. Therefore, despite the predictive and external validity of the model against the NORCCAP study (appendix 3), the panel considered all model estimates as low certainty evidence.

### Discussion

Our microsimulation model analysis suggests that all screening strategies reduce colorectal cancer mortality during 15 years of follow-up, and colonoscopy, sigmoidoscopy, and annual FIT may also reduce colorectal cancer incidence. The extent of absolute risk reduction varies with baseline colorectal cancer risk. Few differences were observed when results were stratified by sex. When outcomes were stratified by age, we observed that FIT screening strategies were estimated to be more effective in younger individuals, while colonoscopy and sigmoidoscopy were more effective in older individuals. FIT screening strategies required the highest overall number of screening tests, and colonoscopy screening resulted in the highest number of colonoscopies, regardless of colorectal cancer risk. Consequently, we observed the highest probability of experiencing a complication in individuals who underwent screening with a single colonoscopy, with increasing risk in older age groups.

Colonoscopy may result in the largest reduction in colorectal cancer incidence, followed by sigmoidoscopy and annual FIT. However, this finding was sensitive to the follow-up setting defined by the guideline panel. The panel chose a 15 year follow-up period because this allowed model predictions to be validated against trial data. With lifetime follow-up, the model predicted that relative incidence and mortality reductions from screening would persist for some more years, resulting in larger absolute numbers of prevented colorectal cancer cases and deaths. This was especially true for FIT, where lifetime follow-up resulted in higher estimates for colorectal cancer incidence reductions, making the test comparable to colonoscopy. However, because longer term follow-up data from trials are lacking, lifetime estimates are more uncertain and were thus not taken into account by the panel.

### Strengths and limitations of this study

Model predictions for colorectal cancer mortality and incidence reduction in this study are considerably higher than those observed in randomised screening trials. These seemingly discrepant results can be explained by our assumption of 100% adherence to screening tests, work-up, and surveillance colonoscopies, whereas trial outcomes are the result of real-world adherence patterns, which are considerably lower. When we replicated the NORCCAP trial population including observed adherence patterns, MISCAN-Colon predictions for colorectal cancer incidence and mortality reduction were in line with the trial results (appendix 3). Moreover, when we replicated the design of an Italian cohort study, the model predicted reductions in colorectal cancer incidence and mortality resulting from FIT screening that aligned well with those results observed in that study (data not shown).[52]

We acknowledge that 100% adherence gives estimates that are higher than what would be expected in a population screening programme, when adherence is never 100%. However, our intention was to inform individuals about expected effectiveness when they (fully) participate in screening rather than considering the impact of a screening programme from a public health perspective and assessing results at the population level. The aim of this study was to support the *BMJ* Rapid Recommendation panel by comparing different screening strategies, stratified by baseline 15-year colorectal cancer risk, using microsimulation modelling. A strength of this work is that we validated our model using the recently published 15-year follow-up results of the NORCCAP trial.[5] To our knowledge, this is the first modelling study to enable individuals to directly link their individual colorectal cancer risk to their predicted benefits and harms of colorectal cancer screening. Individuals can do this through determining their colorectal cancer risk using a calculator, such as the QCancer calculator,[41] incorporating information on age, sex, ethnicity, and other risk factors. The QCancer (10 year) calculator performed better than other prediction tools when externally validated against the UK Biobank cohort. However, like the other colorectal cancer risk prediction tools, it is far from perfect and, with an area under the curve of 0.67 in men and 0.65 in women, it poorly discriminates between those at a lower and those at a higher risk, which may lead to misclassification of individual baseline colorectal cancer risk.[16 53]

Our study has several limitations. First, MISCAN-Colon could not replicate the sex-specific differences in colorectal cancer incidence and mortality reduction as observed in the NORCCAP sigmoidoscopy screening trials[16] (appendix 3 (table 1)), despite the sex-specific adjustments to the model.[5] On the one hand, it may be that the dwell time of adenomas differs between men and women, potentially because the proportion of cancers in the proximal colon is higher in women. In MISCAN-Colon we did not assume sex-specific or localisation-specific differences in duration because of insufficient information from clinical studies or autopsy studies. On the other hand, the observed difference in screening effectiveness of sigmoidoscopy between men and women is higher in the NORCCAP trial than what was observed in the other sigmoidoscopy studies.[16]

Second, at the request of the guideline panel, we modelled only four screening strategies, and, for FIT, applied only one cut-off value (20 µg haemoglobin/g faeces). Applying lower or higher FIT cut-off values may result in higher or lower colorectal cancer screening effectiveness. In view of the results of diagnostic studies, there are also uncertainties regarding the additional benefit of using FIT annually instead of biennially.[54]

Third, it remains unknown whether differences in colorectal cancer risk among the population are caused by variations in the number of adenomas, a faster adenoma progression to malignancy, or a combination of the two. These variations may exist between men and women, different ethnicities, different levels of genetic predisposition or different environments. For this analysis, we assumed that differences in adenoma incidence cause differences in colorectal cancer risk.

Fourth, in MISCAN-Colon we assumed that all cancers developed from precursors via a common pathway. In the model description we refer to this as the adenoma carcinoma pathway with adenoma being the precursor lesions. However, recent evidence suggested that three distinct cancer pathways are relevant: about 60-70% of cancers develop via the conventional adenoma carcinoma sequence, 20-30% via the serrated polyp pathway, and 3% via the Lynch pathway.[55] In the model, we calibrated the average time it takes for a precursor to develop into colorectal cancer. Therefore, all precursor types are included in the modelled mix of slow and rapid progressing lesions. Modelling one common pathway may have consequences for the modelled results. For instance, we may overestimate the effectiveness of FIT and sigmoidoscopy compared with colonoscopy. Evidence is accumulating that FIT might be less sensitive for serrated polyps, and these polyps are usually located in the right side of the colon.[39 40 47 56] These polyps may have higher malignant potential than conventional adenomas. However, evidence for the malignant potential of the precursors from the distinct pathways is not yet decisive.

Fifth, this project focuses on the individual's perspective rather than on the perspective of public health professionals deciding on population-based screening programmes, which was the reason for assuming 100% adherence to screening and follow-up for all screening options. In population-based screening programmes, adherence rates of the various screening options can differ widely across countries.[57-59] When public health professionals make decisions about population-based screening programmes, they should also include evidence on the country-specific adherence rate to determine which screening option is most suitable. In addition, cost effectiveness analysis should be performed. For public

health professionals, a message from this study still may lie in the finding that benefits of screening do not differ much between the screening options.

Sixth, the estimated reduction in all-cause mortality is not observed in large randomised trials of gFOBT and sigmoidoscopy screening, which have not shown a significant reduction of all-cause mortality with screening. The *BMJ* Rapid Recommendations panel did not regard all-cause mortality estimates from the model as clinically relevant when making their recommendations.

Finally, we did not model probability bands. An important strength of this study is the large number of simulations we have performed, with different screening strategies, background colorectal cancer risks, age groups, and sex. The drawback is that to obtain probability bands for all simulations in this article, would require 840 000 simulations, which is too computationally expensive.

### Policy implications and conclusions

Notwithstanding the limitations, this modelling study addresses an important gap in current knowledge on colorectal cancer screening. There is insufficient evidence from clinical studies to determine which screening modality is most effective.[13] Currently, three large randomised trials are under way to assess the comparative effectiveness of colonoscopy and FIT,[60] and one on sigmoidoscopy versus FIT.[53] Our results indicate that the difference in colorectal cancer mortality reduction between screening modalities is substantially smaller than the differences in colorectal cancer mortality between screening and no screening. To achieve sufficient power to demonstrate these differences, the current colorectal cancer screening trials would require very large sample sizes. It is therefore unlikely that a comparison of all evaluated strategies will ever become available from randomised trials. Comparing screening modalities stratified by baseline colorectal cancer risk, age, and sex is even more complicated. In these cases, clinicians and patients must make choices on the basis of the best available evidence, even if it is of low certainty.

Our belief is that our modelling results are genera-lisable to individuals across the Western world. Although there may be some differences in life expectancy, age-specific colorectal cancer incidence, colorectal cancer stage distribution, and colorectal cancer survival compared with Norway, we expect that these differences do not significantly affect relative differences between screening modalities.

This study, together with the other publications in this *BMJ* Rapid Recommendations cluster, supports patients and physicians in the process of shared decision making by quantifying screening benefits, harms, and burdens on an individual level. For example, based on a certain colorectal cancer risk threshold, some low risk individuals may conclude that the undesirable consequences of screening outweigh the desirable consequences. Evaluating the modelling results, we predicted that lifetime follow-up of screened

individuals resulted in different estimates of screening effectiveness compared with 15 year follow-up. This additional finding encourages researchers to continue the follow-up in their randomised cohorts to evaluate longer term benefits of screening.

In conclusion, MISCAN-Colon predicted that all screening modalities reduce colorectal cancer mortality during a 15 year follow-up period, regardless of colorectal cancer risk, age, and sex. A single colonoscopy may be the most effective screening modality in preventing colorectal cancer incidence during 15 years follow-up. Colonoscopy screening is also associated with the highest risk for complications, but overall complication risks are low for colorectal screening. These results will contribute to risk-based colorectal cancer screening recommendations in this *BMJ* Rapid Recommendation project.[15]

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MBu and ILV affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted.

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**Appendices.** 1: MISCAN-Colon model description. 2: Calibration of MISCAN-Colon to Norwegian setting. 3: Validation of MISCAN-Colon against NORCCAP study. 4: MISCAN-Colon predictions with 15 year follow-up stratified for colorectal cancer risk, age, and gender. 5: MISCAN-Colon predictions with lifetime follow-up stratified for colorectal cancer risk, age, and gender.