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RAPID RECOMMENDATIONS

Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a clinical practice guideline

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This *BMJ* Rapid Recommendation article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. *BMJ* Rapid Recommendations represent a collaborative effort between the MAGIC group (http://magicproject.org/) and *The BMJ*. A summary is offered here and the full version including decision aids is on the MAGICapp (https://app.magicapp.org), for all devices in multilayered formats. Those reading and using these recommendations should consider individual patient circumstances, and their values and preferences and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation and contextualisation of our recommendations to local or other contexts. Those considering use or adaptation of content may go to MAGICapp to link or extract its content or contact *The BMJ* for permission to reuse content in this article.

ABSTRACT

Clinical question Recent 15-year updates of sigmoidoscopy screening trials provide new evidence on the effectiveness of colorectal cancer screening. Prompted by the new evidence, we asked: "Does colorectal cancer screening make an important difference to health outcomes in individuals initiating screening at age 50 to 79? And which screening option is best?"

Current practice Numerous guidelines recommend screening, but vary on recommended test, age and screening frequency. This guideline looks at the evidence and makes recommendations on screening for four screening options: faecal immunochemical test (FIT) every year, FIT every two years, a single sigmoidoscopy, or a single colonoscopy.

Recommendations These recommendations apply to adults aged 50-79 years with no prior screening, no symptoms of colorectal cancer, and a life expectancy of at least 15 years. For individuals with an estimated 15-year colorectal cancer risk below 3%, we suggest no screening (weak recommendation). For individuals with an estimated 15-year risk above 3%, we suggest screening with one of the four screening options: FIT every year, FIT every two years, a single sigmoidoscopy, or a single colonoscopy (weak recommendation). With our guidance we publish the linked research, a graphic of the absolute harms and benefits, a clear description of how we reached our value judgments, and linked decision aids.

How this guideline was created A guideline panel including patients, clinicians, content experts and methodologists produced these recommendations using GRADE and in adherence with standards for trustworthy guidelines. A linked systematic review of colorectal cancer screening trials and microsimulation modelling were performed to inform the panel of 15-year screening benefits and harms. The panel also reviewed each screening option's practical issues and burdens. Based on their own experience, the panel estimated the magnitude of benefit typical members of the population would value to opt for screening and used the benefit thresholds to inform their recommendations.

The evidence Overall there was substantial uncertainty (low certainty evidence) regarding the 15-year benefits, burdens and harms of screening. Best estimates suggested that all four screening options resulted in similar colorectal cancer mortality reductions. FIT every two years may have little or no effect on cancer incidence over 15 years, while FIT every year, sigmoidoscopy, and colonoscopy may reduce cancer incidence, although for FIT the incidence reduction is small compared with sigmoidoscopy and colonoscopy. Screening related serious gastrointestinal and cardiovascular adverse events are rare. The magnitude of the benefits is dependent on the individual risk, while harms and burdens are less strongly associated with cancer risk.

Understanding the recommendation Based on benefits, harms, and burdens of screening, the panel inferred that most informed individuals with a 15-year risk of colorectal cancer of 3% or higher are likely to choose screening, and most individuals with a risk of below 3% are likely to decline screening. Given varying values and preferences, optimal care will require shared decision making.

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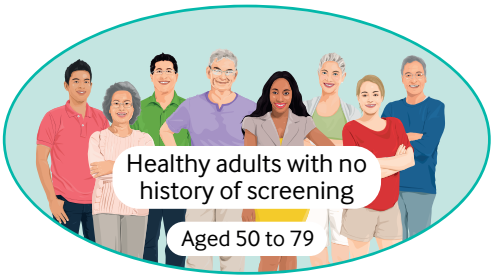
Visual summary of recommendation (1 of 5)

Population



Estimating risk

Understanding a person's risk of cancer can help to determine the benefits and harms of different screening tests for their individual situation.

We suggest using a tool such as the QCancer® calculator to estimate the risk of colorectal cancer for each person in the next 15 years. This calculates risk, based on:

Age | Sex | Ethnicity | BMI | Smoking status | Medical and family history

Link to QCancer® calculator qcancer.org/15yr/colorectal/

Interventions compared

No screening

FIT
Every year

Faecal testing with a faecal immunochemical test (FIT) every year

FIT
Every two years

Faecal testing with a faecal immunochemical test (FIT) every two years

Sigmoidoscopy
Single

Endoscopic examination of only the lower part of the colon

Colonoscopy
Single

Endoscopic examination of the entire colon

Colonoscopy offered if FIT or sigmoidoscopy positive

Recommendations

Favours no screening | Strong | **Weak** | Weak | Strong | Favours screening

People with an estimated 15 year risk of colorectal cancer **below** 3%

We suggest no screening

Favours no screening | Strong | Weak | **Weak** | Strong | Favours screening

People with an estimated 15 year risk of colorectal cancer **above** 3%

We suggest screening with one of the four screening options

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Visual summary of recommendation (2 of 5)

Screening options

Screening options should be chosen in shared decision making, based on a person's individual risk of cancer

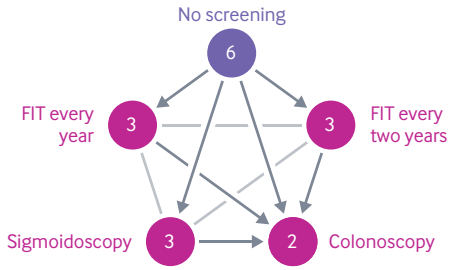
Visit the MAGICapp multiple comparison tool to compare and choose options

http://magicproject.org/190220dist

Evidence summaries

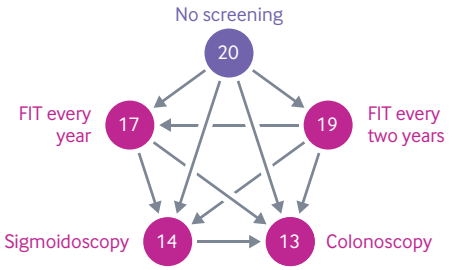
For a person with a 2% risk of colorectal cancer within 15 years

Colorectal cancer mortality
Events per 1000 people



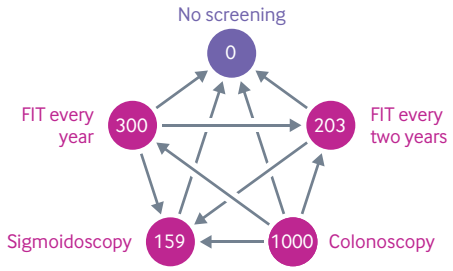
Evidence quality (GRADE score) ★★☆☆ Low

Colorectal cancer incidence
Events per 1000 people



Evidence quality (GRADE score) ★★★☆ Low

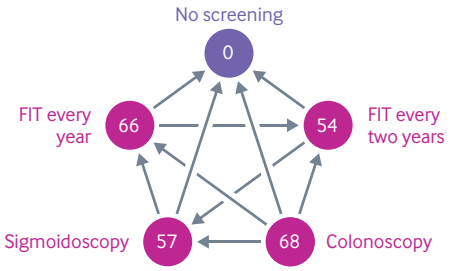
One or more colonoscopies
Events per 1000 people



Evidence quality (GRADE score) ★★☆☆ Low*

* High quality for colonoscopy

Two or more colonoscopies
Events per 1000 people



Evidence quality (GRADE score) ★★★☆ Low

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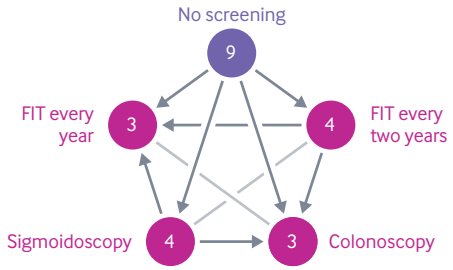
Visual summary of recommendation (3 of 5)

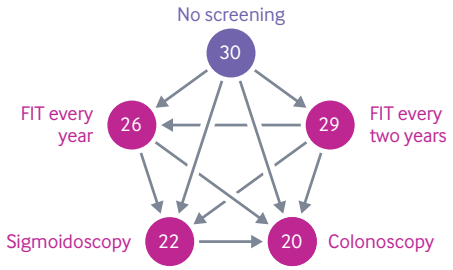
For a person with a 3% risk of colorectal cancer within 15 years

Colorectal cancer mortality
Events per 1000 people



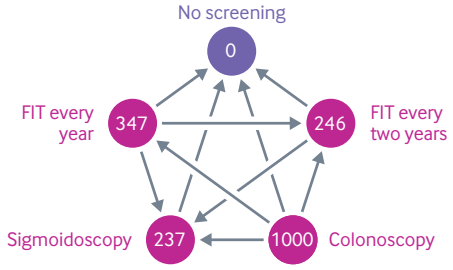
Evidence quality (GRADE score) ★★☆☆ Low

Colorectal cancer incidence
Events per 1000 people



Evidence quality (GRADE score) ★★★☆ Low

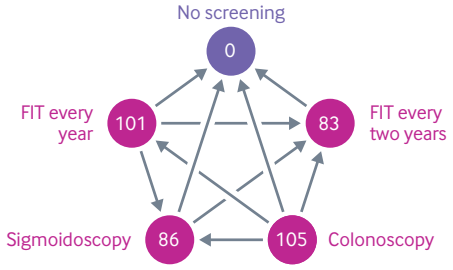
One or more colonoscopies
Events per 1000 people



Evidence quality (GRADE score) ★★☆☆ Low*

* High quality for colonoscopy

Two or more colonoscopies
Events per 1000 people



Evidence quality (GRADE score) ★★★☆ Low

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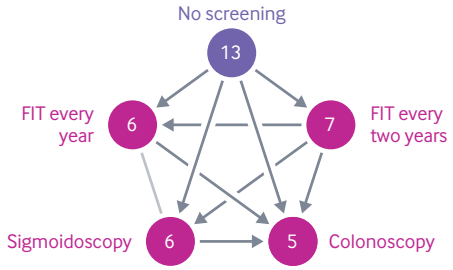
Visual summary of recommendation (4 of 5)

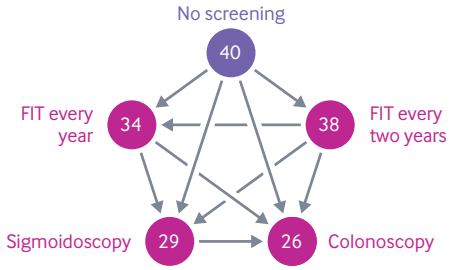
For a person with a 4% risk of colorectal cancer within 15 years

Colorectal cancer mortality
Events per 1000 people



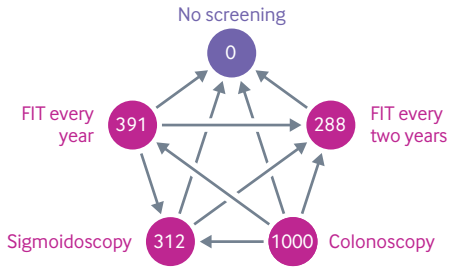
Evidence quality (GRADE score) ★★☆☆ Low

Colorectal cancer incidence
Events per 1000 people



Evidence quality (GRADE score) ★★☆☆ Low

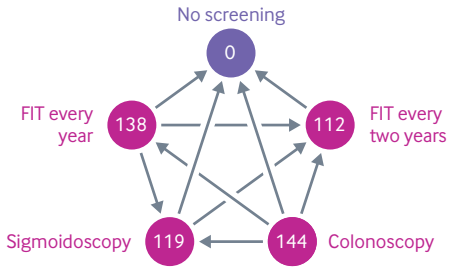
One or more colonoscopies
Events per 1000 people



Evidence quality (GRADE score) ★★☆☆ Low*

* High quality for colonoscopy

Two or more colonoscopies
Events per 1000 people



Evidence quality (GRADE score) ★★☆☆ Low

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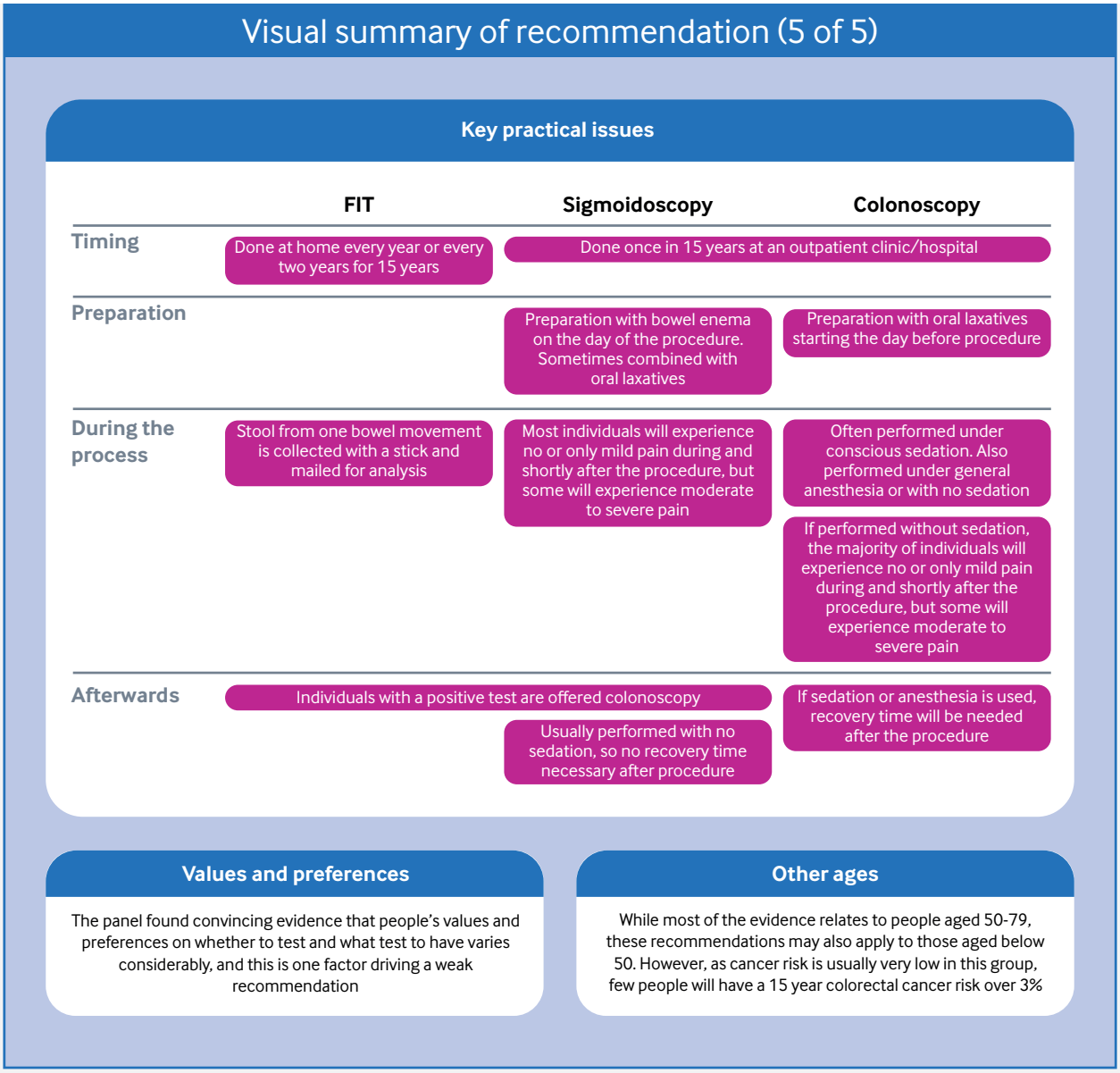

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What is the role of colorectal cancer screening with faecal immunochemical testing (FIT), flexible sigmoidoscopy or colonoscopy for people aged 50 to 79 years?

Recent updates to three of the major trials on sigmoidoscopy screening were published in 2017-19.[1-3] The trials provide evidence on screening effectiveness for up to 15 years after a single sigmoidoscopy. Two of these trials reported a reduction in colorectal cancer mortality and incidence with sigmoidoscopy screening in men, but only a small or no reduction in women.[2 3] This has sparked interest in whether women and men should be screened differently, and in which test is better for screening for colorectal cancer. We concluded that this new evidence could change current recommendations. Our recommendations are based on systematic reviews of benefits and harms of screening and, in the absence of randomised trial results for FIT and colonoscopy, on microsimulation modelling.[4 5]

The lifetime risk of colorectal cancer is approximately 5% in many Western countries, with varying risk in different geographical areas.[6] It is one of the most common cancers in both men and women. An individual's risk of cancer depends on age, sex, and genetics, and may be influenced by lifestyle factors such as alcohol intake, smoking, physical activity, and diet.[7] The five-year survival of colorectal cancer is 65%, with higher survival

HOW THESE RECOMMENDATIONS WERE CREATED

Our international panel included patient partners (individuals with experience of colorectal cancer screening), general practitioners, general internists, gastroenterologists, content experts (those conducting primary studies in colorectal cancer screening and immersed in the field), methodologists, and a nurse practitioner. No panel member reported financial conflicts of interest. Intellectual and professional conflicts were minimised and managed (see appendix 2 for details of panel members and their competing interests). The panel initially decided on the scope of the recommendation and the outcomes that they considered most important for individuals considering screening.

It was out of the scope for these guidelines to address all existing screening options. The panel decided to include the most commonly used options with the most solid evidence base. Randomised trials with sufficient follow-up for estimation of screening benefits have studied only sigmoidoscopy and guaiac faecal occult blood testing (gFOBT). However, today the most widely practiced screening tests are faecal immunochemical test (FIT) and colonoscopy.[8 9] FIT has a higher sensitivity and is more acceptable than gFOBT, and most screening programmes using faecal blood testing have changed to FIT. The panel therefore chose not to include guidance on gFOBT.[16 17] The panel requested the best evidence for four screening options: FIT every year, FIT every two years, a single sigmoidoscopy, and a single colonoscopy. For each option, the panel chose a 15-year time frame because that corresponds to the longest follow-up in the existing randomised sigmoidoscopy screening trials. FIT tests with a cut-off of 20 µg Hb/g faeces were considered positive.

The panel identified the following important outcomes: all-cause mortality, colorectal cancer mortality, colorectal cancer incidence, colorectal bleeding and perforation, other serious adverse events, and number of individuals needing at least one, two, or more colonoscopies. The panel also identified the following practical issues that could influence decisions regarding screening: emotional stress and anxiety related to a positive test, pain, discomfort, and absence from work related to screening procedures.

To inform the recommendations, the panel asked the following questions:

1. What benefit (reduced colorectal cancer mortality or incidence) would most individuals require to undergo colorectal cancer screening? In other words, what are peoples' anticipated values and preferences in trading off benefits versus burdens and harms?
2. In healthy individuals aged 50-79 years, what are the benefits, harms, and burdens over a 15 year period of screening with faecal testing every year or every two years, or a single sigmoidoscopy or colonoscopy, compared with no screening or with one another?

Parallel teams conducted systematic reviews and microsimulation modelling to inform the panel (described in detail in appendices 3-5 and the linked articles[4 5]).

The systematic review of values and preferences did not provide clear evidence of what benefit most individuals would require to undergo screening. The panel therefore identified thresholds for anticipated magnitude of benefit people would require and used this as guidance when deciding on the recommendations (see box 2 and appendix 3 for details).

A dedicated team performed a systematic review and network meta-analysis of randomised trials evaluating benefits and harms of colorectal cancer screening (see linked article[5]).

No randomised trials have addressed the effectiveness of FIT and colonoscopy screening, so the panel requested microsimulation modelling to estimate the benefits, burdens, and harms of the four screening options compared with no screening over a 15 year period (see linked article[4]). The panel also requested a systematic survey of reviews of screening-related burdens and harms that included observational studies designed to evaluate harms after screening, because data from randomised trials were limited (see appendix 4).

The panel asked the teams to explore potential subgroup effects for screening benefits by sex and of screening-related harms by age.

The panel acknowledged that the risk of cancer, and thus the magnitude of expected benefits and harms, varies substantially in the target population for these recommendations. The panel decided to base the recommendation on an individual estimation of colorectal cancer risk over 15 years. Details about the choice of calculator for the prediction of individual risk is provided in appendix 6.

The panel found that the thresholds of required benefit for either colorectal cancer mortality or incidence met at approximately 3% risk for all screening options.

Figure 1 shows the benefits of the different screening tests per 1000 screened, depending on the 15-year risk of colorectal cancer.

The panel followed *BMJ* Rapid recommendations procedures for creating a trustworthy recommendation, including the GRADE approach (see appendix 7). The panel met by videoconferences to discuss the evidence and formulate recommendations,[18 19] and considered the balance of benefits, harms, and burdens of the screening options and no screening, the certainty of the evidence for each outcome, expected variations in individuals' values and preferences, as well as practical issues.[20] Recommendations using GRADE can be strong or weak, for or against a course of action.[18] The panel made the recommendation from an individual perspective, assuming that all options were available and affordable. The recommendation does not take a public health, societal, or health payer perspective. Healthcare systems can adapt these recommendations by including costs and other key issues of relevance, contextualised to national and local circumstances.[21]

The number of individuals in need of two or more colonoscopies presented in this guidance differ slightly from the numbers presented to the panel in the process of making the recommendations (see appendix 3). The difference was due to a coding mistake that has been corrected. The panel decided that these changes did not alter the final recommendations.

One of the content experts on the panel did not wish to be a co-author of this article due to disagreement with the approach and the final recommendations. Two panel members (ILV and DAC) has strong reservations concerning the use of thresholds for the recommendations, due to limitations in the way the thresholds were determined. Box 2 presents the process of developing the thresholds and its limitations.

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Table 1 | Major guideline recommendations addressing colorectal cancer screening for average risk populations; all recommend screening from a certain age, and some recommend against screening in older age; none explicitly incorporates shared decision making based on individual risk and perceived benefits, harms, and burdens. For simplicity, the table includes only the preferred test or first-tier recommendations

Organisation	Screening age	GRADE strength of recommendation	Recommended test and timing
American College of Gastroenterology, 2009	Start 50 years	Strong, for screening	Colonoscopy every 10 years
American College of Physicians, 2015*	Screening for 50-75 years Not recommended >75 years	N/A	High sensitivity gFOBT or FIT every year
			gFOBT or FIT every 3 years *or* Sigmoidoscopy every 5 years
			Colonoscopy every 10 years
US Preventive Services Task Force, 2016	Screening for 50-75 years For 76-85 years, an individual decision	N/A	gFOBT or FIT every year
			FIT-DNA every 1-3 years
			FIT every year *or* Sigmoidoscopy every 10 years
			Sigmoidoscopy every 5 years
			Colonoscopy every 10 years
			CT colonography every 5 years
National Comprehensive Cancer Network Guidelines, 2017	Screening for 50-75 years For 76-85 years, an individual decision	N/A	Colonoscopy every 10 years
			gFOBT or FIT every year
			Faecal DNA test every 3 years
			Sigmoidoscopy every 5-10 years ± gFOBT or FIT every 3 years
			CT colonography every 5 years
United States Multi-Society Task Force of Colorectal Cancer Guidelines, 2017	Screening for age 50-75 years For 76-85 years, consider for those without prior screening	For screening: strong for 50-75, weak for 76-85 years	FIT every year
			Colonoscopy every 10 years
American Cancer Society, 2018	Screening from 45 years Screening for 50-75 years For 76-85 years an individual decision based on preference, life expectancy, and overall health	For screening: weak for 45-49, strong for 50-75, weak for 76-85 years	High sensitivity gFOBT or FIT every year
			Multi-targeted stool DNA every 3 years
			Colonoscopy every 10 years
			CT colonography every 5 years
			Sigmoidoscopy every 5 years
Canadian Task Force on Preventive Health Care, 2016	Screening for 50-74 years Not recommended for >75 years	For screening: weak for 50-59, strong for 60-74 Weak against screening >75 years	gFOBT or FIT every 2 years
			Sigmoidoscopy every 10 years
German Guideline Program in Oncology, 2019	Start 50 years	N/A	Colonoscopy every 10 years
Spanish Society of Medical Oncology, 2014	Screening for 50-74 years	N/A	FIT every two years
			gFOBT every 1-2 years
			Sigmoidoscopy every 5 years
			Colonoscopy every 10 years
National screening programmes in Sweden, New Zealand and United Kingdom†	Screening for 60-74 years	N/A	FIT every 2 years
National screening programmes in Denmark and France	Screening for 50-74 years	N/A	FIT every 2 years
Korean Guidelines for Colorectal Cancer Screening and Polyp Detection, 2012	Start 50 years	Strong, for screening	Colonoscopy every 5 years
Chinese Society of Gastroenterology, 2014	Screening for 50-74 years	N/A	FIT and questionnaire every 3 years
Updated Asia Pacific Consensus Recommendations on colorectal cancer screening, 2015	Screening for 50-75 years	N/A	FIT, interval not mentioned
National Guidelines for Colorectal Cancer Screening in Saudi Arabia, 2015	Screening for 45-70 years Not recommended >70 years	Strong, for screening 54-70 Weak against screening >70 years	Colonoscopy every 10 years
World Gastroenterology Organisation, 2007	Start 50 years	N/A	Colonoscopy every 10 years
NHMRC, Clinical Guidelines for Prevention, Early Detection and Management of Colorectal Cancer, Australia, 2017	Screening for 50-74 years	N/A	FIT every 2 years
National guideline in Japan	Start 40 years	N/A	FIT every year

gFOBT=guaiac faecal occult blood test. FIT=faecal immunochemical test.
The recommendations listed is a selection of recommendations identified through two systematic surveys: one found 15 colorectal cancer screening guidelines published in English between 2007 and 2017 (6 from North America, 4 from Europe, 5 from Asia)[8]; the other survey in high income countries found another 19 guidelines.[9]
*Update of guideline in progress (Amir Qaseem, ACP, personal communication).
†In addition to FIT screening every two years, a one-time sigmoidoscopy is currently being rolled out for people at age 55 in the UK.[10]

observed in localised disease. All patients with colorectal cancer are offered surgical treatment. In addition, patients with advanced disease undergo chemotherapy or radiation.

Screening aims at reducing colorectal cancer mortality and/or incidence by detecting cancer early (by regular testing for faecal blood), or prevention of cancer development (by detecting and removing cancer precursors, adenomas). The awareness of colorectal cancer screening has increased from the early 2000s, and most European countries, North America, and parts of South America, Asia, and Oceania have implemented or are planning implementation of screening (table 1).[11]

This guideline provides recommendations for the most widely used screening tests worldwide. It is the first guideline on colorectal cancer screening to provide

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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.
  - 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.[5]
  - 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.[4]
  - Modelling study of different modalities for colorectal cancer screening
- MAGICApp (https://app.magicapp.org/public/guideline/EQNVKj)
  - Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

explicit judgments of values and preferences, and basing the recommendations on absolute benefits, harms, and burdens of screening in a 15 year period. Within the population under consideration for this guideline, there are groups with different risks of developing colorectal cancer, ranging from less than 1% to more than 15% over 15 years. Most people, however, will be in the range from 1% to 7%. This is the first guideline that gives recommendations based on individual cancer risk. The guideline also includes practical issues important for the screening decision and decision aids for use in the clinical encounter.

The main infographic provides an overview of modelled estimates of the absolute benefits and harms of screening, when the 15-year risk of colorectal cancer is 2%, 3%, or 4%, and assuming 100% adherence to all screening tests, work-up, and surveillance colonoscopies in a 15 year period. A microsimulation model informed by randomised trials and observational studies provided all estimates of benefit and harm.[4] Box 1 shows all evidence linked in this Rapid Recommendation package. Table 2 shows any new evidence that has emerged after initial publication of these recommendations.

Current practice

What is recommended?

Some countries have systematic, population based, screening programmes in which presumed asymptomatic people are invited for screening. In others, including the US, widespread opportunistic screening is common (depending on initiatives from patients or clinicians), although in some settings there are comprehensive screening outreach programmes, such as within the Kaiser Permanente health system.[12]

Most guidelines recommend screening starting at age 50 years, when the risk of cancer in the next 15 years is typically 1-2% (in European and North American populations).[13-15] Screening is performed with many different tests and combination of tests, with different frequencies and in different age groups. However, the most common screening options are faecal testing, sigmoidoscopy, and colonoscopy. Which test is used varies due to different priorities and different interpretation of the existing evidence by guideline developers and screening providers, but also because of differences in peoples' values and preferences.

Current guidelines provide the same recommendations for all individuals above a certain age and do not account for individual differences in cancer risk. Table 1 presents a summary of some of these recommendations based on two surveys published in 2018.[8 9]

The evidence

Evidence summaries are available for those at 2%, 3%, and 4% risk at the start of their screening (see main infographic). Fig 2 provides an overview of the data sources used to inform this guideline.

How do people value colorectal cancer screening?

People's view on the net benefit of screening varies substantially.[22 23] We know this because our literature review found a variety of different recommendations (see table 1), limited uptake of screening in practice (see box 2) and variation in studies of people's values and preferences.

The literature review of studies on values and preferences did not identify evidence informing the magnitude of benefit people would require to undergo colorectal cancer screening. Therefore, before reviewing the evidence of screening benefits, the panel used their own experience to hypothesise what benefit of screening they thought people would require to undergo screening. This process helped minimise the influence of prior guideline recommendations, or potential preconceived beliefs of the net benefit of screening, on the panelists' view on the threshold of required benefits. (See box 3 and appendix 3 for details on this process).

Panel members' views varied, but, after discussion, we decided to use the following thresholds of benefits, at which the panel believed around half of informed individuals would choose screening:

- Sigmoidoscopy or colonoscopy if the screening could reduce colorectal cancer mortality and/or incidence by 10 or more per 1000 screened over a 15 year period
- FIT if the screening could reduce colorectal cancer mortality and/or incidence by 5 or more per 1000 screened over a 15 year period. (Lower threshold because the panel perceived the burdens of testing as smaller for FIT than for sigmoidoscopy or colonoscopy.)

What are the benefits of colorectal cancer screening?

Randomised trials have addressed screening with sigmoidoscopy and gFOBT and provide high to moderate certainty evidence for screening effectiveness: sigmoidoscopy reduces colorectal cancer mortality and incidence after 15 years of follow-up, and gFOBT every year or every

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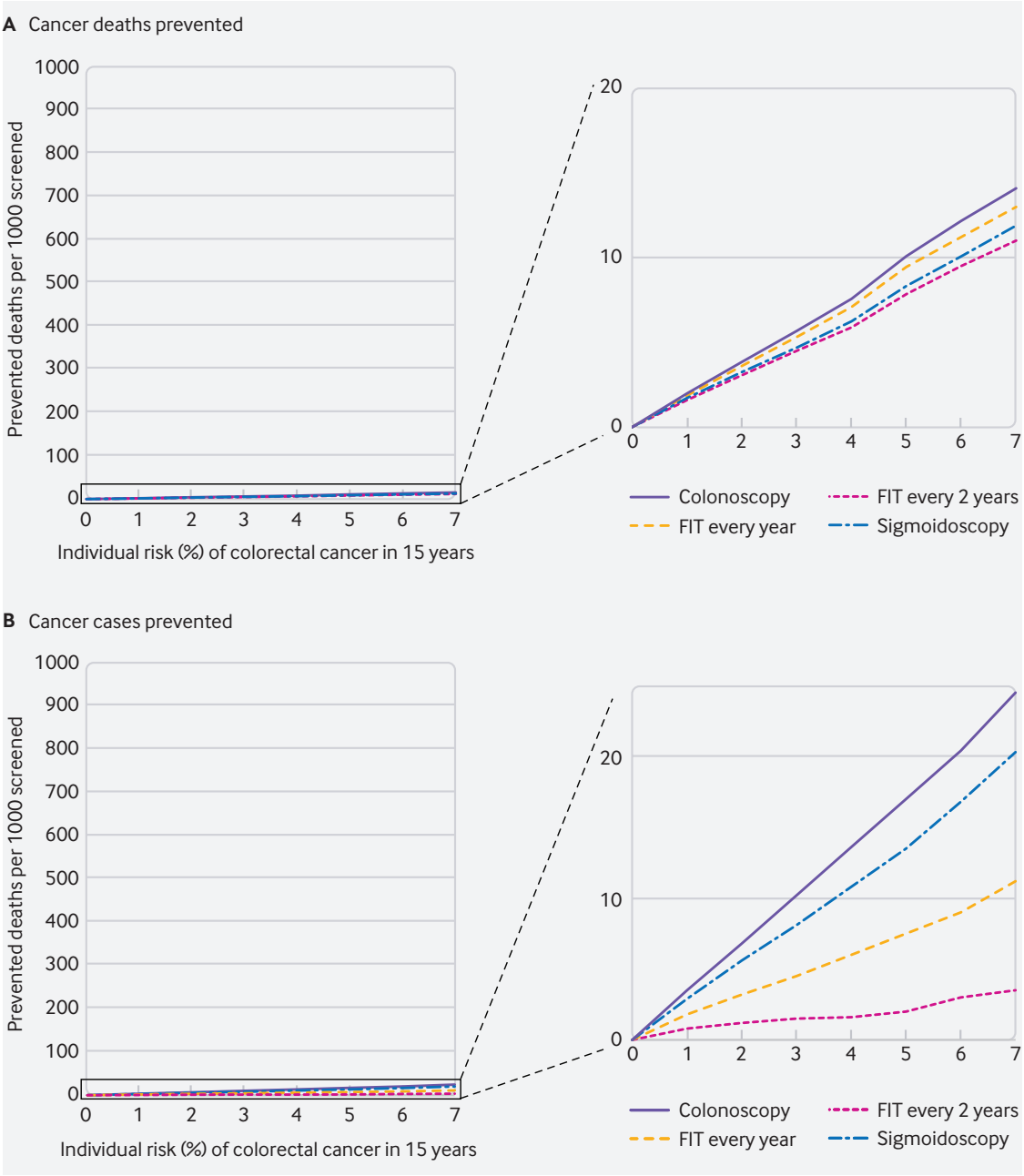

Fig 1 | Number of colorectal cancer (a) deaths and (b) cases prevented by different screening options per 1000 screened individuals, stratified by individuals' 15-year risk of colorectal cancer.

two years reduces colorectal cancer mortality but has little or no impact on cancer incidence. Neither sigmoidoscopy nor gFOBT affects all-cause mortality. For details, see the linked review.[5]

Because of lack of trial data for FIT and colonoscopy, we used a microsimulation model to provide ultimate estimates for clinical decision making. The model has been validated against the results from the trials of sigmoidoscopy and gFOBT, but due to the assumptions inherent in the model, it can only provide estimates of low certainty. The estimates of colorectal cancer incidence and mortality reduction from the model are higher than those observed in randomised screening trials. Our model is based on 100% adherence to screening, work-up and surveillance colonoscopies, whereas the trial estimates reflect substantially lower rates of adherence (see box 2). A linked article provides details of the modelling.[4]

All the modelling data are of low certainty. It is a useful indication, but there is a high chance that new evidence will show a smaller or larger benefit, which in turn may alter these recommendations. Compared with no screening, the model estimates that:

- Colorectal cancer mortality may be reduced similarly by all four screening tests
  - FIT every two years (relative risk 0.5)
  - FIT every year (relative risk 0.41)
  - Single sigmoidoscopy (relative risk 0.48)
  - Single colonoscopy (relative risk 0.37)

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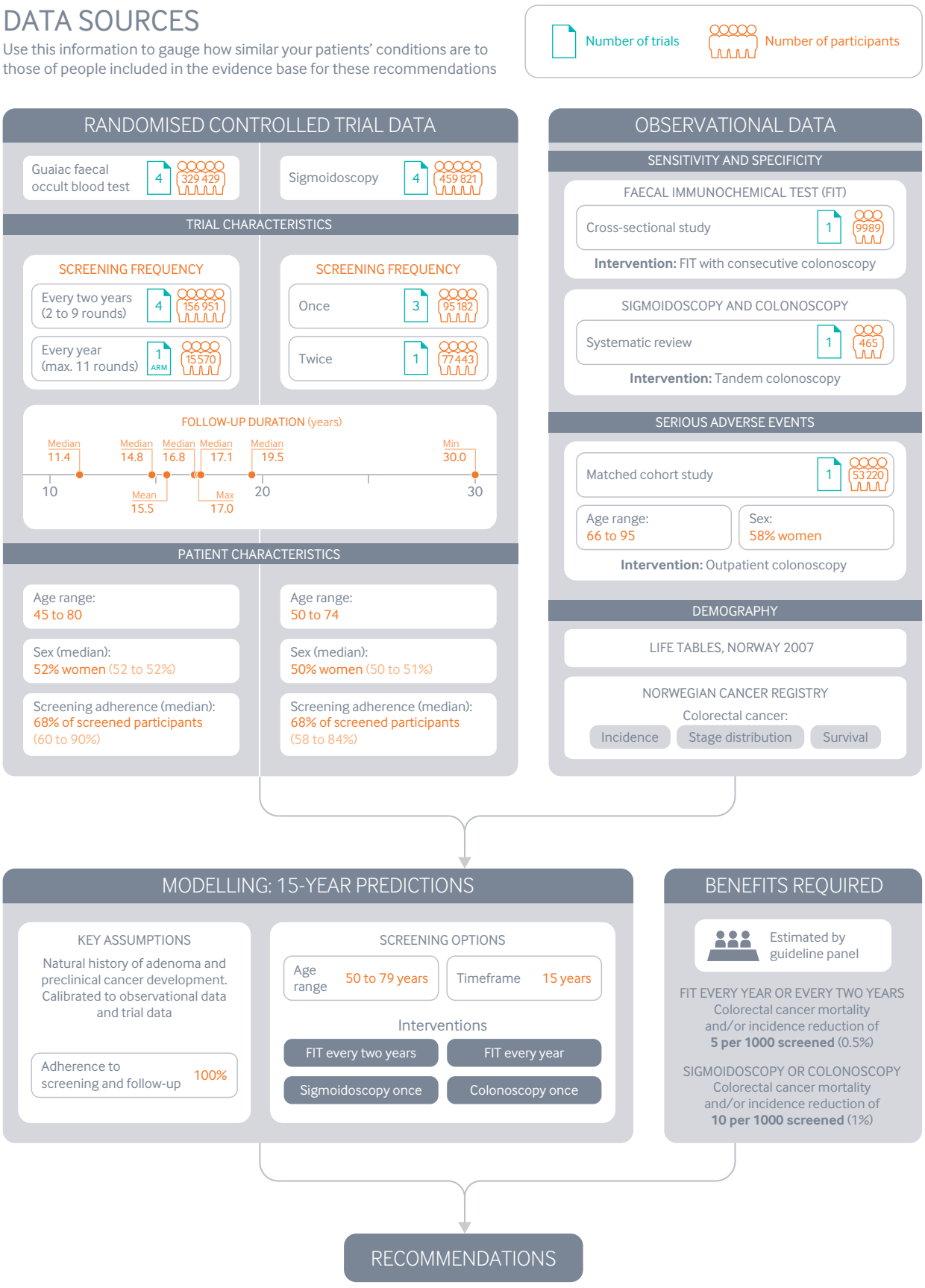

Fig 2| Data sources included in the modelling study of the absolute benefits and harms of different colorectal cancer screening options.

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Box 2 | Screening uptake

Participation in systematic screening is often under 50%, but varies widely:

- In screening programmes with faecal testing in Australia, Europe, America, and Asia, the participation rate varied between 16% and 68%.[11]
- In a European, population based, randomised trial of colonoscopy screening, participation rates were 61% in Norway, 40% in Sweden, 33% in Poland, and 23% in the Netherlands.[24]
- In another randomised trial comparing faecal immunochemical test (FIT) and colonoscopy in Spain, the rate of participation was higher in the FIT group (after one round) than in the colonoscopy group (34% *v* 25%).[25]
- Some organised efforts that incorporate screening outreach and follow-up have demonstrated screening rates of over 80%.[12]

- Colorectal cancer incidence
  - May be reduced little or not at all by FIT every two years (relative risk 0.95)
  - FIT every year may achieve a small reduction (relative risk 0.85)
  - May be reduced by a single sigmoidoscopy (relative risk 0.73)
  - May be reduced by a single colonoscopy (relative risk 0.66).

There was no clinically relevant difference in all-cause mortality when comparing screening with no screening, or between the different screening options.[4]

Do the benefits differ by sex?

Based on the meta-analysis of randomised trial data, the panel believed the subgroup effect that sigmoidoscopy screening is more effective in men than women.[5] They used criteria for credibility of subgroup effects to judge this.[26] However, the relative effect differences of screening in men and women did not translate into an absolute difference to justify different recommendations for the sexes. Appendix 4 presents this evidence and a worked example.

Where did data on burdens and harms of screening and follow-up come from?

Number of colonoscopies needed was considered an important burden of screening by the panel. Colonoscopies are performed either as the primary screening test, after a positive sigmoidoscopy or FIT screening, or as surveillance due to the finding of adenomas. No trial provides estimates of the number of individuals requiring colonoscopies after screening over a 15 year period. Our estimates are derived from the microsimulation model and are of low certainty. The model assigns every individual with a high risk adenoma (several adenomas or an adenomas >10 mm diameter) to surveillance colonoscopy after three years, and thereafter repeated colonoscopies with intervals of three to five years (depending on the findings).[4]

The 15-year estimates for screening related mortality, risk of colorectal perforations and bleedings, other gastrointestinal adverse events, and cardiovascular adverse events are derived from additional modelling of a large cohort from a US registry.[4 27 28] The estimates from this cohort study are consistent with the best current evidence regarding serious harms from screening (see appendix 5). In the model, the harms are driven by the number of colonoscopies needed, and are of low certainty due to modelling of number of colonoscopies (see appendix 1 for full evidence summaries).

Box 3 | Process and limitations of determining thresholds of benefits required to undergo screening

Process of determining a benefit threshold

The panel completed three surveys presenting different hypothetical screening scenarios. For each scenario, the panelists chose whether: almost all (>90%), most (75-90%), or the majority (50-75%) would choose or decline screening. The panelists responded according to their estimates of what most well informed people would choose (see appendix 3 for more details of this process).

- The first survey included hypothetical scenarios of colonoscopy screening with varying absolute risk reductions for colorectal cancer mortality (1, 10, 20, and 30 per 1000 screened) over a 15 year period.
- The second survey focused on what benefit would be required to recommend one screening test over another.
- Initially, the panel chose the same benefit threshold for all tests. However, after reviewing the full evidence summaries (see main infographic), the panel felt that the burdens and harms of FIT were considerably smaller than for sigmoidoscopy or colonoscopy. The panel decided to undertake a third survey presenting scenarios of FIT screening with reductions in colorectal cancer mortality ranging from 1 to 10 per 1000 screened.

Limitations

There are several limitations related to the establishment of these thresholds

- First, because no direct evidence has addressed how much benefit people would require to be willing to undergo screening, the panel relied on indirect evidence and their experience in making their estimates.
- Second, the way the evidence is framed—for instance, for benefits of screening, one could say that colorectal cancer mortality was reduced from 2% to 1% over 15 years or that the percentage of people who do not die from cancer increases from 98% to 99%—influences peoples' decisions. We used only one method to present the benefits.
- Third, the first survey was based on a limited set of potential thresholds with large increments (1, 10, 20, or 30 prevented deaths or cancers). Smaller increments might have led to a different choice—and may have been one factor in the different choice of thresholds for FIT.
- Fourth, the panel made a single recommendation at the "break-even point" where benefits and harms are closely balanced. The panel could have chosen to make additional recommendations at a very low risk (where almost all would choose not to screen), or a very high risk (where almost all would choose screening). The available evidence suggests, however, that there may be those who would decline screening even with a very large benefit, and those who would choose screening even with a very small benefit.

Planned evaluation of harms by age

Limited data exists addressing harms of screening by age. The gastrointestinal adverse events from colonoscopy probably increase with age, but the absolute risk is still

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very small in individuals above 75 years old. The panel therefore decided that these differences would not influence the recommendations (see appendix 5 for details).

Colorectal cancer risk prediction

A recent systematic review and an external validation study of colorectal cancer risk prediction models identified several prediction models, developed in different countries and with similar discrimination, as detailed in appendix 6.[29 30] The QCancer was one of the best performing models for both men and women, with an area under the receiver operating curve (AUC) of 0.85 for women and 0.86 for men in the development cohort,[31] and 0.66 for women and 0.70 for men in the external validation cohort.[29]

The QCancer model was developed within a UK population and may overestimate or underestimate risk for individuals from other countries with different distributions of risk factors and/or incidence of colorectal cancer. We nevertheless suggest this model because it is available as an online calculator; includes only risk factors available in routine healthcare; has been validated in a population separate from the derivation population; has reasonable discriminatory ability; and has a good fit between predicted and observed outcomes (calibration).[29 31] In addition it is the only online risk calculator we know of that predicts risk over a 15 year time horizon.

Understanding the recommendations

If an individual's estimated 15-year risk of colorectal cancer is 3% or more, the panel suggests screening with any one of the four options; if the estimated risk is below 3% the panel suggests no screening. These are weak recommendations, which means that in the context of shared decision making, some people with a risk of over 3% are likely to decline screening, and some with a risk under 3% will choose to screen.

- Our recommendations apply to asymptomatic adults aged 50-79 years with a life expectancy of at least 15 years.
- Our recommendations do not apply to people who
  - Have previously been screened
  - Have a history of polyps or colorectal cancer
  - Have inflammatory bowel disease
  - Have hereditary syndromes that increase the risk of colorectal cancer, such as Lynch syndrome and familial adenomatous polyposis.

Several factors influence individuals' decisions whether to be screened, even when they are presented with the same information:

- Variation in an individual's values and preferences
- A close balance of benefits versus harms and burdens (for example, for a baseline risk of 3%, FIT every two years results in five fewer deaths from colorectal cancer per 1000 screened versus three gastrointestinal or cardiovascular adverse events and 246 needing at least one colonoscopy).
- The estimates of both benefits and harms are associated with considerable uncertainty, as is the estimate of an individual's risk over a 15 year time frame.

The panel did not recommend any of the four screening options over any other. Clinicians should support each individual to choose their most suitable option. These recommendations are based on full adherence to screening and all potential work-up and surveillance colonoscopies in a 15 year period. With full adherence the options have similar reductions in colorectal cancer mortality, but different reductions in colorectal cancer incidence. The tests also have different burdens and practical issues.

Some individuals may value a minimally invasive test such as FIT, and the possibility of invasive screening with colonoscopy might put them off screening altogether. Those who most value preventing colorectal cancer or avoiding repeated testing are likely to choose sigmoidoscopy or colonoscopy. Fig 3 presents practical issues key to the screening decision.

How to estimate an individual's 15-year colorectal cancer risk

We suggest the QCancer calculator for estimating the colorectal cancer risk (see main infographic). The calculator includes age, sex, ethnicity, smoking status, alcohol use, family history of gastrointestinal cancer, personal history of other cancers, diabetes, ulcerative colitis, colonic polyps, and body mass index. To minimise the likelihood of misinterpretation and to facilitate shared decision making, the ideal setting for using the calculator may be a consultation with a healthcare provider.

If the predicted risk for a particular individual is, for example, 3.0%, the appropriate interpretation is: "In a group of 100 people with the same risk factors as you, 3 will develop colorectal cancer within the next 15 years."

As they age, people may revisit their decision

The most important risk factor for colorectal cancer screening is age. After age 50, colorectal cancer risk increases by 0.5-1.5% every five years for most people.[13 14] This translates to an additional reduction in colorectal cancers of 0-2 per 1000 screened individuals for FIT, and of 1-5 per 1000 for colonoscopy and sigmoidoscopy. The additional reduction in colorectal cancer mortality will be 1 per 1000 or smaller. Those who decide not to undertake screening but who think an additional benefit of this magnitude might change their decision, might consider reviewing their risk approximately every five years.

Public health implications

This guideline underlines that people need balanced information to decide whether they wish to screen for colorectal cancer, and public health efforts should focus on shared decision making for individuals who are eligible for screening. Many healthcare systems use the uptake of colorectal cancer screening as a performance indicator.[32 33] As many well informed individuals will choose to forego screening, discussion and information sharing on screening for colorectal cancer would be a better marker of care rather than uptake.

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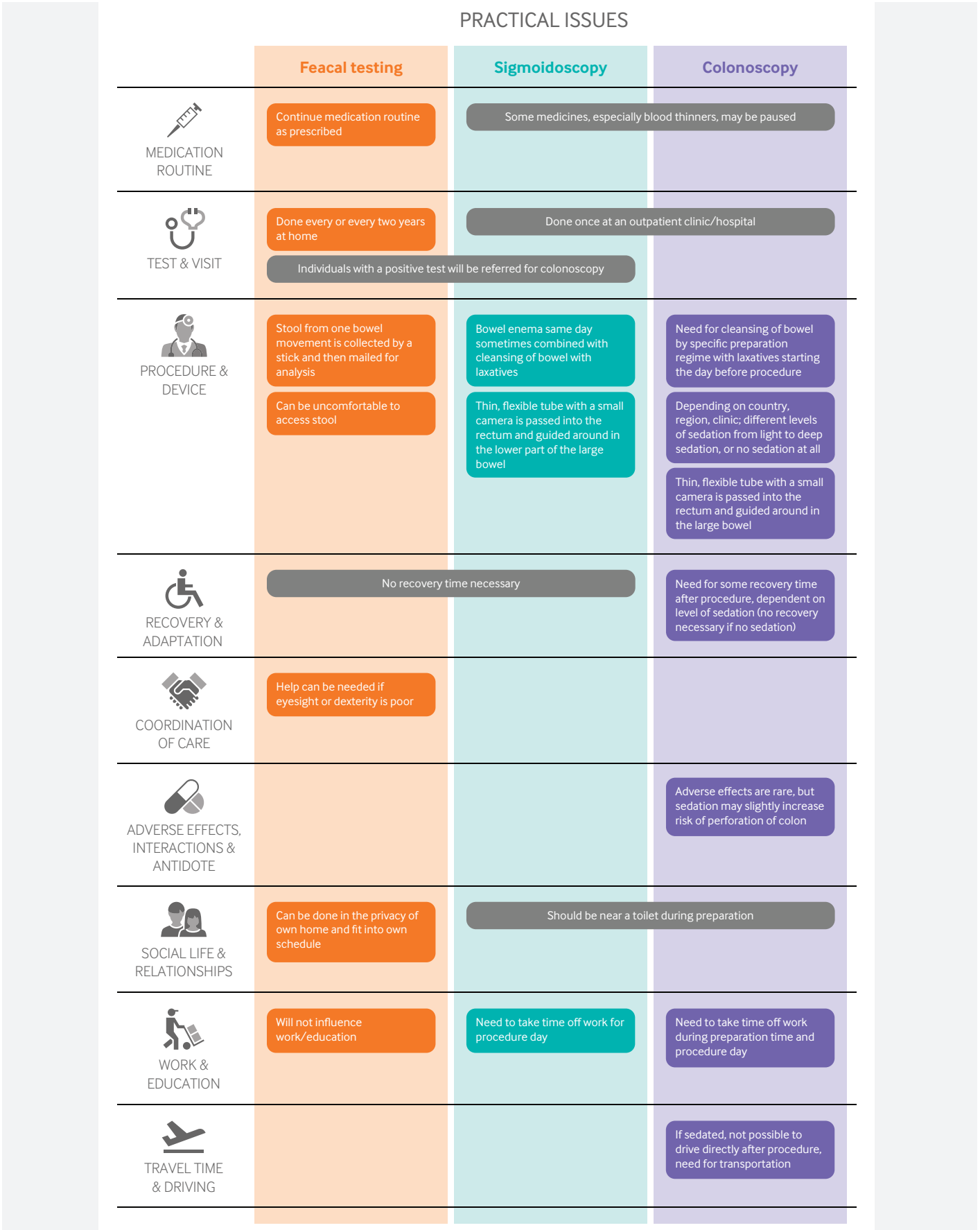

Fig 3| Practical issues for the different methods for colorectal cancer screening

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EDUCATION INTO PRACTICE

- How can you help individuals to make a choice about colorectal cancer screening based on the information you have read in this article?
- If your patients would like to leave the decision regarding screening in your hands, how would you handle the situation?
- What would you tell your colleagues about best practice for colorectal cancer screening?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Three people who have experienced colorectal cancer screening were full panel members. These panel members identified important outcomes, participated in the teleconferences and email discussions on the evidence and recommendation. They also contributed to the identification of practical issues related to the decision of colorectal cancer screening and met all authorship criteria for the present article. We thank them for their time and contribution.

Table 2 | New evidence which has emerged after initial publication

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article.				

Uncertainty

Only a few screening tests and intervals have been tested in randomised trials (once-only sigmoidoscopy and gFOBT every one or two years), but many different screening options are used in clinical practice. There are many uncertainties in terms of what is the most effective screening test or combination of tests, and at what age and interval they should be used. Some jurisdictions use combinations of screening tests; our guidelines do not address such combinations. We chose a 15 year timeframe and do not provide guidance beyond that point. It is uncertain whether there is additional benefit in continued FIT screening beyond 15 years or in a repeated sigmoidoscopy or colonoscopy before or after 15 years.

We found evidence that the relative reductions in incidence and mortality of colorectal cancer were smaller in women than in men after a single sigmoidoscopy, but the absolute effect differences were too small to warrant sex-specific recommendations. Whether the effects of other screening tests differ by sex is unknown.

The process of making these recommendations was challenging, often with opposing views in the panel. Particular challenges were the lack of randomised trials for colonoscopy and FIT (which made us rely on modelled estimates of low certainty for screening benefit) and the uncertainty in people's values and preferences.

Key research questions to inform decision makers and future guidelines include:

- What are the population's values and preferences regarding the magnitude of benefit needed to undergo screening, and the choice of screening test?
- What are the benefits and harms of colonoscopy and FIT screening, and do the effects differ for men and women?

Updates to this article

Table 2 shows evidence that has emerged since the publication of this article. As new evidence is published, a group will assess the new evidence and make a judgement on the extent it is expected to alter the recommendation.

We thank Hilde Iren Flaatten, senior librarian at the Medical Library, University of Oslo, for performing the literature searches. We thank Julia Hippisley-Cox and Stephen Hippisley-Cox for tailoring the QCancer calculator to the purpose of this guideline by adding the possibility of colorectal cancer risk estimation over 15 years, and for setting up a separate online calculator for colorectal cancer only. We thank Carla Berg-Nelson, who contributed as a patient partner with valuable feedback during the initial phase of this project.

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Disclaimer: Participation in the panel and authorship of this manuscript does not constitute organisational endorsement of the recommendations.

Transparency: L M Helsingen and G Guyatt affirm that the manuscript is an honest, accurate, and transparent account of the recommendation being reported; that no important aspects of the recommendation have been omitted; and that any discrepancies from the recommendation as planned have been explained.

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