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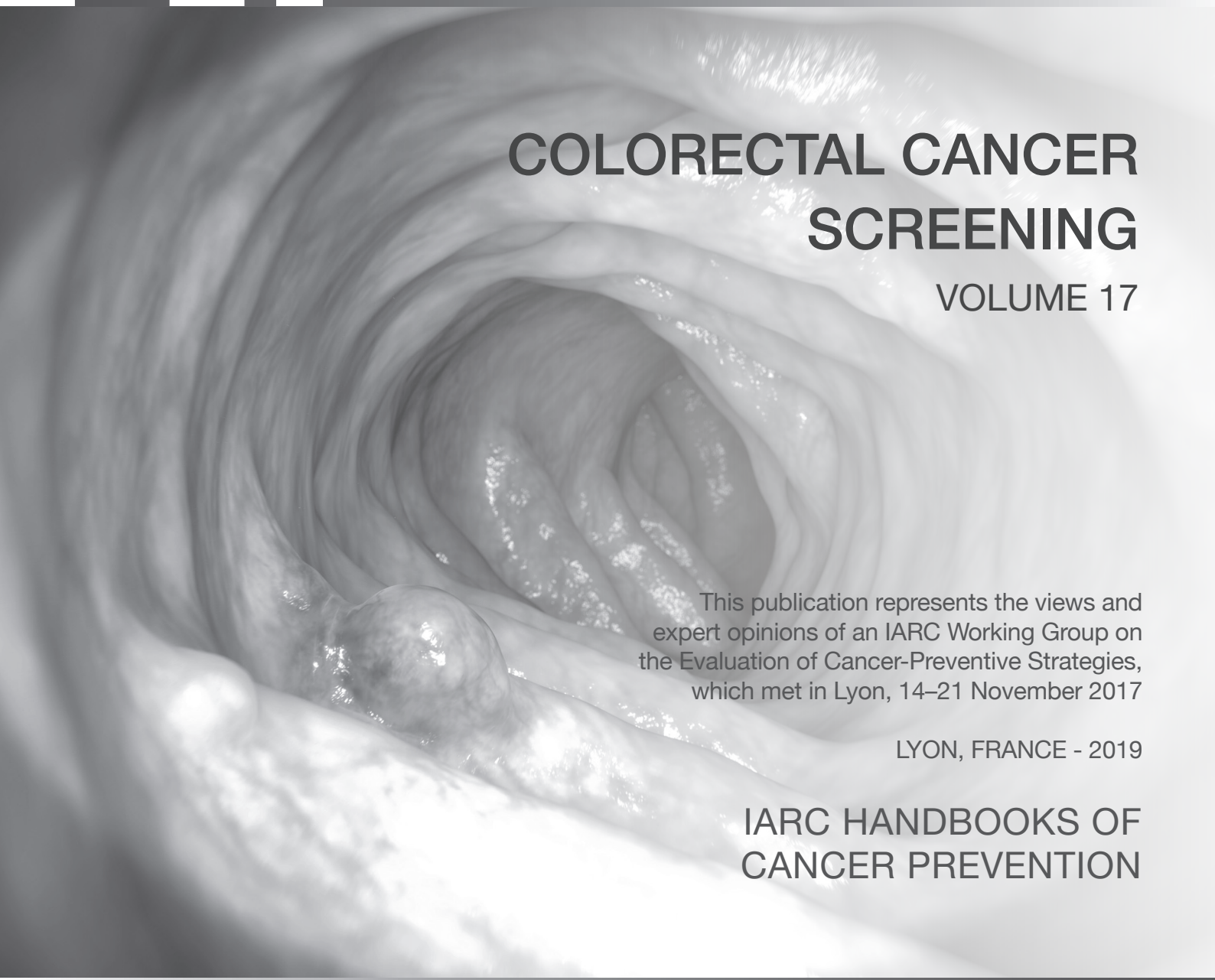

COLORECTAL CANCER SCREENING

VOLUME 17

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3. STUDIES OF COLORECTAL CANCER SCREENING

3.1 Methodological considerations

Methods for colorectal cancer (CRC) screening include endoscopic methods and stool-based tests for blood. The two primary end-points for endoscopic CRC screening are (i) finding cancer at an early stage (secondary prevention) and (ii) finding and removing precancerous lesions (adenomatous polyps), to reduce the incidence of CRC (primary prevention). The primary end-point for stool-based tests is finding cancer at an early stage. Stool-based tests also have some ability to detect adenomatous polyps; therefore, a secondary end-point of these tests is reducing the incidence of CRC.

3.1.1 Randomized controlled trials of colorectal cancer screening

A randomized controlled trial (RCT) that compares a screening arm with a non-screening arm (or with a screening arm with a different screening modality) is considered the reference standard in evaluating the cancer-preventive effects of a screening test. For screening modalities that only detect cancerous lesions (such as those for breast cancer or lung cancer), the primary end-point of a screening RCT is generally mortality from the cancer of interest. For screening modalities that have the potential to detect and remove cancer precursors (such as those for CRC and cervical cancer), a co-primary end-point of the RCT can be the incidence of the cancer of interest.

The observed effect of screening in RCTs is dependent on, among other things, the participation in the intervention group and the limitation of contamination of the control group. Low participation biases the estimate of effect towards its no-effect value, and therefore it must be evaluated and reported. Screening of controls by services outside of the RCT also dilutes the effect of screening on CRC incidence and/or mortality. If the screening modality being evaluated is widely used in clinical practice in the region or regions where the RCT is being conducted, then contamination may be considerable, although it may be difficult and/or costly to estimate its extent. The standard evaluation of the primary end-point is an intention-to-treat analysis. Methods to adjust for contamination and low participation, called per-protocol analyses, have been proposed (Cuzick et al., 1997; Baker et al., 2002). [Note that these methods differ from those that compare participants who were actually screened with those who were not, which is an invalid method with a high potential for selection bias.]

3.1.2 Observational studies on the preventive effects of colorectal cancer screening

Data from observational studies, in which study participants are not randomly allocated to be screened or not screened, should be used with caution, because of their greater propensity to bias. Comparison of the survival, or stage distribution, of screen-detected cases with that of cases diagnosed outside of screening is notoriously flawed, because of lead-time bias, length-time bias, and overdiagnosis bias. Lead time is the period between when a cancer is found by screening and when it would have been detected from clinical signs and symptoms (not directly observable) in the absence of screening. Survival time, by definition, is measured from the date of diagnosis to the date of death. Lead-time bias is the overestimation of survival time due to earlier detection by screening than clinical presentation; it is very difficult to distinguish from earlier diagnosis leading to a real extension of life. Length-time bias reflects disproportionate detection by screening of indolent tumours, which may reside in a preclinical state for longer time periods than aggressive tumours do. Overdiagnosis is an extreme form of length-time bias in which a tumour that would never have been diagnosed without screening is detected by screening.

Using cohort or case–control designs to compare the mortality and/or incidence rates of a group receiving (or invited to receive) screening with those of a group not receiving (or not invited to receive) screening can avoid the above-mentioned biases, but it will usually involve some type of selection bias, because the decision to be screened is not random and may be related to factors that predispose to, or against, developing the cancer. Careful adjustment for known CRC risk factors may partially alleviate this bias. Cohort studies are generally more reliable than case–control studies for assessing the efficacy of screening, although well-designed case–control studies may be useful. Comparison of the incidence or mortality rates in a screened cohort with concurrent (or past) population rates is also prone to the selection biases described above and may also be biased by variation in temporal and regional trends.

Ecological studies that compare incidence or mortality rates in a region or country where screening has been implemented with rates in the same region or country during a previous time period, or with contemporaneous rates in a neighbouring region or country, may be useful but are subject to the standard caveats of ecological studies.

There are several early observational studies that assessed the effects of endoscopy and stool-based tests for blood on CRC incidence and mortality; most of these studies have major methodological issues. Lead-time bias, length-time bias, selection bias, and confounding factors in these studies could lead to overestimation or underestimation of the effect when not adjusted for. Misclassification of the outcome, CRC incidence or death (ascertainment bias), can also bias the effect estimates. In the Effectiveness of Screening for Colorectal Cancer in Average-Risk Adults (SCOLAR) nested case–control study, Goodman et al. (2015) stressed the challenges in observational studies of colonoscopy screening, including distinguishing between indications for having had a colonoscopy (screening or investigation of symptoms). Some observational studies use, for example, a 6-month window to exclude index examinations that were done to investigate symptoms of CRC.

In light of the published RCTs of sigmoidoscopy screening, the Working Group established two criteria for observational studies to be included in the evaluation of effectiveness: the study (i) must be performed in a screening setting and (ii) must not exclude cancer detected at the baseline endoscopy. Moreover, the Working Group established six considerations to weigh the impact of individual studies on the overall estimate: (i) there must be a concurrent control

group, (ii) there must be an adequate length of follow-up, (iii) the sample size must be large enough to detect relevant effects, (iv) the study must be conducted in a setting with contemporary methods, (v) the outcome (and exposure) ascertainment must be reliable, and (vi) potential confounder data must be available and adjusted for in the analysis.

3.1.3 Evaluation of the adverse effects of colorectal cancer screening

An adverse effect of screening is defined as any negative effect on individuals or populations that results from being involved in the screening process compared with not being involved in screening. It is important to quantify not only the frequency of the harm but also its magnitude. It is also important to recognize that the harms in an RCT may be different from the harms in a screening programme.

(a) Definitions of harms

Harris et al. (2014) proposed a taxonomy of the harms of screening. They proposed four domains of harms: physical effects, psychological effects, financial strain, and opportunity costs. Financial strain and opportunity costs [the indirect effect of screening on health-related activities] are not considered in this review. Here, harms are classified on the basis of where in the screening cascade they occur: harms associated with (i) the screening process, (ii) the screening test itself, and (iii) the management of a positive screening result.

Potential harms of the screening process include anxiety, caused by the invitation to screening or awaiting the results of screening, and a negative impact on lifestyle or health-seeking behaviour. The assessment of these outcomes requires validated instruments and is best conducted as a longitudinal study over the course of screening, ideally as part of an RCT, comparing individuals invited to screening with those not invited to screening.

It is possible that reassurance from a negative screening result (whether true-negative or false-negative) could lead to delay in presentation for investigation of symptoms that develop in the interval between scheduled screening tests, with consequent late diagnosis of an interval cancer and possibly death from it. Such an impact on mortality would form part of the overall mortality measured in the screening arm of an RCT of CRC screening and would not be measurable separately from it. However, its presence within the results of the RCT would remove any need to account for it separately when estimating a benefit–harm ratio from the RCT.

No physical harms are incurred with stool-based tests for blood. Potential harms of endoscopic tests include pain, physical damage to the bowel due to endoscopy, possible hospitalization, and the need for surgical repair. The frequency and severity of such harms can be estimated from a representative screened cohort.

Potential harms associated with the management of a positive screening result include physical harm from the workup and treatment and harm from the psychological response to knowledge of the result and any aspect of its management. Apart from the possible harms of treating a screen-detected cancer, the harms experienced are largely independent of whether the screening result is true-positive or false-positive. Some people restrict the definition of a true-positive to invasive cancer, whereas others include advanced adenoma in the definition, and still others may include detection and removal of precancerous lesions (polypectomy).

(b) Overdiagnosis

An overdiagnosed cancer is defined as a cancer detected as a result of screening that would not have been diagnosed if screening had not taken place. The lower the pathological grade of a screen-detected cancer and the shorter

the individual's life expectancy at the time the cancer is diagnosed, the more likely it is that the cancer is an overdiagnosed cancer. The harm associated with overdiagnosis comes from labelling the individual as a cancer patient and from any adverse effects of the treatment of the cancer.

(i) Quantification of overdiagnosis

Screening that leads to the earlier diagnosis of cancer will always cause an apparent increase in cancer incidence, some of which is due to advancing the time of diagnosis of cancers that would have been diagnosed anyway, and some of which is due to overdiagnosis. To quantify overdiagnosis accurately, it would be necessary to follow up identical screened and unscreened cohorts until the rise in the cancer incidence rate in the screened cohort has stabilized, and then stop screening and continue to follow up the cohorts until the cancer incidence rates are approximately the same in the screened and unscreened cohorts. The total excess rate of cancer in the screened cohort is then the rate of cancer overdiagnosis. In practice, such a quantification process is rarely possible, although it could be approximated by a well-done RCT that adopts most of the above-mentioned features. There are various other ways to estimate overdiagnosis, but few or none that are likely to produce a highly accurate result (Carter et al., 2015; Ripping et al., 2017; Davies et al., 2018).

When quantifying overdiagnosis, one may consider it (i) as a cumulative lifetime risk of overdiagnosis associated with participation in screening; (ii) as the ratio of the cumulative rate of overdiagnosis to the cumulative rate of cancer in unscreened individuals, expressed as a percentage; (iii) as the percentage of cancers in screened individuals that are overdiagnosed; or (iv) as the percentage of screen-detected cancers that are overdiagnosed. In a screening programme that also *prevents* cancer (via detection and treatment of precursors), so that screened people have a lower cumulative rate of diagnosis of cancer than unscreened people, it is practically impossible to determine whether some of the screen-detected cancers are overdiagnosed cancers. Although the reduction in cancer incidence indicates a clear benefit, some harm from the detection and treatment of precancerous lesions that would never have become symptomatic invasive cancers in the person's lifetime is also likely.

There are three types of harms of overdiagnosis as usually defined: (i) labelling of an individual as a cancer patient (which may cause anxiety and lead to problems obtaining health insurance and life insurance); (ii) the immediate side-effects of treatment; and (iii) the long-term consequences of diagnosis, including, for example, intensive surveillance. Quantification of these harms is an important contributor to obtaining an accurate estimate of the balance of benefits and harms of screening. Each of these types of harms will apply to some degree to the detection and treatment of simple polyps or adenomas at varying degrees of advancement during the course of screening for CRC.

(ii) Overdiagnosis of precancerous lesions

The proportion of polyps that would cause symptoms if not removed is low but increases as one moves from non-adenomatous polyps to non-advanced adenomas and to advanced adenomas (including multiple non-advanced adenomas). The Working Group could not agree about whether to use the term overdiagnosis to include simple polyps, non-advanced adenomas, or even adenomas. Some felt that it should be possible to estimate how many adenomas would not have progressed to cancer and that this number should be reported as being overdiagnosed. (That group did not wish to attempt to quantify how many adenomas may have been diagnosed in the absence of screening, as a result of colonoscopies in response to bowel symptoms.) Other Working Group members felt that the term overdiagnosis was not helpful and that

it was more appropriate to report the number of polyps, non-advanced adenomas, and advanced adenomas and the consequences of each of those diagnoses. It was agreed that the frequency of detection of polyps, non-advanced adenomas, and advanced adenomas should be reported, as should the consequences of such detection, including potential harms and their frequency.

There was a lack of agreement among Working Group members about whether some or all of the harms associated with treatment of these precancerous lesions should be attributed to screening.

3.1.4 Interval cancers

An interval cancer is defined as a cancer that is diagnosed between routine screens, that is, cancers diagnosed after a positive screening test that were not diagnosed as a result of that screening test. Thus, interval cancers are cancers that were missed by screening or by investigation after a positive screening test, or that have developed since the most recent screening test was done.

For most screening, the interval cancer rate will depend on the screening interval: the shorter the interval, the smaller the chance of developing an interval cancer. For this reason, it may be useful to consider cancers diagnosed x years after a negative screening result (where $x = 1, 2, 3, \ldots$) and to censor the follow-up when the individual is next screened. The interval cancer rate may also be higher after the first screen than it is after subsequent screens, because of the higher prevalence of cancer at the time of the first screen and a consequently higher risk of an incident cancer in the first interval between screens.

Although interval cancers are considered by some people to be a harm of screening, they are better conceived of as a lack of benefit due to the (probably unavoidable) imperfect sensitivity of the test. There is no suggestion that an interval cancer would not also have been diagnosed in the absence of screening. Nonetheless, interval cancers are an indicator of test insensitivity, and if the interval cancer rate in the screened population is greater than the quality assurance benchmark for the test, reasons for this performance deficiency should be sought and addressed.

3.1.5 Benefit–harm ratio and cost–effectiveness

Screening should be implemented only if its benefits outweigh its harms and if the financial resource requirements are reasonable in relation to the net benefit of screening (i.e. if screening is cost-effective).

(a) Benefit–harm ratio

All forms of screening are associated with both benefits and harms. The updated sets of criteria for screening published by the World Health Organization (Andermann et al., 2008) and the United States Preventive Services Task Force (Harris et al., 2011) both explicitly mention the balance between benefits and harms as a decisive criterion for the implementation of a screening intervention. The difficulty with this criterion is how to objectively weigh the benefits and harms of screening, because they are measured differently. How much harm is acceptable for every CRC death, or every incident CRC case, that can be prevented by screening? A growing number of studies consistently find that the attributes of screening tests, such as efficacy, process, and cost, are significant determinants of the choice of implementing a screening programme and of the screening method (Mansfield et al., 2016).

Informed decisions with respect to screening can be aided by giving people considering screening an outcomes table, which presents quantitative information about all potential benefits and harms of screening, so that people can decide whether they want to participate in screening. Such an outcomes table is a useful tool for patient information, but governments or guideline-issuing institutes still need to

determine for the population as a whole whether the benefit–harm ratio is favourable. This can be done simply, but subjectively, by committee consensus or, more objectively, by translating benefits and harms into summary measures of health benefit or harm, such as quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs) gained or lost (see below). This has been done very rarely.

(b) Cost–effectiveness

QALYs and DALYs are two summary measures of health or life gained or lost that can be used to estimate the net outcome of health interventions. They each incorporate years of life and quality of the life in a single measure. QALYs are a measure, in the aggregate, of the gain or loss of life of a group subject to the intervention weighted by a measure of the quality of the life. Quality of life, for this purpose, is generally measured in terms of a person's ability to carry out the activities of daily life, free of pain and mental disturbance, with a weight of 1 for fully able and a weight of 0 for totally unable. One DALY can be thought of as one *lost* year of disability-free life, where years of life lost to death have a weight of 1 and years of life lived free of any disability have a weight of 0, with the experience of a group measured in DALYs aggregated, as described above for QALYs.

To extrapolate outcomes from RCTs to lifetime QALYs and DALYs, mathematical models are typically used to track the benefits and harms of the intervention, accounting in the QALY weights used for any adverse effects of the intervention that intervention-arm participants experienced, taking account of the deaths, aggregating the QALYs or DALYs in each arm, and calculating the difference between the two arms as the net benefit of the intervention expressed as QALYs gained or DALYs averted, each of which can be expressed as positive or negative values.

Cost–effectiveness analysis formally compares the health outcomes with the economic costs of different interventions, thereby assisting decision-makers to identify the interventions that will yield the greatest health benefits, given their resource constraints (Cantor, 1994). The costs that are considered depend on the perspective but generally include not only those of the intervention itself (in this case, screening) but also those of diagnostic follow-up and workup and adverse effects. Potential longer-term savings from treatment leading to prevented cases of disease (or advanced disease) are also included. The results of a cost–effectiveness analysis are summarized in an incremental cost–effectiveness ratio. The QALYs gained or DALYs averted with a particular strategy (in this *Handbook*, a CRC screening prevention programme) compared with an alternative strategy (no CRC screening programme) are included in the denominator, and the additional (incremental) costs of that strategy (compared with the same alternative) are included in the numerator, yielding an incremental cost per DALY averted or per QALY gained (Cantor, 1994). Future costs and benefits of the intervention are usually discounted to their present value (Sanders et al., 2016).

To ensure efficient use of resources, the cost–effectiveness of an intervention such as screening should be compared not only with the situation without screening but also, if applicable, with alternative screening interventions. For example, the costs and effects of endoscopic screening should be compared with those of stool-based screening strategies, and the costs and effects of 10-yearly endoscopy should be compared with those of single endoscopy. The incremental cost–effectiveness ratio is also used for this comparison.

The World Health Organization principles for population screening state that screening should be implemented only when there is a good balance between costs and benefits (Wilson & Jungner, 1968). Unfortunately, there is no universal definition of "good balance"; for example, in the USA an intervention that provides an additional year

of life at an incremental cost of US$ 100 000 per life year gained has been accepted as a reasonable balance between costs and effects (Weinstein, 2008). The National Institute for Health and Care Excellence in the United Kingdom considers interventions with an incremental cost–effectiveness ratio of less than £20 000 per QALY gained to be cost-effective (NICE, 2013). Interventions with cost–effectiveness ratios in the range of £20 000 to £30 000 per QALY gained can still be considered acceptable, depending on additional criteria, whereas interventions costing more than £30 000 per QALY gained are generally not considered to be cost-effective. The World Health Organization has suggested using cost–effectiveness thresholds of 1–3 times the annual per capita gross domestic product of the country (WHO, 2014). Such an approach is particularly relevant in cost–effectiveness studies for CRC screening (see Sections 3.2.6, 3.3.6, and 3.5.4), which have been performed mostly in high-income countries. Consequently, the findings with respect to costs and benefits of screening may be very different in low- and middle-income countries, which generally have lower background cancer risks, different cost levels, and vastly different abilities to pay.

(c) Using cost–effectiveness analyses to determine age limits and intervals for screening

Cost–effectiveness analyses can address more than just the question of whether a certain intervention is cost-effective. RCTs are the reference standard for evaluation of the effectiveness of interventions; however, only a limited number of strategies can be evaluated in RCTs, whereas the number of different potential strategies is endless. Screening strategies can differ in the test modality used, the age at which to begin screening, the age at which to end screening, and the screening interval. Valid cost–effectiveness models offer the opportunity to extrapolate beyond the observations in the RCTs and assess and compare alternative intervention strategies in an efficient way. Furthermore, such models can estimate the budget and resource impact of these strategies, so that only strategies that are feasible in a particular setting can be considered. For example, for the implementation of the CRC screening programme in the Netherlands, cost–effectiveness modelling had shown that the most cost-effective screening strategy to implement was faecal immunochemical test (FIT) screening with a low cut-off level for a positive test (Wilschut et al., 2011a). However, in case of limited colonoscopy capacity, the modelling indicated that the most cost-effective alternative would be to offer FIT screening with a higher cut-off level for a positive test (Wilschut et al., 2011b).

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3.2 Stool-based tests for blood

3.2.1 Techniques

(a) Introduction

Faecal occult blood tests (FOBTs), used as primary tests for CRC screening, are based on the detection of gastrointestinal occult blood in stool (Young et al., 2015; Schreuders et al., 2016). However, CRC and precancerous lesions are not the only sources of blood in faeces. In addition to other conditions (e.g. inflammatory bowel disease or colitis), other lesions such as haemorrhoids, hyperplastic polyps, and diverticular disease can lead to blood in the stool (Digby et al., 2013). The probability that FOBTs will detect gastrointestinal bleeding depends on the anatomical site of the bleeding, patient characteristics (transit time of faeces, consistency of faeces, degradation of haemoglobin [Hb] in the intestine), and factors that affect the bleeding of gastrointestinal lesions (intermittent bleeding) (Ahlquist et al., 1989); in addition, factors intrinsic to the test, such as its capacity to detect the activity or the presence of the Hb molecule or other blood constituents, will influence the detection of bleeding (Young et al., 2015). Depending on the origin of the bleeding, faeces will contain Hb, haem, or the globin moiety at different degradation stages (Rose et al., 1989; Young et al., 1990; Rockey et al., 1999).

Recently, a stool-based test combining DNA with a faecal immunochemical component has been developed for CRC screening (see Section 3.7.1).

(b) Methods and equipment

(i) gFOBT

The guaiac FOBT (gFOBT) was developed at the beginning of the 20th century by the German gastroenterologist Boas (Boas, 1914). gFOBT was the first test to be widely used for CRC screening and to be evaluated in RCTs (see Section 3.2.2). gFOBT detects blood by the use of paper impregnated with guaiac, which is extracted from the wood resin of *Guaiacum* trees, to which hydroperoxidase is added. When it comes into contact with haem (but not exclusively), the hydroperoxidase oxidizes guaiac, leading to a blue colour that is evaluated as a qualitative result (positive or negative for the presence of blood). The standard gFOBT consists of three paper cards, each with two panels, requiring sampling from three separate faeces samples (Schreuders et al., 2016). gFOBT can be analysed with or without rehydration. gFOBT does not detect Hb concentrations of less than approximately 600 µg Hb/g faeces; when gFOBT is rehydrated, the analytical sensitivity is higher, but more false-positive results are obtained (Tinmouth et al., 2015). One manufacturer has developed a high-sensitivity gFOBT (HSgFOBT) with performance similar to that of rehydrated gFOBT (Allison et al., 1996). Results of gFOBT are read with the naked eye, which leads to a subjective evaluation. Results are not quantifiable using automated instrumentation and are therefore not suited to high-throughput screening programmes.

(ii) FIT

FIT for Hb was developed in the late 1970s by the clinical pathologist Barrows. The method was based on using goat anti-Hb antibodies and demonstrated improved sensitivity and specificity compared with gFOBT in the detection of small amounts of Hb in faeces (Barrows et al., 1978). FIT detects the globin moiety of human Hb by immunoassay methodology using different methods. Two of the most widely used methods are lateral flow immunochromatography (qualitative) and immunoturbidimetry (quantitative) (Phalguni et al., 2015). FIT can detect human blood with high analytical sensitivity (Rockey, 1999), which ranges from 1 µg to 300 µg Hb/g faeces, depending on the FIT characteristics and the manufacturer. However, FIT does not usually detect small quantities of blood from the upper gastrointestinal tract (i.e. above the stomach),

because it is degraded by digestive proteolytic enzymes (Rockey et al., 1999).

In qualitative FIT, each manufacturer can adjust the conditions of the analysis at a specific concentration of Hb. Quantitative FIT has a detection limit that ranges from 6 µg to 50 µg Hb/g faeces. FIT typically relies on samples in which faeces are collected using specimen sampling devices designed for direct processing on analysers; this allows for high-throughput, standardized methodology and therefore decreases performance variability (Tinmouth et al., 2015).

The concentration of faecal Hb associated with colonic lesions increases along the adenoma–carcinoma sequence, from normal mucosa to hyperplastic polyps through to non-advanced polyps and then from advanced polyps to carcinoma (Carroll et al., 2014). Several studies have shown that there is an association between Hb concentration and the detection of colorectal neoplasia (Liao et al., 2013; Auge et al., 2014; van Doorn et al., 2015; Chen et al., 2016). Therefore, the performance of quantitative FIT depends on the cut-off level used to define a positive test result. If the FIT cut-off level is increased, fewer but more advanced lesions will be detected and fewer colonoscopies will be required (Allison et al., 2014). By using quantitative FIT, screening programmes can choose the faecal Hb cut-off level appropriate to their resources (Halloran et al., 2012; Allison et al., 2014).

(c) Technical factors that affect FOBT results and quality control

(i) gFOBT

In gFOBT, any dietary Hb or myoglobin (e.g. from meat, especially if raw or half-cooked) as well as drugs or foods that have peroxidase properties (e.g. some uncooked fruits and vegetables, such as cabbage and green beans) can potentially lead to a positive test result, although there is no consistent evidence that positivity rates differ substantially between gFOBT participants with or without restrictions of those foods (Rozen et al., 1999; Pignone et al., 2001). In contrast, antioxidants in drugs or foods (e.g. vitamin C or vitamin E) have the potential to lead to a negative test result by interfering with the oxidation of guaiac (Jaffe et al., 1975; Müftügil, 1985; Allison et al., 2014). There is no consistent evidence of medications with anticoagulant properties, such as aspirin, non-steroidal anti-inflammatory drugs, or warfarin, causing positive gFOBT results in individuals without disease (Norfleet, 1983; Greenberg et al., 1996, 1999; Kahi & Imperiale, 2004; Clarke et al., 2006) or altering the positive predictive value of gFOBT (Sawhney et al., 2010; Lee et al., 2012; Gandhi et al., 2013). Finally, the dark-green or black appearance of faeces in patients treated with iron supplements, antacids, or antidiarrhoeal treatments with bismuth can be confounded with the blue colour of a positive gFOBT (Laine et al., 1988; Rockey, 1999).

Factors that can affect gFOBT reading include interobserver variability, reproducibility of reads by laboratory personnel (Niv, 1990; Fleisher et al., 1991; Selinger et al., 2003), temperature, the design of the gFOBT card, the colour of the laboratory walls, and the brightness of the artificial lighting (Halloran et al., 2012).

Professional external quality assessment schemes are unusual, and internal quality control is usually restricted to a performance monitor feature included in the gFOBT cards. Staff training, including double reading of positive results, has a large effect on the reliability and validity of interpretation (Rabeneck et al., 2008).

(ii) FIT

FIT is analytically sensitive to low concentrations of all types of intact human Hb (excluding fetal Hb) and therefore has a significantly improved analytical specificity, avoiding cross-reactivity with dietary Hb as well as other dietary components (Allison et al., 2014).

Table 3.2.1 Comparison of the main characteristics of gFOBT and FIT for colorectal cancer screening

gFOBT	FIT
Chemical reaction	Immunochemical reaction
Nonspecific for human haemoglobin	Specific for human haemoglobin
Larger faecal specimen	Smaller faecal specimen
Cumbersome specimen collection	Less cumbersome specimen collection
Qualitative	Qualitative or quantitative
Subjective interpretation of test results	Objective interpretation of test results
Manual analysis	Automated analysis (high-throughput)
Basic quality control procedures	Advanced quality control procedures
Nonspecific for lower intestinal tract	Higher analytical specificity for lower intestinal tract
Lower sensitivity and detection rate for advanced neoplasia	Higher sensitivity and detection rate for advanced neoplasia

FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test.

Quantitative FIT is becoming the most commonly used stool-based method for CRC screening (Schreuders et al., 2015). Many different quantitative FIT devices are commercially available; they vary in collection method, Hb stability, analytical methodology, polyclonal or monoclonal antibody characteristics, or calibration material. One of the major differences among the FITs from different manufacturers is that they use different faecal sample collection devices, which vary in the amount of faeces collected and the volumes of preservation buffers used (Fraser et al., 2012). The observed/apparent discrepancies in diagnostic performance of quantitative FITs can be largely reduced by adjusting the cut-off level to provide specific positivity rates or defined levels of specificity (Gies et al., 2018).

Manufacturers of automated quantitative FITs provide an internal quality control, and participation in an external quality assessment scheme is particularly important for national screening programmes in which different laboratories are involved (Halloran et al., 2012). Another important issue that must be taken into account is the sample quality. The globin moiety (detected with FIT) is less stable than the haem moiety (detected with gFOBT); therefore, proteolysis of globin should be avoided between sample collection and analysis. Samples show good stability at refrigerator temperatures but marked deterioration with rising temperature. Samples refrigerated at 4 °C showed no significant degradation over a period of 21 days (daily degradation, 0.3% ± 0.4%), whereas with storage at 28 °C a daily degradation of 3.7% ± 1.8% was shown (Vilkin et al., 2005; Rozen et al., 2006; Halloran et al., 2012). A decrease in positivity, a lower detection rate, and a loss of clinical sensitivity have been reported during seasons with high temperatures (van Roon et al., 2012; Doubeni et al., 2016). Manufacturers invest effort in developing new preservation buffers to improve stability, but sample conservation still represents a challenge to the organization of FIT-based screening programmes. Table 3.2.1 summarizes the main characteristics of gFOBT and FIT.

(d) Screening performance

Screening performance refers to the ability of the test to detect cancer and to distinguish cancer from non-cancer conditions. The ultimate effectiveness of CRC screening tests depends on their performance within a screening programme, i.e. across multiple rounds of testing and the complete screening episode in subjects who

Table 3.2.2 Performance of gFOBT for detection of colorectal cancer, advanced adenoma, or advanced neoplasia

Reference	Test used	Sensitivity (%)	Specificity (%)
Colorectal cancer			
Bang et al. (1986)	Hemoccult II (without rehydration)	25.0	97.6
Ahlquist et al. (1993)	Hemoccult II (without rehydration)	25.0	–
Castiglione et al. (1994)	Hemoccult II (with rehydration)	85.7	–
Castiglione et al. (1994)	Hemoccult II SENSA (HSgFOBT)	71.7	–
Allison et al. (1996)	Hemoccult II (without rehydration)	37.1	97.7
Allison et al. (1996)	Hemoccult II SENSA (HSgFOBT)	79.4	86.7
Lieberman et al. (2001)	Hemoccult II (with rehydration)	50.0	94.0
Sung et al. (2003)	Hemoccult II (without rehydration)	25.0	79.0
Imperiale et al. (2004)	Hemoccult II (without rehydration)	12.9	95.2
Allison et al. (2007)	Hemoccult II SENSA (HSgFOBT)	64.0	91.0
Park et al. (2010)	Hemoccult II (without rehydration)	30.8	92.4
Parra-Blanco et al. (2010)	Hemofec (without rehydration)	54.2	96.9
Advanced adenoma			
Allison et al. (1996)	Hemoccult II (without rehydration)	30.8	98.1
Allison et al. (1996)	Hemoccult II SENSA (HSgFOBT)	68.6	87.5
Imperiale et al. (2004)	Hemoccult II (without rehydration)	11.0	–
Allison et al. (2007)	Hemoccult II SENSA (HSgFOBT)	41.0	–
Ahlquist et al. (2008)	Hemoccult II (without rehydration)	11.0	98.0
Ahlquist et al. (2008)	Hemoccult II SENSA (HSgFOBT)	21.0	97.0
Park et al. (2010)	Hemoccult II (without rehydration)	13.6	92.4
Parra-Blanco et al. (2010)	Hemofec (without rehydration)	19.8	97.4
Advanced neoplasia (colorectal cancer + advanced adenoma)			
Allison et al. (1996)	Hemoccult II (without rehydration)	32.4	98.1
Allison et al. (1996)	Hemoccult II SENSA (HSgFOBT)	71.2	87.5
Lieberman et al. (2001)	Hemoccult II (with rehydration)	24.0	–
Sung et al. (2003)	Hemoccult II (without rehydration)	14.0	–
Park et al. (2010)	Hemoccult II (without rehydration)	16.7	92.9
Parra-Blanco et al. (2010)	Hemofec (without rehydration)	23.8	97.7

gFOBT, guaiac faecal occult blood test; HSgFOBT, high-sensitivity gFOBT.

successfully complete diagnostic follow-up of positive test results.

Wide ranges of sensitivities of gFOBT (any type) for the detection of CRC and advanced adenomas have been described (Table 3.2.2). For FIT (any type), the pooled sensitivity and specificity for the detection of CRC (based on a meta-analysis) have been estimated to be 79% (95% confidence interval [CI], 69–86%) and 94% (95% CI, 92–95%), respectively (Lee et al., 2014). However, different sensitivities and specificities have been reported using different FIT strategies (Table 3.2.3). Several studies conducted in average-risk screening populations have shown that the sensitivity of FIT is higher than that of gFOBT in detecting both CRC and advanced neoplasia.

Another important issue for stool-based tests for blood is the cumulative performance over multiple screening rounds. A study conducted in Italy in the context of a FIT-based screening programme in the population aged 50–69 years

Table 3.2.3 Performance of FIT for detection of colorectal cancer

Number of subjects	Number of lesions	Number of studies	FIT procedure	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
111 125	422	19	All (qualitative and quantitative)	79 (69–86)	94 (92–95)
54 275	196	11	Cut-off level < 20 µg Hb/g faeces	86 (75–92)	91 (69–93)
13 796	63	6	Cut-off level 20–50 µg Hb/g faeces	63 (43–79)	96 (94–97)
42 075	156	4	Cut-off level > 50 µg Hb/g faeces	67 (59–74)	96 (94–98)
86 481	317	13	Pooled; 1 sample	78 (65–87)	95 (93–96)
15 892	78	4	Pooled; 2 samples	77 (59–89)	93 (90–95)
19 514	89	6	Pooled; 3 samples	80 (66–89)	93 (89–95)

CI, confidence interval; FIT, faecal immunochemical test.
Based on a meta-analysis by Lee et al. (2014).

showed, after five rounds of biennial screening, cumulative detection rates for CRC (0.85%) and advanced adenoma (5.9%) similar to those reported in one round of primary screening with colonoscopy between screens in a programme in Italy (subjects aged 50–69 years; 0.85% for CRC and 5.9% for advanced adenoma) and in a trial in the USA (subjects aged 50–84 years; 0.7% for CRC and 7.6% for advanced adenoma or sessile serrated lesions ≥ 1 cm) (Zorzi et al., 2018). These data suggest that the efficacy of FIT screening is closely related to the cumulative sensitivity of repeated tests; therefore, comparisons between FIT and other screening strategies should not be based on a single round of FIT. For quantitative FIT, a study showed that, after 5 years of follow-up, participants with a FIT result of between 8 µg and 10 µg Hb/g faeces (below the established cut-off level for positivity) had a significant 8-fold higher cumulative incidence of advanced neoplasia than those with a baseline of undetectable faecal Hb (Grobbee et al., 2017a). A study in Taiwan, China, reported an increase in the risk of interval cancer with increasing concentrations of faecal Hb, with relative risks ranging from 1.6 in those with concentrations of 50–99 µg Hb/g faeces to 2.9 in those with concentrations higher than 149 µg Hb/g faeces (Chiu et al., 2017). Information about the comparison of the performance of gFOBT versus FIT in relation to the detection rate of advanced neoplasia is summarized in Section 3.4.2.

(e) Additional factors that affect performance

The ability of stool-based tests to detect faecal blood is closely related to the characteristics of the colorectal lesions as well as their localization.

Because sessile serrated lesions are typically flat, non-ulcerated, and without haemorrhagic features, FOBTs fail to detect these lesions (Heigh et al., 2014), and because of their low prevalence, they are unlikely to represent a suitable target for FOBT-based screening programmes (Zorzi et al., 2017). In relation to the localization, Brenner et al. (2017) reported a higher sensitivity of FIT in the detection of advanced adenomas in the distal colon (44%; 95% CI, 38–51%) than in the proximal colon (20%; 95% CI, 14–28%).

Faecal Hb concentration varies with sex and age; it is higher in older people and in men (McDonald et al., 2011). Variations are also seen across countries and even between neighbourhoods in the same city; these differences are related to the level of socioeconomic deprivation (Fraser et al., 2014, 2015; Buron et al., 2017). FOBT performance differs between men and women (Brenner et al., 2010a). Using FIT with the same cut-off level for both sexes results in a higher sensitivity and a lower specificity for advanced colorectal neoplasia in men than

in women (Grobbee et al., 2017b). Regardless of these differences, screening programmes currently use the same strategies for both sexes in relation to the cut-off level and the screening intervals. Adjusting cut-off levels on the basis of age and sex could contribute to the efficacy of FIT-based CRC screening programmes and optimize the use of available endoscopy resources.

3.2.2 Randomized controlled trials

(a) Descriptions of RCTs

Five RCTs on screening with gFOBT have been published. The characteristics of these trials are presented in Table 3.2.4.

In the Minnesota trial, which started in 1975, 46 551 participants aged 50–80 years were randomly assigned to CRC screening once a year, to screening every 2 years, or to a control group (Mandel et al., 1993). Participants were recruited from among volunteers for the American Cancer Society and other groups in Minnesota, USA. Participants submitted six guaiac-impregnated paper slides (the Hemoccult test) containing two smears from each of three consecutive stools. The slides were mailed to a central laboratory for testing, and because of the potential for drying (and associated decrease in sensitivity of the test) caused by delays in mail delivery, the slides were rehydrated with a drop of water during processing, beginning in 1977. This procedure was fully implemented in 1982 and was used until the end of trial screening (82.5% of slides rehydrated). Participants with one or more slides that tested positive were advised to undergo diagnostic evaluation. Initially, this was with rigid sigmoidoscopy or single-contrast barium enema, which was replaced with colonoscopy in 1978.

In contrast to the Minnesota trial, the other four RCTs did not have an annual screening arm, and the slides were rehydrated in only one of those trials.

In the Nottingham trial, 152 850 individuals, identified from general practice registers in Nottingham, United Kingdom, were randomly assigned to biennial screening with Hemoccult (two samples from each of three consecutive stools) or to a control group (Hardcastle et al., 1996). Controls were not told about the study. A repeat test was sent to individuals with up to four slides that tested positive. To limit false-positive rates, those individuals were advised to restrict their diets for 2 days before taking two samples from each of three consecutive stools. Only participants with five or more slides that tested positive on the first test and those with one or more slides that tested positive on the repeat test were advised to undergo colonoscopy.

In the Funen trial, 137 485 residents of Funen, Denmark, identified from the population register of Funen County, were randomized to biennial screening with Hemoccult II, to a control group, or to not be enrolled in the study (Kronborg et al., 1996). Controls were not told about the study and continued to use health-care facilities as usual. Participants were asked to provide two samples from each of three consecutive stools. Individuals with one or more slides that tested positive were invited for colonoscopy.

In the Gothenburg trial, 68 308 residents of Gothenburg, Sweden, aged 60–64 years in three cohorts (those born in 1918–1922, 1923–1927, and 1928–1931) were randomized to screening with Hemoccult II or to a control group (Kewenter et al., 1994). A second screening round was offered 16–24 months after the initial round. Participants were asked to provide samples on 3 days. The slides were rehydrated, except those from participants born in 1918–1920. The results from the three cohorts were pooled. Participants in the 1928–1931 cohort with a positive test result on the first or second screening were retested with Hemoccult II, and only those with a positive result on the retest were invited for workup. This included an interview with a physician to determine whether the participant had experienced abdominal symptoms or rectal bleeding in the previous 6 months. A rectal examination,

Table 3.2.4 Descriptions of randomized controlled trials on colorectal cancer screening with gFOBT

Trial Country Reference[a]	Randomization	Number of subjects randomized	Accrual period for screening		Age at entry (years)	Intervention	Screening interval (years)	Number of screening rounds	Attendance at first round (%)
			Invited group	Control group					
Minnesota trial USA Mandel et al. (1993)	Individual	46 551	1975–1977	1975–1977	50–80	R-gFOBT[b]	1 2	11 (annual) 6 (biennial)	NR
Nottingham trial United Kingdom Hardcastle et al. (1996)	Individual	152 850	1981–1991	1981–1991	45–74	gFOBT	2	3–6	53.4
Funen trial Denmark Kronborg et al. (1996)	Individual	137 485	1985	1985	45–75	gFOBT	2	9	66.8
Gothenburg trial Sweden Kewenter et al. (1994)	Individual	68 308	1982–1990	1982–1990	60–64	R-gFOBT[c]	2	2–3	63.0
Finnish screening programme Finland Malila et al. (2008)	Cluster	360 492 [sic][d]	2004–2012	2004–2012	60–69	gFOBT	2	NA	68.8

gFOBT, guaiac faecal occult blood test; NA, not applicable; NR, not reported; R-gFOBT, gFOBT with rehydration.

[a] Reference of the first publication, in which the design of the trial is presented.

[b] 82.5% of the slides were rehydrated.

[c] [91.7%] of the slides were rehydrated.

[d] This value should probably be 362 492, as the sum of 181 210 and 181 282 (see text).

proctoscopy, sigmoidoscopy, and double-contrast barium enema were performed. Those with a negative workup were retested again with three Hemoccult II slides. Then those with one or more slides that tested positive underwent colonoscopy (Kewenter et al., 1988).

In Finland in 2004–2012, while the national CRC screening programme was being implemented, men and women aged 60–69 years were randomized to be invited or not to biennial CRC screening with gFOBT without rehydration. A total of 181 210 subjects were allocated to the screening arm and 181 282 to the control arm, covering 43.5% of the target population in Finland aged 60–69 years at the end of 2012 (Malila et al., 2008; Pitkäniemi et al., 2015).

(b) Results of RCTs

The published results on CRC mortality and incidence of the most recent follow-ups of the five RCTs are shown in Table 3.2.5.

For the Minnesota trial (Shaukat et al., 2013), after a mean follow-up of 30 years, the cumulative CRC mortality rate was 42 per 100 000 person-years in the annual screening group (200 deaths; 1.8%) and 50 per 100 000 person-years in the biennial screening group (237 deaths; 2.2%), compared with 63 per 100 000 person-years in the control group (295 deaths; 2.7%). Screening reduced CRC mortality (relative risk [RR], 0.68; 95% CI, 0.56–0.82 with annual screening; RR, 0.78; 95% CI, 0.65–0.93 with biennial screening). In stratified analyses, reductions in CRC mortality in the biennial screening group were significantly larger in men than in women (RR, 0.63; 95% CI, 0.48–0.82 in men; RR, 0.92; 95% CI, 0.72–1.18 in women). In addition, reductions in CRC mortality were largest in men aged 60–69 years compared with men younger than 60 years or older than 70 years ($P_{\text{interaction}} < 0.04$). An earlier publication from the Minnesota trial, on CRC incidence after 18 years of follow-up, reported cumulative CRC incidence ratios of 0.80 (95% CI, 0.70–0.90) in the annual screening group and 0.83 (95% CI, 0.73–0.94) in the biennial screening group (Mandel et al., 2000). [The Working Group noted that the reduction in CRC incidence in this RCT could be attributed to greater referral to colonoscopy among the participants because of a higher positivity rate for gFOBT with rehydration.]

For the Nottingham trial (Scholefield et al., 2012), after a median follow-up of 19.5 years, the cumulative CRC mortality rate was 91 per 100 000 person-years (1176 deaths) in the biennial screening group, compared with 100 per 100 000 person-years (1300 deaths) in the control group. Screening reduced CRC mortality (RR, 0.91; 95% CI, 0.84–0.98). There was no significant difference in the reductions in CRC mortality in men and women separately or in those younger than 60 years compared with those 60 years or older. There was no significant difference in CRC incidence between the screening group and the control group (RR, 0.97; 95% CI, 0.91–1.03).

For the Funen trial (Kronborg et al., 2004), after 17 years of follow-up (1985–2002), the cumulative CRC mortality rate was 84 per 100 000 person-years in the biennial screening group (362 deaths), compared with 100 per 100 000 person-years in the control group (431 deaths). Screening reduced CRC mortality (RR, 0.84; 95% CI, 0.73–0.96). CRC incidence was similar in the screening group and the control group (RR, 1.02; 95% CI, 0.93–1.12).

For the Gothenburg trial (Lindholm et al., 2008), after 9 years of follow-up, the cumulative CRC mortality rate was 53 per 100 000 person-years in the biennial screening group (252 deaths), compared with 64 per 100 000 person-years in the control group (300 deaths). Screening reduced CRC mortality (RR, 0.84; 95% CI, 0.71–0.99). There was no difference in CRC incidence between the screening group and the control group (RR, 0.96; 95% CI, 0.86–1.06).

In the Finnish screening programme (Pitkäniemi et al., 2015), after a median follow-up of 4.5 years, the cumulative CRC mortality rate

Table 3.2.5 Results of randomized controlled trials on colorectal cancer screening with gFOBT

Trial Country Reference	Age at enrolment/ screening (years)	Duration of follow-up (years)	Number of subjects	CRC mortality		CRC incidence	
				RR	95% CI	RR	95% CI
Minnesota trial USA Shaukat et al., (2013)	50–80	Mean, 30[a]	46 551	0.68 0.78	(0.56–0.82) (annual) (0.65–0.93) (biennial)	0.80 0.83	(0.70–0.90) (annual) (0.73–0.94) (biennial)
Nottingham trial United Kingdom Scholefield et al. (2012)	45–74	Median, 19.5	152 850	0.91	(0.84–0.98)	0.97	(0.91–1.03)
Funen trial Denmark Kronborg et al. (2004)	45–75	Mean, 17	137 485	0.84	(0.73–0.96)	1.02	(0.93–1.12)
Gothenburg trial Sweden Lindholm et al. (2008)	60–64	Mean, 9	68 308	0.84	(0.71–0.99)	0.96	(0.86–1.06)
Finnish screening programme Finland Pitkäniemi et al. (2015)	60–69	Median, 4.5	360 492 [sic][b]	1.04	(0.84–1.28)	1.11	(1.01–1.23)

CI, confidence interval; CRC, colorectal cancer; gFOBT, guaiac faecal occult blood test; RR, relative risk.

[a] Incidence ratios based on 18 years of follow-up (Mandel et al., 2000).

[b] This value should probably be 362 492 (see Table 3.2.4).

Table 3.2.6 Results of meta-analyses of randomized controlled trials on the efficacy of colorectal cancer screening with gFOBT

Reference	Maximum duration of follow-up (years) of all RCTs included	Population		Number of CRC deaths		CRC mortality	
		Screened	Control	Screened	Control	RR	95% CI
Towler et al. (1998)[a,b]	10	172 734	156 908	885	928	0.84	0.77–0.93
Moayyedi & Achkar (2006)[c]	18	122 778	122 439	1002	1146	0.87	0.80–0.95
Hewitson et al. (2008)[a,b]	17	172 734	156 908	1477	1592	0.84	0.78–0.90
Fitzpatrick-Lewis et al. (2016)[a,d]	30	156 737	156 443	1990	2326	0.82	0.73–0.92

CI, confidence interval; CRC, colorectal cancer; gFOBT, guaiac faecal occult blood test; RCT, randomized controlled trial; RR, relative risk.

[a] Towler et al. (1998), Hewitson et al. (2008), and Fitzpatrick-Lewis et al. (2016) included all of the RCTs described in Table 3.2.4 except the Finnish screening programme.

[b] Towler et al. (1998) and Hewitson et al. (2008) included both the annual screening arm and the biennial screening arm of the Minnesota trial.

[c] Moayyedi & Achkar (2006) did not include the Gothenburg trial and included only the biennial screening arm of the Minnesota trial.

[d] Fitzpatrick-Lewis et al. (2016) included only the annual screening arm of the Minnesota trial and excluded 875 subjects whose records were not traceable in the Office for National Statistics database at the time of the analysis.

was 21.1 per 100 000 person-years in the biennial screening group (170 deaths), compared with 20.4 per 100 000 person-years in the control group (164 deaths). There was no reduction in CRC mortality (RR, 1.04; 95% CI, 0.84–1.28) or in CRC incidence (RR, 1.11; 95% CI, 1.01–1.23) as a result of screening.

(c) Results of meta-analyses of RCTs

The results of the four published meta-analyses of RCTs on the efficacy of CRC screening with gFOBT are shown in Table 3.2.6. The first meta-analysis was published in 1998 (Towler et al., 1998), and the most recent was published in 2016 (Fitzpatrick-Lewis et al., 2016). Three of the meta-analyses (Towler et al., 1998; Hewitson et al., 2008; Fitzpatrick-Lewis et al., 2016) included the results from the Minnesota, Nottingham, Funen, and Gothenburg trials described in Table 3.2.4, although Fitzpatrick-Lewis et al. (2016) included only the annual screening arm of the Minnesota trial. The other meta-analysis (Moayyedi & Achkar, 2006) did not include the Gothenburg trial and excluded the results from the annual screening arm of the Minnesota trial. The findings across the different meta-analyses are remarkably consistent, showing a modest significant reduction in CRC mortality. The relative risks for CRC mortality ranged from 0.82 to 0.87. Screening with gFOBT reduced the incidence of late-stage CRC by 8% (RR, 0.92; 95% CI, 0.85–0.99), based on a pooled estimate of results from the Minnesota trial and the Nottingham trial with a combined sample of 220 284 individuals and a median follow-up of 14.25 years (Fitzpatrick-Lewis et al., 2016).

(d) FIT

There is only one cluster randomized trial that evaluated FIT screening and CRC mortality in rural China (Zheng et al., 2003; Fitzpatrick-Lewis et al., 2016). In 1989, residents aged 30 years and older from 21 townships in Jiashan County were enrolled in the trial. The residents were randomized to a screening group (10 townships) or to a control group (11 townships), which did not undergo screening. The screening and control townships were matched by age and population size into 10 pairs. Participants in the screening group completed a single FIT based on reverse passive haemagglutination. Participants with a positive FIT result underwent sigmoidoscopy

or colonoscopy. There were 94 423 participants in the screening group and 97 838 individuals in the control group. Duration of follow-up was 5–6 years, and causes of death in 1989–1996 were certified by qualified physicians. At the end of the study period, 361 deaths from CRC had occurred in the screened group and 357 in the control group. There was no significant difference in CRC mortality between the screened group and the control group (RR, 0.88; 95% CI, 0.72–1.07). [The Working Group noted that the limitations of this trial included enrolment of younger people and short follow-up.]

3.2.3 Observational studies on preventive effects

This section summarizes the observational studies assessing the preventive effects of screening with gFOBT or FIT versus no screening, with CRC mortality and/or CRC incidence as an outcome. Studies that compare gFOBT with FIT in terms of the detection rates of adenoma, neoplasia, or CRC are summarized in Section 3.4.2.

(a) Cohort studies

A total of nine cohort studies (including a nested case–control study) conducted in China, Denmark, Finland, France, Italy, Japan, Scotland, and Taiwan, China, have reported on CRC mortality and/or CRC incidence after screening with gFOBT or FIT, mostly in the age group 50–69 years (Table 3.2.7).

(i) gFOBT

A nested case–control study with annual gFOBT screening after age 40 years and matched for age, sex, and family history of both CRC and adenomas was conducted in Italy in 1978–1995. A large but non-significant reduction in CRC mortality was reported (odds ratio [OR], 0.64; 95% CI, 0.36–1.15) for attenders (ever screened) versus non-attenders (never screened). Also, the reduction in CRC mortality increased with the number of screening tests: having two or three tests reduced the risk by 29%, whereas having four or more tests reduced the risk by up to 66% (Bertario et al., 1999).

In a pilot study conducted in Finland, the population aged 50–63 years from three municipalities in southern Finland was invited to screening. A total of 1785 individuals were screened only once with a gFOBT developed in Finland (Malila et al., 2007). After 25 years of follow-up, no effects on CRC mortality or CRC incidence were observed compared with the general Finnish population, in terms of standardized mortality and incidence rates. The pilot study was stopped after one screening round, because of costs and low specificity. [The Working Group noted as limitations that this was a small population with only one round of screening, the participation rate was high (69%), and the positivity rate of the gFOBT used was higher than in other studies, i.e. 19%.]

The large matched cohort study by Libby et al. (2012) included the Scottish arm of the United Kingdom pilot of gFOBT screening, which covered individuals resident in three Scottish National Health Service Boards (Steele et al., 2009). The pilot consisted of three rounds of biennial gFOBT screening carried out in more than 379 655 individuals aged 50–69 years. Follow-up was up to 10 years, and the overall screening participation was 60.6%. A 10% relative reduction in CRC mortality was reported with an intention-to-screen analysis comparing those invited versus those not invited to screening (RR, 0.90; 95% CI, 0.83–0.99), and a 17% relative reduction was reported after adjusting for participation (RR, 0.83; 95% CI, 0.79–0.87). [The Working Group noted that the reported 95% confidence interval of the mortality relative risk adjusted for participation appeared to be too narrow and recalculated it to be 0.74–0.92. Although the effect appeared to be stronger in men and in younger age groups, the Working Group attributed this to

Table 3.2.7 Cohort studies evaluating the effectiveness of colorectal cancer screening with stool-based tests for blood

Reference Location	Recruitment period Age at entry (years) Duration of follow-up (years)	Study population Reference population	Number of screening rounds Screening interval (years)	Temporal and geographical similarity of comparison group	Adjustments	CRC mortality and/or incidence, risk estimate (95% CI)	Comments
gFOBT							
Bertario et al. (1999) Milan, Italy	1978–1995 ≥ 40 Median, 7 (follow-up from 1996)	Nested case–control from a larger population-based cohort of 21 879 who participated in an organized CRC screening programme Study (cases): 95 deaths, ascertained by death certificates from municipality archives Reference (controls): 475 controls (5 per case, randomly sampled), same source as cases Matched by age, sex, area of birth; alive at the time of the case's diagnosis	1 or more (1–3, 80%) 1	Same period Same population	Age, sex, family history of CRC, personal history of adenomatous polyps	Mortality Ever vs never screened: OR: 0.64 (0.36–1.15) Time from index date (yr): ≤ 1: 2.32 (0.85–6.35) ≤ 2: 1.09 (0.48–2.44) ≤ 3: 0.88 (0.42–1.85) ≤ 4: 0.80 (0.39–1.61) ≤ 5: 0.78 (0.40–1.52) ≤ 6: 0.81 (0.43–1.52) Number of gFOBT tests: 1: 1.00 2 or 3: 0.71 (0.44–1.14) ≥ 4: 0.34 (0.16–0.75)	"Attenders" defined as those who underwent a second gFOBT within 2 yr of study admission; gFOBT without rehydration used in 1978–1983, and gFOBT with rehydration used in 1984–1995
Malila et al. (2007) Southern Finland, 3 municipalities	1979–1980 50–63 25	Study (invited and screened): 1785 Reference: the entire Finnish population	1 Once only	Same period Same counties	Age and sex	Mortality SMR: 1.17 (0.75–1.73) Incidence SIR: 1.09 (0.80–1.44)	A second test was used to classify the population into screen-negatives and screen-positives. If still positive, colonography or endoscopy was offered at the central hospital A gFOBT without rehydration, developed in Finland, was used

Table 3.2.7 (continued)

Reference Location	Recruitment period Age at entry (years) Duration of follow-up (years)	Study population Reference population	Number of screening rounds Screening interval (years)	Temporal and geographical similarity of comparison group	Adjustments	CRC mortality and/or incidence, risk estimate (95% CI)	Comments
Libby et al. (2012) Scotland, 3 counties	2000–2007 50–69 Maximum, 10 (follow-up from 2000)	Study (invited and screened): 379 655 Reference: 379 655 matched controls from non-pilot health boards	3 2	Same period Different counties	Age, sex, and socioeconomic deprivation	Rate ratio Mortality 0.90 (0.83–0.99) 0.83 (0.79–0.87), adjusted for participation Men: 0.89 (0.79–0.99) Women: 0.94 (0.82–1.09) 50–59 yr: 0.86 (0.74–0.99) 60–69 yr: 0.94 (0.84–1.05)	Non-participants had increased CRC mortality vs controls, RR, 1.21 (1.06–1.38); gFOBT without rehydration was used
Hamza et al. (2014) Burgundy, France	1988–2009 45–74 Maximum, 21 (followed up until December 2009)	Study: 45 642 residents of 12 districts were invited to screening, 2409 had first screen Reference: population in 17 non-screened districts with the same CRC incidence as the screened population at the start	11 2	Same period Other districts in Burgundy	Age, sex, and socioeconomic status	Mortality SMR: 0.87 (0.80–0.94) Incidence SIR: 1.01 (0.96–1.06) Men: 0.85 (0.77–0.94) Women: 0.90 (0.80–1.02)	No differences by duration of follow-up or age group (> 65 vs < 65) Larger proportion of stage I CRC in those invited to screening vs non-respondents (44.1% vs 17.4%) Lack of strict randomization of controls gFOBT without rehydration was used
Bjerrum et al. (2016) Denmark, 2 counties	2005–2006 50–74 10 (follow-up from 2005); median, 8.9	Incidence-based mortality cohort study Study (invited and screened):166 277 Reference: 1 240 348 remaining Danes of the same age	1 Once only	Same period Different counties	Age and sex	Mortality (incidence-based) HR: 0.92 (0.86–0.99) Incidence HR: 0.94 (0.90–0.97) All-cause mortality HR: 0.95 (0.94–0.96)	Non-responders had higher CRC mortality and all-cause mortality vs controls [Probably gFOBT without rehydration was used (because of relatively low positivity), but not stated in the publication]

Table 3.2.7 (continued)

Reference Location	Recruitment period Age at entry (years) Duration of follow-up (years)	Study population Reference population	Number of screening rounds Screening interval (years)	Temporal and geographical similarity of comparison group	Adjustments	CRC mortality and/or incidence, risk estimate (95% CI)	Comments
FIT							
Ventura el al. (2014) Florence, Italy	1993–1999 50–70 15 (followed up until 2008)	Study (invited and screened): 6961 Reference (invited but unscreened): 26 285	5 (average, 3.5) 2	Same period Same population	Age and sex	Mortality SMR: 0.59 (0.37–0.93) Incidence HR (overall): 0.78 (0.65–0.93) HR (first 6 yr): 1.06 (0.82–1.37) HR (after 6th yr): 0.60 (0.46–0.79)	Women had lower incidence, HR, 0.55 (0.48–0.63), with men as reference No differences in incidence by cancer location (distal vs proximal) SMR computed using the European standard population and SIR using the invited but unscreened population
Giorgi Rossi et al. (2015) Reggio Emilia Province, Italy	2005 (screened cohort) 1997 (non-screened cohort) 50–69 8	Incidence-based mortality cohort study Study (invited and screened): 171 785 (70% of invitees) Reference: population from the non-screened cohort with a similar age and sex structure	4 2	Different period Same counties	Age and sex	Mortality (incidence-based) IRR: 0.64 (0.52–0.78) Cumulative incidence IRR: 0.90 (0.83–0.97) All-cause mortality IRR: 0.73 (0.63–0.85)	Screened and non-screened cohorts were followed up at different time periods; showed no secular trends in CRC mortality/incidence between 1997 and 2005
Chiu et al. (2015) Taiwan, China	2004–2009 50–69 Average, 3; maximum, 6 (followed up until 2009)	Study (invited and screened): 1 160 895 References: Invited but unscreened: 4 256 804 Uninvited: not clear	1–3 2	Same period Same population	Increase in annual CRC incidence rate in Taiwan, China (1.97%) and self-selection bias (in invited vs uninvited analyses)	Cumulative mortality Screened vs unscreened: RR: 0.38 (0.35–0.42) Invited vs uninvited: RR: 0.90 (0.84–0.95)	

Table 3.2.7 (continued)

Reference Location	Recruitment period Age at entry (years) Duration of follow-up (years)	Study population Reference population	Number of screening rounds Screening interval (years)	Temporal and geographical similarity of comparison group	Adjustments	CRC mortality and/or incidence, risk estimate (95% CI)	Comments
gFOBT/FIT							
Jin et al. (2013) Beijing Military General Hospital, China	1987–2005 > 50 Maximum, 22 (followed up until 2008)	Dynamic cohort of army officers (75% male) Study (invited and agreed to screen): 3863 Reference (invited and did not agree to screen, same cohort): 1241	18 1	Same period Same population	Age, sex, education level, family history of malignant tumours, body mass index, smoking, alcohol consumption, physical exercise, meat intake, and aspirin use	Mortality RR: 0.36 (0.18–0.71) Incidence RR: 0.51 (0.30–0.87)	Study of gFOBT triaged with FIT No differences in age, sex, or other major risk factors for CRC mortality or all-cause mortality observed between the 2 groups gFOBT with rehydration was used

CI, confidence interval; CRC, colorectal cancer; FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized mortality ratio; vs, versus; yr, year or years.

a possible lack of statistical power.] The reduction in CRC mortality started from approximately 4 years after initial screening.

In a study conducted in 12 districts of Burgundy, France, residents aged 45–74 years were invited to biennial gFOBT screening. The average participation rate in the first round was 52.8%. A significant reduction of 13% in CRC mortality was observed after 11 screening rounds compared with CRC mortality in the population in 17 non-screened districts (standardized mortality ratio [SMR], 0.87; 95% CI, 0.80–0.94) [the Working Group calculated the participation-adjusted SMR (0.74; 95% CI, 0.63–0.86)], whereas no difference in the CRC incidence rate was observed (standardized incidence ratio [SIR], 1.01, 95% CI, 0.96–1.06) (Hamza et al., 2014).

An incidence-based mortality cohort study (Bjerrum et al., 2016) was conducted in Denmark in 2005–2006 (the study design was published in Lindebjerg et al., 2014), to assess whether participation in once-only gFOBT screening has an effect on CRC incidence and mortality. The study included 182 152 citizens aged 50–74 years (166 277 screened), and the participation rate was 48.5%. After a median of 8.9 years of follow-up, CRC mortality was lower in the screened group compared with the reference group of Danes of the same age (hazard ratio [HR], 0.92; 95% CI, 0.86–0.99). [The Working Group calculated the participation-adjusted HR for CRC mortality (0.82; 95% CI, 0.70–0.95).] A negative association with all-cause mortality was also reported (HR, 0.95; 95% CI, 0.94–0.96). Because CRC mortality and all-cause mortality were almost the same, the authors could not conclude that one round of gFOBT screening had an effect on reducing CRC mortality. CRC incidence was also lower in the screened group compared with the population in the rest of Denmark (adjusted HR, 0.94; 95% CI, 0.90–0.97). [The Working Group calculated the participation-adjusted HR for CRC incidence (0.74; 95% CI, 0.63–0.86). The Working Group highlighted as limitations that the study evaluated only one screening round and that it did not adjust for pre-screening differences in health status between the compared groups.]

(ii) FIT

Ventura et al. (2014) compared CRC mortality and incidence between two cohorts in Italy. One cohort was screened biennially with FIT for up to 11 years after the first screening round (average, 3.6 FITs), and the other cohort was unscreened (defined as those who had been invited to screening but did not comply with the first round). The study reported lower CRC mortality (SMR, 0.59, 95% CI, 0.37–0.93) and lower overall incidence (HR, 0.78; 95% CI, 0.65–0.93) in the attenders versus the non-attenders. [Some contamination in the reference group is likely in this study, with individuals who would not have attended the first round but attended the subsequent rounds. However, the direction of this potential bias would be towards the null effect.]

In a screening programme in northern Italy, launched in 2005, residents aged 50–69 years were invited to screening with biennial FIT (Giorgi-Rossi et al., 2015). After four screening rounds, the study reported a reduction of 36% in incidence-based CRC mortality (RR, 0.64; 95% CI, 0.52–0.78) compared with a historical non-screened cohort in the same area. A decrease of 10% in CRC incidence was observed after 8 years in the screened cohort compared with the control cohort (incidence rate ratio, 0.90; 95% CI, 0.83–0.97). [Data needed for the calculation of the participation-adjusted RR were not available in the published literature.]

In a study by Chiu et al. (2015), the first million individuals aged 50–69 years (20% of the target population) in Taiwan, China, were screened with biennial FIT, and the average follow-up was 3 years. The study reported a 62% decrease in CRC mortality (RR, 0.38; 95% CI, 0.35–0.42) in the screened group versus the invited but unscreened group, which resulted

in a 10% decrease (95% CI, 0.84–0.95) when adjusted for self-selection bias and increasing CRC incidence trends in Taiwan, China. [The Working Group noted that follow-up was short, leading to a possible length-time bias, and that the cumulative CRC mortality in the unscreened group could indicate that individuals previously diagnosed with CRC may have been included, leading to an overestimation of the magnitude of the effect.]

(iii) gFOBT/FIT

Jin et al. (2013) performed a study at Beijing Military General Hospital, China, in 1987–2005. A total of 3863 army officers older than 50 years were screened with annual gFOBT. Those with a positive gFOBT result completed FIT, and those with a positive FIT result were referred for colonoscopy. After 21 years of follow-up, the study reported a relative risk of CRC mortality of 0.36 (95% CI, 0.18–0.71) and a relative risk of CRC incidence of 0.51 (95% CI, 0.30–0.87). [The Working Group considered that this was a very small population in which to evaluate CRC mortality.]

(b) Case–control studies

Case–control studies can complement the results from RCTs and help to address questions related to screening efficacy and frequency (Weiss, 2013).

A total of six case–control studies, in France, Italy, Japan, and the USA, have been published that assessed CRC mortality-associated odds ratios in screened versus unscreened individuals. In addition, some reported mortality trends in relation to (i) the number of screening rounds and (ii) the time since the last screen (Table 3.2.8).

(i) gFOBT

Three studies were published in the USA between 1993 and 1999 (Selby et al., 1993; Lazovich et al., 1995; Scheitel et al., 1999). All three reported a decrease in CRC mortality with gFOBT screening (annual or biennial), ranging from 28% to 31%. Also, in one study, the magnitude of the reduction in CRC mortality was significantly larger after four rounds of biennial screening compared with one, two, or three rounds of screening (Scheitel et al., 1999). In addition, Lazovich et al. (1995) observed a significant reduction in CRC mortality only in those aged 74 years and younger at diagnosis of CRC.

In a study in Italy, Zappa et al. (1997) reported an odds ratio for CRC mortality of 0.60 (95% CI, 0.4–0.9) comparing ever screened versus never screened (205 cases and 1030 controls). The reduction in CRC mortality decreased with an increasing number of years since the most recent screening test.

A study conducted in France was published in 1999 (Faivre et al., 1999) and updated in 2014 (Hamza et al., 2014; see Section 3.2.3(a)). This population-based case–control study (178 cases and 712 population-based controls) reported an odds ratio for CRC mortality of 0.64 (95% CI, 0.46–0.91) for individuals screened with biennial gFOBT versus non-screened individuals, as well as decreasing CRC mortality with an increasing number of screening rounds (P_{trend} = 0.03). No significant reduction in CRC mortality was observed more than 24 months after the most recent round of screening.

(ii) FIT

Two case–control studies were conducted in the same region in Japan. One evaluated FIT screening and CRC mortality (Saito et al., 1995), and the other reported on FIT screening and CRC stage distribution (Nakajima et al., 2003).

Saito et al. (1995) reported a significant reduction of 60% in CRC mortality in those screened within 1 or 2 years of the case diagnosis compared with those who were unscreened; the reduction in CRC mortality decreased after 3 years and became non-significant after 4 or more years. The authors also reported trends of

Table 3.2.8 Case–control studies evaluating the effectiveness of colorectal cancer screening with stool-based tests for blood

Reference Location	Year programme began Study period Age of included subjects (years)	Description of cases and controls	Number of screening rounds Screening interval (years)	Adjustments	CRC mortality, OR (95% CI)	Comments
gFOBT						
Selby et al. (1993) Northern California, USA Kaiser Permanente Medical Care Program (KPMCP)	1979 1981–1987 ≥ 50	Cases: 486 deaths, from KPMCP, identified by the SEER cancer registry. Death ascertained through registry or by automated linkage to California state death certificates Controls: 727, same source as cases. Matched for age, sex, and date of health plan entry. Alive at the time the case died	1 or more 1 or 2	Number of health check-ups, screening sigmoidoscopies and rectal examinations during the 10 yr before the index date, and personal history of colorectal polyps or CRC	Within 5 yr of screening test: 0.69 (0.52–0.91) Within 2 yr of screening test: 0.76 (0.55–1.03)	Probably gFOBT without rehydration was used
Lazovich et al. (1995) Washington State, USA Group Health Cooperative (GHC) of Puget Sound	1983 1986–1991 ≥ 50	Cases: 248 deaths from GHC, aged 40–84 yr at diagnosis. Ascertained from the Seattle-Puget Sound SEER cancer registry. Cause of death from medical records or from death certificate. Screening history from medical records (both cases and controls) Controls: 496 (2 per case, randomly selected), same source as cases. Matched by year of birth, sex, and year of enrolment at GHC	At least 1 2	–	Ever screened: 0.72 (0.51–1.02)	In stratified analyses, a reduction in risk was seen only in those aged ≤ 74 yr, OR, 0.65 (0.44–0.97) [Possible misclassification of diagnostic tests as screening]

Table 3.2.8 (continued)

Reference Location	Year programme began Study period Age of included subjects (years)	Description of cases and controls	Number of screening rounds Screening interval (years)	Adjustments	CRC mortality, OR (95% CI)	Comments
Zappa et al. (1997) Florence District (rural area), Italy	1982 1984–1995 40–70	Cases: 206 deaths from CRC after age 41 yr, identified from the Florence cancer and mortality registry Screening histories of both cases and controls ascertained by automated linkage with the archives of the Centre for the Study and Prevention of Cancer in Florence Controls: 1030 (5 per case, randomly selected), same source as cases, alive at time of diagnosis of case. Matched by sex, age, and place and length of residence	At least 1 Average, 2.5	Place of birth (as indicator of socioeconomic status and lifestyle), marital status, education level, prevalent job, smoking, and family history of CRC	Ever vs never screened: 0.60 (0.4–0.9) Time (years) since most recent gFOBT test Never: 1.00 1 < 3: 0.54 (0.03–0.9) 3–6: 0.77 (0.4–1.7) > 6: 0.78 (0.3–2.2)	gFOBT without rehydration was used until 1992, then gFOBT with rehydration was used, and lastly FIT was used
Faivre et al. (1999) Burgundy, France	1988 Until 1994 45–74 8–9 yr of follow-up available for all case–control sets	Cases: 178 deaths (diagnosed in 1988–1999 and died up to December 1996) identified from the population-based cancer registry or through the data collection system of the screening programme or general practitioners. Screening histories collected from medical records Controls: 712 (4 per case, randomly sampled), same source as cases. Matched by sex, year of birth, and place of residence. Alive at the time the matched case died	1–4 2	–	Ever vs never screened: 0.67 (0.48–0.94) Number of rounds: Never: 1.00 1: 1.04 (0.67–1.58) 2: 0.50 (0.29–0.88) 3: 0.52 (0.28–0.94) 4: 0.30 (0.12–0.76) Time (months) since most recent screen: Never: 1.00 1–3: 2.02 (1.12–3.65) 4–12: 0.58 (0.34–0.99) 13–24: 0.40 (0.23–0.68) 25–36: 0.32 (0.10–1.10) 37–48: 0.84 (0.22–3.22) 49–60: 0.41 (0.05–3.72) > 60: 2.09 (0.61–7.14)	Population-based case–control study. gFOBT screening offered to all residents of the 12 districts No differences in CRC mortality by sex or cancer subsite (proximal colon, distal colon, or rectum) Screening history taken from the time screening started to the date of diagnosis of the case gFOBT without rehydration was used

Table 3.2.8 (continued)

Reference Location	Year programme began Study period Age of included subjects (years)	Description of cases and controls	Number of screening rounds Screening interval (years)	Adjustments	CRC mortality, OR (95% CI)	Comments
Scheitel et al. (1999) Rochester, Minneapolis, USA	Screening 10 yr before diagnosis in cases 1970–1993 ≥ 45	Cases: 218 deaths, Rochester community residents, ascertained by death certificates Controls: 435 from the same area (2 per case). Matched by age, institution of diagnosis of the case, and sex, identified through the Mayo Clinic or Olmsted Medical Center registers. Alive at the time the case died	At least 1 NR	Number of periodic health examinations, number of hospitalizations, family history of CRC, and personal history of colon polyps	Years before date of CRC diagnosis of case: 0–1: 0.38 (0.13–1.08) 0–2: 0.61 (0.30–1.26) 0–3: 0.83 (0.45–1.52)	Population-based case–control study Both gFOBT without rehydration and the haem-derived porphyrin assay test were used
FIT						
Saito et al. (1995) Aomori Prefecture, Japan	1986 or 1987 40–79	Cases: 193 deaths between 1986 and 1992, identified from death certificates or the Aomori cancer registry. Cause of death from hospital medical records Controls: 577 (3 per case, randomly selected), same source as cases, alive at time of diagnosis of case, and had been living in the same area. Matched by sex and year of birth. Without history of previous CRC	At least 1 1	–	Screening within a range of the case diagnosis (years) Unscreened: 1.00 0–1: 0.40 (0.17–0.92) 0–2: 0.41 (0.20–0.82) 0–3: 0.48 (0.25–0.92) 0–4: 0.69 (0.34–1.39) 0–5: 0.77 (0.34–1.74) Time (years) since last screen: 0–1: 0.40 (0.11–0.92) 1–2: 0.39 (0.12–1.33) 2–3: 0.58 (0.16–2.07) 3–4: 0.90 (0.09–8.68) 4–5: 1.20 (0.16–9.20)	Screening histories for both cases and controls were retrieved from the staff at the Aomori Screening Centre

CI, confidence interval; CRC, colorectal cancer; FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; NR, not reported; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results Program; yr, year or years.

increasing CRC mortality with time since the last screen [no P_{trend} was reported].

In a subsequent analysis in a subset of the same population, Nakajima et al. (2003) reported that subjects who had undergone at least one FIT screen during the previous 4 years had a reduced risk of developing advanced CRC (stage T2 to T4) by 28–46%, compared with those who were unscreened. The odds ratios for developing advanced cancer within 2–5 years after FIT were lower for the rectum (OR, 0.32–0.73) than for colon (OR, 0.84–1.18).

(iii) gFOBT and FIT

An additional case–control study in Japan showed a large reduction in CRC mortality based on only 28 CRC cases (Hiwatashi et al., 1993). [The Working Group excluded this study from the evaluation primarily because of the sample size limitations and the use of a mixture of gFOBT and FIT screening.]

(c) Ecological studies

Two ecological studies conducted in Italy compared CRC mortality and incidence in late screened areas versus early screened areas within the same geographical regions. Both of these studies reported reductions in CRC mortality (Table 3.2.9). [The Working Group considered that these results should be interpreted with caution because of limitations in study design.]

The first ecological study covered individuals aged 40–69 years in two regions in Tuscany, Italy: the Empolese–Mugello district, where screening with biennial gFOBT or FIT started in 1980 (early screened regions), and the provinces of Florence and Prato, where screening was implemented in 1985–2006 (late screened regions) (Costantini et al., 2008). The reduction in CRC mortality was larger in the early screened regions than in the late screened regions: the estimated annual percentage decrease in the age-adjusted CRC mortality rate was 2.7% (95% CI, 1.7–3.7%) in the early screened regions and 1.3% (95% CI, 0.8–1.7%) in the late screened regions. [The Working Group noted that gFOBT was used until 1996, and FIT later.]

The second ecological study evaluated the impact of a biennial FIT-based screening programme implemented in 2002–2009 in Veneto, Italy, for residents aged 50–69 years, by comparing early screened areas, where screening started in 2002–2004, with late screened areas, where screening was implemented in 2008–2009 (Zorzi et al., 2015). Before the implementation of screening, CRC mortality and incidence rates in the two areas were similar. Compared with 1995–2000, the 2006–2011 CRC mortality rates were 22% lower in the early screened areas than in the late screened areas (RR, 0.78; 95% CI, 0.68–0.89), and the mortality reduction was larger in women than in men. A substantial increase in the percentage of stage I CRCs detected by screening was observed in 2006 (> 50%) compared with no screening programme in 2000–2001 (12%), which could explain the observed reduction in mortality rates in the population in the early screened areas. [A possible limitation of this study is the contamination in the late screened areas by the presence of opportunistic screening before the introduction of the organized screening programmes.]

(d) Meta-analyses

A meta-analysis of both RCTs and observational studies evaluated the effects of gFOBT screening on CRC mortality (Elmunzer et al., 2015). Overall, the study reported a reduction of 18% in CRC mortality (n = 17; RR, 0.82; 95% CI, 0.76–0.88) and a significant reduction of 20% when only observational studies were included (n = 12; RR, 0.80; 95% CI, 0.71–0.91).

A recent meta-analysis included 44 studies (both RCTs and observational studies) published in 1992–2016 and evaluated the effects of five different CRC screening methods (gFOBT, FIT, sigmoidoscopy, colonoscopy, and a combination of sigmoidoscopy plus gFOBT) (Zhang

Table 3.2.9 Ecological studies evaluating the effectiveness of colorectal cancer screening with stool-based tests for blood

Reference Location	Recruitment period Age at entry (years) Duration of follow-up (years)	Study population reference population	Number of screening rounds Screening interval (years)	Temporal and geographical similarity of comparison group	Adjustments	CRC mortality and/or incidence, risk estimate (95% CI)	Comments
Costantini et al. (2008) Tuscany, Italy, 2 regions	Study population: Empolese–Mugello district, 1980 (early screened) Reference population: Florence and Prato provinces, 2000 (late screened) 40–69 until 1996 50–69 since 1996 Follow-up: 1985–2006	Study (early screened): 17 500 tested each year Reference (late screened): 38 000 tested each year	Early screened: 13 Late screened: 8 2	Different period Different population	Age at death, sex, calendar year, and geographical area (early screened or late screened)	Mortality rate Annual decrease (%) Early screened: 2.7 (1.7–3.7) Late screened: 1.3 (0.8–1.7)	gFOBT with and without rehydration was used until 1996, and FIT thereafter No differences were observed between early screened and late screened regions in overall cancer mortality rates, and both areas had similar patterns of increasing CRC incidence In the early screened area, a slight reduction in incidence was observed in 2000–2004 (after longer follow-up) A significant interaction of geographical area and calendar year in relation to mortality was found
Zorzi et al. (2015) Veneto Region, Italy, 2 areas	Study population: 2002–2004 (early screened) Reference population: 2008–2009 (late screened) 50–69 Followed-up until 2011 Early screened: 9–11	Study (early screened): 294 319 Reference (late screened): 360 468	Early screened: 3 or 4 Late screened: 1 2	Different period Same counties	Age and sex	Mortality Early screened vs late screened (2006–2011 vs 1995–2000): RR: 0.78 (0.68–0.89) Women RR: 0.64 (0.51–0.80) Men RR: 0.87 (0.73–1.04)	The study used FIT Incidence rates not available for all the local health units. In early screened areas, incidence rates reached a peak at introduction of screening and then returned to the baseline in 2007

CI, confidence interval; CRC, colorectal cancer; FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; RR, relative risk.

et al., 2017). When gFOBT was compared with no screening in a total of 19 studies including 2 264 603 participants, the meta-analysis reported a reduction of 14% in CRC mortality (RR, 0.86; 95% CI, 0.82–0.90), and a statistically non-significant reduction in CRC incidence, based on nine studies (RR, 0.99; 95% CI, 0.96–1.03). When FIT was compared with no screening in three observational studies (two cohort studies and one case–control study), the same meta-analysis reported a reduction of 59% in CRC mortality (RR, 0.41; 95% CI, 0.29–0.59), and a reduction of 21% in CRC incidence, based on only two studies (RR, 0.79; 95% CI, 0.69–0.92). [The Working Group noted the mixture of experimental and observational study designs included in this meta-analysis, which limits its interpretation in terms of effectiveness. Also, in the pooled estimate of FIT, one observational study in a non-screened Japanese population was included.]

3.2.4 Adverse effects

This section considers the harms of screening with stool-based tests for blood, from observational studies and RCTs. One might consider three sources of harms: harms attributable to the process of screening per se, harms directly attributable to the test, and harms of managing individuals with a positive screening result. These harms can be psychological harms or physical harms.

(a) Psychological harms

Parker et al. (2002) sent the 30-question General Health Questionnaire (a self-administered instrument for identifying minor psychiatric disorders in the general population) to 2184 people 1 month before gFOBT screening and to 1693 people 3 months after screening. Among the 843 people who completed both questionnaires, there was no significant difference in the proportion showing probable psychiatric morbidity before and after screening. The same study compared suicides among all randomized individuals in the Nottingham trial of gFOBT-based CRC screening (Hardcastle et al., 1996). There were 48 [0.06%] suicides among 74 998 controls compared with 53 [0.07%] among 75 253 people invited to screening. [The Working Group noted that the percentages reported in the article are slightly different, so either the absolute numbers or the percentages in the article must be incorrect, but this would not affect the similarity between the two groups.]

Laing et al. (2014) carried out surveys at 7–14 days and at 4 months after gFOBT screening and assessed short-term situational anxiety (using the State-Trait Anxiety Inventory) (Spielberger et al., 1983), frequency of CRC-specific worry, and mood disturbance. At 7–14 days after screening, 55 respondents with positive screening results had higher situational anxiety (mean score, 38.8) compared with 110 respondents with negative screening results matched on age and sex (mean score, 30.9; $P_{\text{difference}} = 0.007$). Respondents with positive screening results were also nearly 4 times as likely to report CRC-related mood disturbances compared with respondents with negative screening results (RR, 3.82; 95% CI, 1.09–13.43). [The Working Group noted the small sample size of the study.] There was a non-significant increase in the frequency of colon cancer-specific worry (based on answers to the question, "How often do you worry about getting colon cancer?") in those with positive screening results. At 4 months after receipt of the screening result, both situational anxiety and mood disturbance (in both groups) had returned to baseline (pre-screening) levels.

Lindholm et al. (1997) sent a questionnaire to individuals invited to participate in the Gothenburg trial of gFOBT screening (Kewenter et al., 1994). A total of 2932 participants completed the questionnaire, and 16% of them reported that they were very worried or extremely worried when they received the invitation. Subsets of participants were also interviewed by telephone. Of the 156 participants interviewed after

receiving a positive gFOBT result, 60% were very worried or extremely worried after they received that result. Of the 96 participants with a negative result on a second gFOBT, only 4% remained very worried or extremely worried after they received their second result.

In another study, Mant et al. (1990) identified 56 individuals who had received a positive gFOBT result followed by a negative gFOBT result or colonoscopy. Using a structured questionnaire, they interviewed 54 of them about their experience (e.g. "How distressed were you at the initial result?"). Two thirds reported some degree of distress after the initial positive result, but of those, only 14% were very distressed.

In the study by Parker et al. (2002), anxiety scores (using the State-Trait Anxiety Inventory) were highest after notification of a positive gFOBT result (mean scores of 44) but fell immediately after notification of a negative colonoscopy (mean scores of 31). [The Working Group noted that these findings highlight the importance of prompt follow-up of positive findings, to minimize the duration of anxiety.]

Another potential harm from screening per se is an inappropriate reaction to a negative screening result, such as ignoring subsequent cancer symptoms or adopting an unhealthy lifestyle. Miles et al. (2015) asked 296 people with CRC to complete a questionnaire on quality of life, depression, and perceived diagnostic delay. Patients with interval cancer after a negative gFOBT result reported greater perceived diagnostic delay than did patients with screen-detected disease, after adjustment for age, sex, deprivation (using the Scottish Index of Multiple Deprivation), time since diagnosis, receipt of radiotherapy or chemotherapy, and presence of comorbidities (OR, 0.37; 95% CI, 0.17–0.83; P = 0.02). However, there were no differences in perceived diagnostic delay between CRC patients with interval cancers and those not offered screening. [Hence, the Working Group noted that there is no evidence supporting that a negative screening result leads to delayed diagnosis.] Similarly, Bouvier et al. (2001) found that interval cancers (after gFOBT screening) had later stage at diagnosis than screen-detected CRC, but earlier stage at diagnosis than CRC detected in individuals who had not been screened. They also found no increased delay in cancer diagnosis in screening non-responders compared with individuals not invited for screening. [The Working Group concurred that a high rate of false-negatives does not have adverse effects, although it does of course reduce the efficacy of screening.]

(b) Physical harms of FOBT tests

There are no reports of physical harms directly associated with FOBT screening. Theoretically, one might imagine that poor hygiene associated with FOBT procedures could lead to the spread of gastrointestinal infections, but there are no published studies of such harm.

(c) Physical harms of follow-up treatment

This section considers (i) harm done while investigating a positive screening result and (ii) harm done by the treatment of an overdiagnosed CRC.

To assess the harm done while evaluating a positive screening result, one might simply consider the proportion of those screened who have a positive test result and the harms of investigating such a result. Most FOBT-positive subjects are referred for colonoscopy. Good data are available on the harms associated with screening colonoscopy (see Section 3.3.4), but fewer data are available about the harms of triage colonoscopy (i.e. colonoscopy as a result of a positive FOBT screening result). Apart from discomfort (from both the bowel preparation and the endoscopy itself), the main harms are the risks of serious bleeding, perforation of the bowel, and other serious complications leading to hospitalization. The nature of the harms is the same as with screening colonoscopy, but the frequencies of such harms are different, because

FOBT-positive subjects are more likely to require a polypectomy (Rao et al., 2009).

Table 3.2.10 presents serious harms from colonoscopy in studies of FOBT-based screening expressed as major events per 10 000 screens. Table 3.2.10 includes both RCTs and reports from routine screening programmes. [The Working Group calculated the harms per 10 000 screens. The Working Group found it difficult to ascertain how many screens were carried out in some of the studies, and approximated those from the numbers of colonoscopies and the screening positivity in some cases.] The studies had a varying number of screening rounds (range, 1–11). Based on 11 CRC screening studies (four RCTs, five programmes or pilot programmes, and two cohort studies), the colonoscopy rate (test positivity, expressed as colonoscopies per 100 screens) for stool-based testing for blood ranges from 1.0% to 8.5%, and up to 9.8% if considering the rehydrated slides of the Mandel et al. (1993) trial only. The serious harms generally increased in studies with a larger proportion receiving colonoscopy. In the reports of the two largest programmes, each with more than half a million screens (Steele et al., 2009; Logan et al., 2012), the combined rate of serious adverse events was less than 1 per 10 000 screens. Higher rates of bleeding were reported in a regional programme in France (Denis et al., 2013) and in one small study in Spain (Quintero et al., 2012), and higher rates of perforations were reported in an early trial from Sweden (Kewenter & Brevinge, 1996). In the four studies (with a total of nearly 2 million FOBT screens and 30 000 colonoscopies) that reported on deaths from colonoscopy, there were none.

(d) False-positive results

Often the frequency of the harm of a positive screening result is expressed in terms of the harm of a false-positive screening result (on the grounds that there is no real harm associated with a true-positive screening result). There is then a question about what constitutes a false-positive screening result. Given that most authors would say that the aim of FOBT is to diagnose cancer earlier, a false-positive result would be a positive test result in an individual who does not have CRC. However, many authors consider a positive test result in the presence of an advanced adenoma to be a true-positive, and some would consider it to be a true-positive if there was any adenoma.

(e) Overdiagnosis

The four RCTs of gFOBT with individual randomization all reported on CRC incidence, and none of them showed any evidence of net overdiagnosis. For the Funen trial (Kronborg et al., 2004), the relative incidence was 1.02 (95% CI, 0.93–1.12) over 17 years. For the Gothenburg trial (Lindholm et al., 2008), it was 0.96 (95% CI, 0.86–1.06) over up to 19 years. For the Nottingham trial (Scholefield et al., 2012), it was 0.97 (95% CI, 0.91–1.03) after a mean of 17 years. Scholefield et al. (2012) included a graph of cumulative incidence, which was initially larger in the screening arm, but the curves crossed at 5 years. In contrast, the Minnesota trial (Mandel et al., 2000) showed a reduction in CRC incidence ratios of 0.80 (95% CI, 0.70–0.90) for the annual screening arm and 0.83 (95% CI, 0.73–0.94) for the biennial screening arm (see Section 3.2.2). The cumulative CRC incidence curves in the screening and non-screening arms crossed at 7 years. [The Working Group concluded that depending on the sensitivity of the stool-based tests, there would be overdiagnosis of CRC if screening were to be offered to individuals with less than 5–7 years of residual life expectancy.]

(f) Harms related to the detection of adenomas

The potential harms of detection of adenomas (whether or not they are overdiagnosed) include the effects of labelling the individual as a patient, the effects of adenoma removal, and the effects of

Table 3.2.10 Serious harms from colonoscopy after a positive stool-based test for blood

Reference Country	FOBT used Setting	Number of FOBT screening tests	Test positivity (%) Number of colonoscopies	Perforation, *n* (% of colonoscopies) [per 10 000 screens]	Bleeding, *n* (% of colonoscopies) [per 10 000 screens]	Other serious events, *n* (% of colonoscopies) [per 10 000 screens]
Mandel et al. (1993, 2000); Towler et al. (1998) USA	gFOBT, with or without rehydration RCT	[> 124 959] [< 510 250] (6–11 rounds)	2.4 (without rehydration) 9.8 (with rehydration) 8.5 (combined) 12 246	4 (0.03) [0.08–0.32]	11 (0.09) [0.21–0.88]	NR
Kewenter & Brevinge (1996) Sweden	gFOBT RCT	23 916	4.1 FS: 2108 Colonoscopy: 190	FS: 3 (0.1) Colonoscopy: 2 (1.1) Combined: [2.1]	FS: 0 (0) Colonoscopy: 1 (0.5) Combined: [0.4]	NR
Robinson et al. (1999) England, United Kingdom	gFOBT RCT	136 548 (3–6 rounds)	1.1 1474	5 (0.34) [0.36]	1 (0.07) [0.07]	Deaths: 0
Faivre et al. (2004) France	gFOBT Cohort study	133 878 (6 rounds)	1.5 1298	0 (0) [0]	0 (0) [0]	Deaths: 0
Denis et al. (2007) France	gFOBT Pilot programme	90 706	3 2724	2 (0.07) [0.22]	4 (0.15) [0.44]	Hospitalizations (minor bleeding): 9 (0.33) [0.99]
Dancourt et al. (2008) France	gFOBT or FIT Cohort study	17 215	6.99 1205	0 (0) [0]	0 (0) [0]	NR
Steele et al. (2009) Scotland, United Kingdom	gFOBT Programme	507 345	1.7 8631	0 (0) [0]	0 (0) [0]	Hospitalizations: 25 (0.28) [0.49] Deaths: 0
Logan et al. (2012) England, United Kingdom	gFOBT Programme	1 079 293	1.6 17 518	17 (0.1) [0.15]	12 (0.07) [0.11]	Hospitalization: 5 (0.03) [0.04] Hemicolectomy: 1 (0.01) [0.01] Deaths: 0
Quintero et al. (2012) Spain	FIT RCT	9089 (106 had screening colonoscopy)	6.5 587	0 (0) [0]	8 (1.4) [8.8]	Hypotension or bradycardia: 2 (0.3) [2.2]
Denis et al. (2013) France	gFOBT Pilot programme	342 212	3 10 277	10 (0.09) [0.29]	31 (0.3) [0.90]	NR
Parente et al. (2013) Italy	FIT Programme	81 218	6.2 (round 1); 5.8 (round 2) 4373	2 (0.05) [0.25]	5 (0.1) [0.62]	Hospitalization: 5 (0.1) [0.62]

FIT, faecal immunochemical test; FOBT, faecal occult blood test; FS, flexible sigmoidoscopy; gFOBT, guaiac FOBT; NR, not reported; RCT, randomized controlled trial.

offering more intensive surveillance for individuals with advanced adenomas. The serious harms of polypectomy (such as causing major bleeding or perforation) are described and quantified in Section 3.3.4.

3.2.5 Benefit–harm ratio of FOBT screening

(a) Background

This section describes the balance between benefits and harms (i.e. benefit–harm ratio) of CRC screening with stool-based tests for blood, based on data from modelling studies that included both endoscopy and stool-based testing for blood, as well as additional studies that only presented results on gFOBT or FIT. The benefits and harms of CRC screening with stool-based tests for blood have been discussed previously (see Section 3.2.2, Section 3.2.3, and Section 3.2.4). The value of FOBT screening can be measured with life years gained (LYG) or QALYs gained. Both are common measures used in health economics, and they translate to the benefit (years of life) and harms and burdens (quality of life) a person may receive as a result of screening. It is important to note that there is not necessarily a standard for how these quality adjustments are included for different studies. Therefore, it is important for authors to carefully define the terms and for readers to understand them.

(b) Systematic reviews of life years gained

The United States Preventive Services Task Force (USPSTF) updated its review for CRC screening in 2016 (Bibbins-Domingo et al., 2016). A systematic literature review (Lin et al., 2016) and a modelling decision analysis (Knudsen et al., 2016) informed the USPSTF review. The modelling was from the three CRC microsimulation models of the Cancer Intervention and Surveillance Modeling Network (Knudsen et al., 2016) (see Table 3.3.14 in Section 3.3.5).

The USPSTF reviewed the current established tests of colonoscopy, sigmoidoscopy, HSgFOBT, and FIT and the emerging tests of computed tomography (CT) colonography and multitarget stool DNA (mt-sDNA). The evidence supported with high certainty that CRC screening provided benefit that is substantially larger than its harms (i.e. there is high certainty that the net benefit is substantial). Here, LYG for gFOBT, HSgFOBT, and FIT are discussed, compared with no screening (comparison between CRC screening tests is addressed in Section 3.4; see text and tables). In the decision analysis for the USPSTF, the LYG with screening for individuals at average risk aged 50–75 years for annual FIT were 231–260 LYG per 1000 individuals aged 40 years and required 1739–1899 colonoscopies (diagnostic and surveillance) per 1000 individuals screened in a lifetime. These numbers amount to a ratio of 6.7–8.5 colonoscopies per LYG. The efficiency ratio (the ratio of incremental colonoscopies per additional LYG compared with a less intensive strategy) varied from 17 to 24 colonoscopies per LYG. The LYG with screening for individuals at average risk aged 50–75 years for annual HSgFOBT were 232–261 LYG per 1000 individuals aged 40 years and required 2230–2287 colonoscopies (diagnostic and surveillance) per 1000 individuals screened in a lifetime. These numbers amount to a ratio of 8.5–9.8 colonoscopies per LYG. These results suggest that FIT and HSgFOBT with 100% participation can achieve comparable LYG, but that the repeated FIT over 25 years requires considerably fewer colonoscopies.

(c) QALYs and DALYs from modelling studies

This section reviews modelling studies on CRC screening with gFOBT (including HSgFOBT) and FIT. There are 18 studies that have evaluated the impact of FIT and gFOBT screening on QALYs (Table 3.2.11). All of the studies concluded that CRC screening influenced QALYs positively and resulted in a net gain in

QALYs. QALYs gained by screening with gFOBT varied from 2 QALYs per 1000 (Sharp et al., 2012) to 131 QALYs per 1000 (Lam et al., 2015) and up to 486 QALYs per 1000 (Wong et al., 2015) for a population with polyps. When screening with FIT, the net benefit was slightly higher than that for gFOBT, varying from 4 QALYs per 1000 (Dan et al., 2012) to 801 QALYs per 1000 (Wong et al., 2015) for a population with polyps. In those studies where both gFOBT and FIT were included, QALYs gained for FIT were higher than QALYs gained for gFOBT. [The wide variability across studies could be from different assumptions for the model inputs or definition of QALYs, and the Working Group highlighted that internal comparisons are more useful than comparisons across studies. In addition, the variability in estimates can be partly explained by the age of the population to which the estimates were standardized and by different strategies for intervals between screens.]

Only three modelling studies reported their results as DALYs averted for the impact of gFOBT (Table 3.2.12). Ginsberg et al. (2010) considered three regions (East Africa, eastern Europe, and the Americas), and the results ranged from 1.8 DALYs per 1000 individuals in East Africa to 17.8 DALYs per 1000 individuals in the Americas. For an Australian population at average risk aged 55–69 years, Stone et al. (2004) reported 1.5 DALYs per 1000 individuals for biennial gFOBT. For women in Hong Kong Special Administrative Region, China, Woo et al. (2007) reported 7 DALYs per 1000 individuals for annual FOBT and 3 DALYS per 1000 individuals for biennial FOBT.

3.2.6 Cost–effectiveness studies

(a) Background

A screening test can provide high value if its health benefits justify its cost. Determining what the justification boundaries are will vary according to the patient, the payer, the hospital, and even policy measures. From a payer perspective, a typical cost–benefit level in the USA is US$ 100 000 per LYG, whereas lower levels are used elsewhere. Moreover, costs for CRC screening depend on the screening test and strategy used.

Costs for the FOBT strategies can include the test itself, evaluation of each test, subsequent diagnostic colonoscopy for positive FOBT test results with potential pathology costs for evaluation of polyps, surveillance colonoscopy for patients with adenoma, and potential cancer treatment. Administrative costs for FOBT screening, including repeat testing (annually or biennially), processing of the test with reporting back to the primary care provider and to the patient, and scheduling those with positive test results for colonoscopy, are not commonly included in the cost structure, even though there are significant costs associated with the administration of a stool-based test for blood (Heitman et al., 2010; Pignone et al., 2011). Even "no screening" has an associated cost, which is the cost of treating cancers that arise symptomatically in the population. The FOBT tests themselves have limitations; not all positive test results are true positives, and not all negative test results are true negatives. For FIT, the cut-off level for positivity can be varied to accommodate the colonoscopy capacity for screening for a given area.

(b) Cost–effectiveness studies and systematic reviews

In 2000, only a few years after the publication of the results from several RCTs showing CRC mortality reduction with gFOBT screening, Helm et al. (2000) estimated the cost–effectiveness of the Minnesota trial (Mandel et al., 1993), the Nottingham trial (Hardcastle et al., 1996), and the Funen trial (Kronborg et al., 1996). Based on the European trials, gFOBT screening cost US$ 2500 per LYG compared with no screening. In 2004, Whynes et al. (2004) followed up the 1996 Nottingham trial of gFOBT with a

Table 3.2.11 Studies of quality-adjusted life years gained from screening with FOBT compared with no screening[a]

Reference Country	Population simulated[b]	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	QALYs gained per 1000 screened individuals	Considered disutility from screening?
Heitman et al. (2010) Canada	Cohort age 50–75 yr at average risk of CRC	68	FIT-high-performance annually	73/76	47	
			FIT-mid-performance annually	71/74	45	
			FIT-low-performance annually	46/48	27	
			gFOBT-high[c] annually	29/30	16	
			gFOBT-low[c] annually	20/23	12	
Telford et al. (2010) Canada	Cohort age 50–75 yr at average risk of CRC	73	FOBT-low annually	44/55	69	Uncertain if reported incidence/mortality reductions pertain to 100% adherence
			FIT annually	65/74	105	
Barouni et al. (2012) Islamic Republic of Iran	Cohort age 50–75 yr at average risk of CRC	68	gFOBT annually	39/50	68	
			FIT annually	60/69	104	
Dan et al. (2012) Singapore	Cohort age 50–75 yr at average risk of CRC	NR	FIT annually	27/26	4	
Sharp et al. (2012) Ireland	Cohort age 30–100 yr at average risk of CRC	53	FIT biennially, age 55–74 yr	15/36	23	
			FIT biennially, age 55–64 yr	NR/NR	17	
			FIT biennially, age 65–74 yr	NR/NR	8	
			gFOBT biennially, age 55–74 yr	1/12	7	
			gFOBT biennially, age 55–64 yr	NR/NR	5	
			gFOBT biennially, age 65–74 yr	NR/NR	2	
Whyte et al. (2012) England, United Kingdom	Cohort age 60–74 yr at average risk of CRC	54	FIT biennially	19/28	31.6	
			gFOBT biennially	9/15	15.4	
Dinh et al. (2013) USA	Cohort age 50–75 yr at average risk of CRC	100	FIT annually	69/68	96	
Sharaf & Ladabaum (2013) USA	Cohort age 50–100 yr at average risk of CRC	100	FIT annually	62/76	77	
			gFOBT annually	47/65	67	
Ladabaum et al. (2014) Germany	Cohort age 50–75 yr at average risk of CRC	100	FIT Annually, age 50–54 yr, Biennially, age 55–75 yr	51/63	102	
			gFOBT Annually, age 50–54 yr, Biennially, age 55–75 yr	34/45	76	

Table 3.2.11 (continued)

Reference Country	Population simulated[b]	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	QALYs gained per 1000 screened individuals	Considered disutility from screening?
Lam et al. (2015) Hong Kong Special Administrative Region, China	Cohort age 50–75 yr with pre-existing adenomas or CRC	NR	FIT annually	NR/NR	225	
			FIT biennially	NR/NR	179	
			gFOBT annually	NR/NR	131	
			gFOBT biennially	NR/NR	81	
Wong et al. (2015) Hong Kong Special Administrative Region, China	Cohort age 50–75 yr with pre-existing adenomas	60	FIT annually	NR/NR	801	
			FIT biennially	NR/NR	672	
			gFOBT annually	NR/NR	486	
			gFOBT biennially	NR/NR	321	
Kingsley et al. (2016) USA	Cohort age 50–100 yr at average risk of CRC	67	FIT annually	NR/NR	89	No
Ladabaum & Mannalithara (2016) USA	Cohort age 50–80 yr at average risk of CRC	100	FIT annually	60/77	78	
			FIT biennially	48/70	72	
Lee & Park (2016) Republic of Korea	Cohort age 50–80 yr at average risk of CRC	25	gFOBT annually	NR/NR	246	
Pil et al. (2016) Belgium	Cohort age 56–74 yr at average risk of CRC					
	Men	43–51	FIT biennially	26.6/23	12	
	Women	53–50	FIT biennially	21.5/19	5	
Sekiguchi et al. (2016) Japan	Cohort age 40 yr at average risk of CRC	61.5	FIT annually	58/NR	202	
Aronsson et al. (2017) Sweden	Cohort age 60–80 yr at average risk of CRC	40	FIT twice (baseline and 3 years)	12/NR	26	No
			FIT biennially	NR/NR	51	

Table 3.2.11 (continued)

Reference Country	Population simulated[b]	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	QALYs gained per 1000 screened individuals	Considered disutility from screening?
Goede et al. (2017) Canada	Cohort age 50–75 yr at average risk of CRC	100	FIT annually	NR/NR	40	
	Cohort age 50–74 yr at average risk of CRC		gFOBT biennially	NR/NR	20	
			FIT200[d] biennially	NR/NR	31	

CRC, colorectal cancer; FIT, faecal immunochemical test; FOBT, faecal occult blood test; gFOBT, guaiac FOBT; NR, not reported; QALYs, quality-adjusted life years; yr, year or years.

[a] Includes studies published after Patel & Kilgore (2015) (for studies within and outside the USA and studies in the USA) or after Lansdorp-Vogelaar et al. (2011) (for studies in the USA).

[b] Signifies the population at the start of the simulation, i.e. cohort age 50 years signifies a population of people aged 50 years that are followed up until death or a certain age, and cohort age 50–75 years signifies a population of people aged 50–75 years that are followed up until death or for a certain period. None of the studies considered the anxiety associated with screening and diagnostic follow-up or the potential negative impact of a negative screening test result on an unhealthy lifestyle in their estimates of QALYs.

[c] In Heitman et al. (2010), "FOBT-high" was erroneously labelled "FOBT-low". To correct this issue, the published "FOBT-low" values were assigned to the "FOBT-high" category listed in this table, and the published "FOBT-high" values were assigned to the "FOBT-low" category listed in this table.

[d] FIT with a cut-off level of 200 ng Hb/mL.

Table 3.2.12 Studies measuring disability-adjusted life years averted from screening with gFOBT compared with no screening

Reference	Country	Population simulated[a]	Participation rate (%)	Strategy evaluated	Mortality reduction (%)	DALYs averted per 1000 individuals	Considered disability from screening?
Stone et al. (2004)	Australia	Cohort age 55–69 yr, population in 1996	NR	gFOBT biennially	NR	1.5	
Woo et al. (2007)	Hong Kong Special Administrative Region, China	Cohort age 50–74 yr, female population in 2001	100 100	gFOBT annually gFOBT biennially	17 8	7 3	
Ginsberg et al. (2010)	Canada, Cuba, USA	Cohort age 50–80 yr at average risk of CRC	57 62	gFOBT annually gFOBT biennially	NR	17.8 12.0	No
	East Africa		NR NR	gFOBT annually gFOBT biennially	NR	2.6 1.8	
	Eastern Europe		NR NR	gFOBT annually gFOBT biennially	NR	8.1 5.5	

CRC, colorectal cancer; DALYs, disability-adjusted life years; gFOBT, guaiac faecal occult blood test; yr, year or years.

[a] Signifies the population at the start of the simulation, i.e. cohort age 50 years signifies a population of people aged 50 years that are followed up until death or a certain age, and cohort age 50–75 years signifies a population of people aged 50–75 years that are followed up until death or for a certain period.

Table 3.2.13 Systematic reviews of studies of cost–effectiveness of screening with FOBT compared with no screening

Reference	Country	Studies included	Cost–effectiveness ratios per life year gained
Pignone et al. (2002)	USA	5 studies evaluating annual gFOBT	Annual gFOBT: US$ 5691–17 805
Lansdorp-Vogelaar et al. (2011)	All	16 studies evaluating annual gFOBT 8 studies evaluating biennial gFOBT (2 with annual and biennial gFOBT)	Annual gFOBT: cost savings–US$ 56 300 Biennial gFOBT: US$ 3400–15 500
Patel & Kilgore (2015)	USA	5 studies evaluating FIT and gFOBT (including HSgFOBT) 1 study evaluating FIT only 1 study evaluating gFOBT only	Annual gFOBT: cost savings–US$ 5360 Annual HSgFOBT: cost savings–US$ 10 Annual FIT: cost savings–US$ 800

FIT, faecal immunochemical test; FOBT, faecal occult blood test; gFOBT, guaiac FOBT; HSgFOBT, high-sensitivity gFOBT.

cost–effectiveness analysis. Under conservative assumptions, the cost of screening in the Nottingham trial was £1584 (US$ 2582) per LYG as a result of screening. These studies suggested that gFOBT screening had an acceptable cost for the benefit gained.

Three systematic reviews on the cost–effectiveness of gFOBT or FIT compared with no screening have been published (Pignone et al., 2002; Lansdorp-Vogelaar et al., 2011; Patel & Kilgore, 2015) (Table 3.2.13). Pignone et al. (2002) included seven cost–effectiveness studies, five of which included gFOBT. Given the time period of the review, only the lower-sensitivity gFOBT was included. All studies found gFOBT to be cost-effective, with costs ranging from US$ 5691 to US$ 17 805 per LYG. Lansdorp-Vogelaar et al. (2011) reviewed 22 modelling studies that included gFOBT strategies scheduled either annually or biennially. The cost per LYG ranged from cost savings to US$ 56 300 per LYG. [As noted above, internal comparisons of gFOBT are more informative than comparisons across the different modelling groups.] The studies in Patel & Kilgore (2015) overlapped with those in Lansdorp-Vogelaar et al. (2011) but included five additional studies for gFOBT or FIT (Vijan et al., 2001; Parekh et al., 2008; Knudsen et al., 2012; Dinh et al., 2013; Ladabaum et al., 2014; see Table 3.2.14). All gFOBT CRC screening strategies assessed were more cost-effective than no screening.

Since the review by Patel & Kilgore (2015), two new models have been published that evaluated the cost–effectiveness of CRC screening in the USA (Kingsley et al., 2016; Barzi et al., 2017) and one in the Republic of Korea (Lee & Park, 2016). One model has published updated results (Ladabaum & Mannalithara, 2016) (Table 3.2.14). The findings of these studies are consistent with those of Patel & Kilgore (2015). These newer studies often included evaluations of both gFOBT and FIT. Kingsley et al. (2016) and Barzi et al. (2017) demonstrated cost savings for annual FIT and gFOBT. Since the review by Lansdorp-Vogelaar et al. (2011), 14 new studies have been published that evaluated the cost–effectiveness of gFOBT or FIT screening outside the USA: three in Canada (Heitman et al., 2010; Telford et al., 2010; Goede et al., 2017), four in Europe (Sharp et al., 2012; Whyte et al., 2012; Pil et al., 2016; Aronsson et al., 2017), and seven in Asia (including the Middle East) (Barouni et al., 2012; Dan et al., 2012; Wang et al., 2012; Lam et al., 2015; Wong et al., 2015; Lee & Park, 2016; Sekiguchi et al., 2016), showing that FOBT screening was predominantly cost saving (Table 3.2.13).

Table 3.2.14 summarizes the cost–effectiveness for the studies presented in the previous

Table 3.2.14 Studies of cost–effectiveness of screening with FOBT compared with no screening[a]

Reference Country	Population simulated	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	Currency	QALYs or LYs gained per 1000 screened individuals	Cost difference	Cost difference (US$)[c]	Cost per QALY (US$)[c]
Aronsson et al. (2017) Sweden	Cohort age 60–80 yr at average risk of CRC	40	FIT twice (3-yr interval)	11.7/NR	Euros	26 QALYs	–17 600	–18 507	Cost saving
			FIT biennially	NR/NR	Euros	51 QALYs	136 700	143 747	2839
Barzi et al. (2017) USA	Cohort age 50–75 yr at average risk of CRC	NR	FIT annually	6/12	United States dollars	6 LYs	–112	–112	Cost saving
			FIT biennially	5/14		10 LYs	–229	–229	Cost saving
			gFOBT annually	12/17		10 LYs	–251	–251	Cost saving
			gFOBT biennially	5/14		13 LYs	–361	–361	Cost saving
Kingsley et al. (2016) USA	Cohort age 50–100 yr at average risk of CRC	67	FIT annually	NR/NR	United States dollars	89 QALYs	–524	–524	Cost saving
Ladabaum & Mannalithara (2016) USA	Cohort age 50–80 yr at average risk of CRC	100	FIT annually	60/77	United States dollars	78 QALYs	–613	–613	Cost saving
			FIT biennially	48/70	United States dollars	72 QALYs	–809	–809	Cost saving
Sekiguchi et al. (2016) Japan	Cohort age 40 yr at average risk of CRC	61.5	FIT annually (starting at age 40 yr)	58/NR	Yen	202 QALYs	–61 392	–510	Cost saving
Lam et al. (2015) Hong Kong Special Administrative Region, China	Cohort age 50 yr with pre-existing adenomas or CRC	NR	FIT annually	NR/NR	Hong Kong dollars	225 QALYs	11 600	1496	6644
			FIT biennially	NR/NR	Hong Kong dollars	179 QALYs	7790	1006	5617
			gFOBT annually	NR/NR	Hong Kong dollars	131 QALYs	19 774	2549	19 461
			gFOBT biennially	NR/NR	Hong Kong dollars	81 QALYs	10 471	1350	16 666

Table 3.2.14 (continued)

Reference Country	Population simulated	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	Currency	QALYs or LYs gained per 1000 screened individuals	Cost difference	Cost difference (US$)[c]	Cost per QALY (US$)[c]
Wong et al. (2015) Hong Kong Special Administrative Region, China	Cohort age 50–75 yr with pre-existing adenomas	60	FIT annually	NR/NR	United States dollars	801 QALYs	2527	2527	3155
			FIT biennially	NR/NR	United States dollars	672 QALYs	2978	2978	4431
			gFOBT annually	NR/NR	United States dollars	486 QALYs	2001	2001	5870
			gFOBT biennially	NR/NR	United States dollars	321 QALYs	1680	1680	5234
Ladabaum et al. (2014) Germany	Cohort age 50–75 yr at average risk of CRC	100	gFOBT annually, age 50–54 yr; biennially, age 55–75 yr	51/63	Euros	102 QALYs	–1014	–1756	Cost saving
			FIT annually, age 50–54 yr; biennially, age 55–75 yr	34/45	Euros	76 QALYs	–1239	–1708	Cost saving
Dinh et al. (2013) USA	Cohort age 50–75 yr at average risk of CRC	100	FIT annually	69/68	United States dollars	96 QALYs	–1426	–1426	Cost saving
Sharaf & Ladabaum (2013) USA	Cohort age 50–100 yr at average risk of CRC	100	FIT annually	62/76	United States dollars	77 QALYs	–498	–498	Cost saving
			gFOBT annually	47/65	United States dollars	67 QALYs	–411	–411	Cost saving

Table 3.2.14 (continued)

Reference Country	Population simulated	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	Currency	QALYs or LYs gained per 1000 screened individuals	Cost difference	Cost difference (US$)[c]	Cost per QALY (US$)[c]
Sharp et al. (2012) Ireland	Cohort age 30–100 yr at average risk of CRC	53	FIT biennially, age 55–74 yr	15/36	Euros	23 QALYs	40	52	2253
			FIT biennially, age 55–64 yr	NR/NR	Euros	17 QALYs	20	26	1524
			FIT biennially, age 65–74 yr	NR/NR	Euros	8 QALYs	14	18	2267
			gFOBT biennially, age 55–74 yr	1/12	Euros	7 QALYs	33	43	6108
			gFOBT biennially, age 55–64 yr	NR/NR	Euros	5 QALYs	18	23	4664
			gFOBT biennially, age 65–74 yr	NR/NR	Euros	2 QALYs	15	19	9718
Dan et al. (2012) Singapore	Cohort age 50–75 yr at average risk of CRC	NR	FIT annually	27/26	United States dollars	4 QALYs	126	126	31 500
Heitman et al. (2010) Canada	Cohort age 50–75 yr at average risk of CRC	68	FIT-high annually	73/76	Canadian dollars	47 QALYs	103	98	2085
			FIT-mid annually	71/74	Canadian dollars	45 QALYs	−68	−65	Cost saving
			FIT-low annually	46/48	Canadian dollars	27 QALYs	104	99	3664
			HSgFOBT[b] annually	29/30	Canadian dollars	16 QALYs	294	280	17 484
			gFOBT[b] annually	20/23	Canadian dollars	12 QALYs	183	174	14 510
Telford et al. (2010) Canada	Cohort age 50–75 yr at average risk of CRC	73	gFOBT annually	44/55	Canadian dollars	69 QALYs	632	601	10 022
			FIT annually	65/74	Canadian dollars	105 QALY	654	710	6223

Table 3.2.14 (continued)

Reference Country	Population simulated	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	Currency	QALYs or LYs gained per 1000 screened individuals	Cost difference	Cost difference (US$)[c]	Cost per QALY (US$)[c]
Goede et al. (2017) Canada	Cohort age 50–74 yr at average risk of CRC	100	FIT annually	NR/NR	Canadian dollars	40 QALYs	−228 300	−169 784	Cost saving
			gFOBT biennially	NR/NR	Canadian dollars	20 QALYs	220 915	164 292	
			FIT200[d] biennially	NR/NR	Canadian dollars	31 QALYs	−130 000	−96 679	Cost saving
Pil et al. (2016) Belgium	Cohort age 56–74 yr at average risk of CRC								
	Men	43–51	FIT biennially	26.6/23	Euros	12 QALYs	19	21	1582 1725
	Women	53–50	FIT biennially	21.5/19	Euros	5 QALYs	18	20	3628
Lee & Park (2016) Republic of Korea	Cohort age 50–80 yr at average risk of CRC	25	gFOBT annually	NR/NR	United States dollars	246 QALYs	−440	−440	Cost saving
Knudsen et al. (2010); Lansdorp-Vogelaar et al. (2010) USA MISCAN	Cohort age 65 yr at average risk of CRC	100	FIT annually	42.1/59.3	United States dollars	80.1 LYs	62	62	800
			gFOBT annually	31.6/51.9	United States dollars	65.7 LYs	−83	−83	Cost saving
			HSgFOBT annually	43.9/63.0	United States dollars	81.1 LYs	1	1	10
USA SimCRC	Cohort age 65 yr at average risk of CRC	100	FIT annually	54.4/70.4	United States dollars	79.8 LYs	−251	−251	Cost saving
			gFOBT annually	40.4/55.6	United States dollars	59.9 LYs	−285	−285	Cost saving
			HSgFOBT annually	56.1/70.4	United States dollars	81.1 LYs	−325	−325	Cost saving

Table 3.2.14 (continued)

Reference Country	Population simulated	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	Currency	QALYs or LYs gained per 1000 screened individuals	Cost difference	Cost difference (US$)[c]	Cost per QALY (US$)[c]
USA CRC-SPIN	Cohort age 65 yr at average risk of CRC	100	FIT annually	63/NR	United States dollars	84.7 LYs	−402	−402	Cost saving
			gFOBT annually	46/NR	United States dollars	64.0 LYs	−441	−441	Cost saving
			HSgFOBT annually	67/NR	United States dollars	87.3 LYs	−495	−495	Cost saving
Barouni et al. (2012) Islamic Republic of Iran	Cohort age 50–75 yr at average risk of CRC	68	gFOBT annually	39/50	United States dollars	68 QALYs	−632	−632	Cost saving
			FIT annually	60/69	United States dollars	104 QALYs	−654	−654	Cost saving
Whyte et al. (2012) England	Cohort age 60–74 yr at average risk of CRC	54	FIT biennially	19/28	Pounds sterling	31.6 QALYs	−63	−99	Cost saving
			gFOBT biennially	9/15	Pounds sterling	15.4 QALYs	−35	−55	Cost saving

CRC, colorectal cancer; CRC-SPIN, Colorectal Cancer Simulated Population Model for Incidence and Natural History; FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; HSgFOBT, high-sensitivity gFOBT; LYs, life years; MISCAN, Microsimulation Screening Analysis; NR, not reported; QALYs, quality-adjusted life years; SimCRC, Simulation Model of Colorectal Cancer; yr, year or years.

[a] Includes studies published after Patel & Kilgore (2015) (for studies in the USA) or published after Lansdorp-Vogelaar et al. (2011) (for studies outside the USA).

[b] In Heitman et al. (2010), "HSgFOBT" was erroneously labelled "gFOBT (low sensitivity)". To correct this issue, the published "gFOBT" values were assigned to the "HSgFOBT" category listed in this table, and the published "HSgFOBT" values were assigned to the "gFOBT" category listed in this table.

[c] Currency conversion method: the given currency was converted into United States dollars based on the conversion rate on 1 January of the publication year.

[d] FIT with a cut-off level of 200 ng Hb/mL.

paragraph. All studies found that FOBT screening was either cost saving or below US$ 31 500 per LYG [costs were presented as published and also standardized to United States dollars of the year in which the study was published]. These results with cost estimates also showed wide variability. Screening with FIT annually had higher QALYs gained than screening with FIT biennially but required more screening resources. Strategies with wider age ranges screened also had higher QALYs gained but required more resources. The cost–effectiveness of FOBT screening has been evaluated across the world, with reports from Asia, Europe, and North America showing benefit with acceptable levels of cost. Given the wide variation in costs across countries and studies, the cost per LYG from different studies can only be compared qualitatively.

(c) Comparison of cost–effectiveness of FIT versus gFOBT

The modelling studies also estimated the cost–effectiveness (or comparative effectiveness) of FIT and gFOBT (see Section 3.4.3).

A next step is to assess whether there are optimal strategies that balance LYG and resources required. Strategies to consider are the screening test, intervals of rescreening, and age groups for screening.

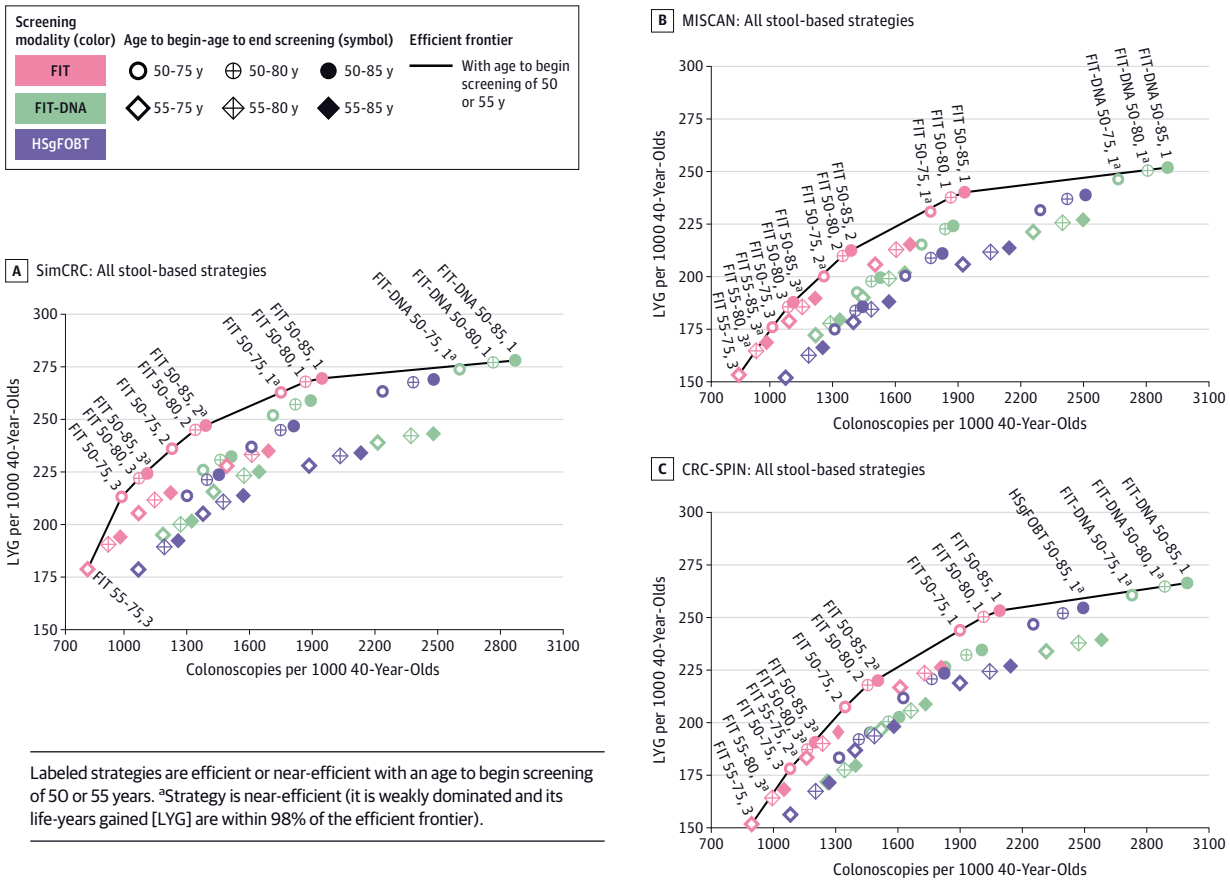
The Cancer Intervention and Surveillance Modeling Network provided a decision analysis for the USPSTF, based on three different microsimulation models (Knudsen et al., 2016), to inform the USPSTF review for different CRC screening tests in the population at average risk, starting at age 50 or 55 years and ending at age 75, 80, or 85 years for those with consistently negative screening results since starting screening. Repeat intervals of 1, 2, or 3 years were considered for FOBT. The USPSTF is not allowed to use costs per se. Instead, the number of colonoscopies for a strategy (per 1000 individuals) was used to represent costs. Fig. 3.2.1 is a comparison of LYG on the vertical axis relative to the number of colonoscopies required (per 1000 individuals aged 40 years) for the process of screening (with surveillance for patients with adenoma) over the ages screened on the horizontal axis. The line connecting the strategies on the outer envelope of data points represents strategies that provide the largest incremental increase in LYG per additional colonoscopy required for that strategy. This line is called the efficient frontier. Efficient screening strategies are on the efficient frontier, and near-efficient strategies have LYG within 98% of the efficient frontier. The strategies on the efficient frontier are all acceptable choices provided the resources required are available. Fig. 3.2.1 shows the efficient frontier for FIT and HSgFOBT screening. When evaluated together, the FIT strategies comprised almost all points on the efficient or near-efficient frontier. In addition, under the assumption of higher sensitivity and specificity of FIT relative to HSgFOBT, the FIT-based screening strategies provide more LYG for each level of colonoscopy resources across all age groups and repeat intervals. The strategy to start screening at age 50 years and end screening at age 75 years with annual FIT testing provided the optimal strategy given about 1700 colonoscopies per 1000 individuals with 25 years of screening. Note that the strategies that start screening at older ages or with longer intervals before retesting are along the curve with fewer LYG but also fewer colonoscopies required. It is a societal choice as to what resources to commit to reach a given level of LYG.

(d) Additional cost–effectiveness considerations

(i) Strategies for limited budgets

Although RCTs are considered to be the reference standard for efficacy, it is not feasible to compare multiple strategies within an RCT setting (especially in a community setting). The microsimulation modelling groups can provide virtual trials that can explore many

Fig. 3.2.1 Lifetime number of colonoscopies and life years gained for a cohort of individuals aged 40 years screened with FIT or HSgFOBT, from different microsimulation models



FIT, faecal immunochemical test.
The life years gained (LYG) and the colonoscopy burden are plotted for each screening strategy for faecal immunochemical test (FIT) and high-sensitivity guaiac faecal occult blood test (HSgFOBT), for screening starting at age 50 or 55 years and ending at age 75, 80, or 85 years, and repeat intervals of 1, 2, or 3 years. Three different microsimulation models are presented: Simulation Model of Colorectal Cancer (SimCRC), Microsimulation Screening Analysis (MISCAN), and Colorectal Cancer Simulated Population Model for Incidence and Natural History (CRC-SPIN). Strategies providing the largest incremental increase in LYG per additional colonoscopy were connected by a continuous line, thereby composing the efficient frontier. All strategies on the efficient frontier were considered efficient CRC screening options.

(Knudsen et al. (2016)).

more possible strategies based on the performance (sensitivity and specificity of advanced neoplasia) of FOBT from RCTs or observational studies. Other scenarios have also been explored with modelling for the best balance between LYG and resources in population screening. For example, in a setting where there is a limited budget that can cover only a fraction of the population, a programme of annual or biennial FIT for those aged 50–64 years would provide more LYG in a population setting compared with a one-time colonoscopy (van der Steen et al., 2015). If there is limited colonoscopy capacity to support screening, FIT could be used with a higher Hb cut-off level, to provide cost-effective strategies for a lower level of endoscopy service. However, FIT with a lower cut-off level of 10 µg Hb/g faeces is the most effective health outcome and cost compared with gFOBT (Wilschut et al., 2011).

(ii) FOBT screening in the context of new treatments

Lansdorp-Vogelaar et al. (2009) showed that as the costs for cancer care rise with increased use of newer and more expensive biological drugs, FOBT testing would be cost saving compared with no screening, because of preventing advanced cancers and deaths from CRC and avoiding costs of expensive biological drugs. Parekh et al. (2008) showed similar results.

(iii) Hybrid strategies

Early on in the development of CRC screening, Eddy (1990) suggested a hybrid strategy using sigmoidoscopy at 5-year intervals with FOBT annually, although this hybrid approach is not used very frequently in practice. More recently, Whyte et al. (2012) suggested starting with sigmoidoscopy at age 55 years and with biennial FIT at age 60 years as an effective and cost-effective strategy for the United Kingdom.

Dinh et al. (2013) suggested a screening strategy of annual or biennial FIT starting at age 50 years and a single colonoscopy at age 66 years as a favourable strategy for population screening. Knudsen et al. (2012) determined that those with a negative colonoscopy at age 50 years could be followed up with annual HSgFOBT or annual FIT with approximately the same benefit as rescreening at 10 years with colonoscopy.

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3.3 Endoscopic methods

3.3.1 Techniques

(a) Introduction

The endoscopic methods for CRC screening use flexible cameras to directly visualize the rectum and colon. These techniques have five primary roles within the CRC screening process: (i) primary screening; (ii) follow-up of other abnormal screening tests (diagnosis); (iii) removal of precancerous lesions (prevention); (iv) removal of early cancers (treatment); and (v) long-term follow-up of patients who are at high risk because of previous neoplasms or increased individual risk (surveillance) (Tiro et al., 2014). Although these roles differ substantially in concept, they are similar with respect to equipment, expertise of personnel, quality control, screening performance, and the host factors that affect the examination. In this section, these concepts are summarized for the two main endoscopic techniques for CRC screening: sigmoidoscopy and colonoscopy.

(b) Endoscopic techniques for CRC screening

Sigmoidoscopy and colonoscopy are the two primary endoscopic techniques for CRC screening.

Sigmoidoscopy is the insertion of an endoscopic camera, typically flexible, for examination of the rectum and sigmoid colon; it can also potentially evaluate the descending colon, splenic flexure, and distal transverse colon. The process includes insertion of the scope into the anus, injection of air through the scope to expand the intestinal lumen and allow better visualization (also called insufflation), and passage of the scope to the desired extent of the examination. This is followed by gradual withdrawal of the scope. The examination of the intestinal lining for polyps and other abnormalities is performed both on insertion and on withdrawal, as is the washing and suctioning of any residual liquid. Because sigmoidoscopy is usually performed without sedation, the extent of the examination depends on patient comfort, bowel preparation, and instrument length (see Sections 3.3.1(d) and 3.3.1(f)). Sigmoidoscopy can remove smaller polyps and biopsy larger polyps; patients who are found to have precancerous polyps can be referred for colonoscopy.

The goal of colonoscopy is examination of the entire colon, from rectum to caecum. In many countries and settings, colonoscopy is commonly performed with sedation, which allows for instrument manipulation with greater patient comfort. Colonoscopy can remove small polyps and most large polyps; advanced techniques enable the removal of polyps up to several centimetres in size.

(c) Equipment and expertise of personnel

(i) Equipment

Gastrointestinal endoscopic procedures use flexible tubes with four main components: an imaging system, illumination devices, channels for passing instruments and performing suction, and mechanisms for adjusting the direction and performance characteristics of the tube (Konda et al., 2015). Scopes are provided by several different manufacturers; the primary differences are the imaging methods and the controls.

Imaging is provided through either small charge-coupled device-type camera chips or a fibre-optic bundle (Classen & Phillip, 1984). Camera chip-based units either directly detect or impute colours; these require a base unit for converting the electronic signals into images (Cho, 2015). In contrast, fibre-optic-based devices directly transmit images, although these are becoming less commonly used because of their lower optical resolution and fewer advanced imaging options compared with chip-based devices (Classen & Phillip, 1984; Cho, 2015). Numerous visualization methods have

been tested for enhancing polyp detection, such as narrow-band imaging and the use of dyes (chromoendoscopy), although none of them has convincingly increased the number of polyps detected in populations at average risk, independent of inspection time (Nagorni et al., 2012; Pasha et al., 2012; Omata et al., 2014; Bisschops et al., 2017). Several additional mechanical devices, scope designs (e.g. wide-angle viewing and multiple-screen images), and scope attachments for increasing visualization and polyp detection have been developed. Some of these may improve polyp detection; however, given their variety, an in-depth review of this topic is beyond the scope of this *Handbook*.

Illumination is provided by small light portals at the scope tip, using single or multiple sources; light sources can also be manipulated for image enhancement (Longcroft-Wheaton et al., 2012; Nagorni et al., 2012; Wallace et al., 2014). Some guidelines recommend high-definition white light endoscopes as the standard for screening, although the equipment version and imaging methods may vary by location. Continued improvements in imaging resolution are likely to further enhance screening performance. Single or multiple instrument channels within the scope allow the passage of forceps for biopsy, snares for polyp removal, devices for applying thermal current, and other tools.

(ii) Bowel preparation

A bowel preparation is needed before a sigmoidoscopy or a colonoscopy, to remove the stool and to enable adequate visualization of the colon. For bowel cleansing, it is recommended that patients have a low-residue or full-liquid diet on the day before the colonoscopy (Johnson et al., 2014); a clear liquid diet is not necessary and is associated with lower compliance.

Recommended bowel preparations before sigmoidoscopy include sodium phosphate enemas, often with an additional oral laxative, such as magnesium citrate. The combination of an oral agent and an enema is associated with a better preparation (Levin et al., 2005).

Numerous bowel preparations for colonoscopy exist, although the most effective ones include the patient receiving a dose within 4–6 hours of the colonoscopic examination (Johnson et al., 2014; Martel et al., 2015). The most common method currently used for colonoscopy is the split-dose preparation, such as with 4 litres of polyethylene glycol, in which the patient receives one half of the preparation the evening before the examination and the other half on the day of the examination. Patients who receive split-dose preparations are significantly more likely to have an adequate bowel preparation than those who receive day-before preparations (OR, 2.51; 95% CI, 1.86–3.39) (Martel et al., 2015). Patients also report being more willing to repeat a split-dose preparation than a single-dose day-before preparation. Same-day regimens may have equal effectiveness and can be considered for patients who undergo an examination in the afternoon (Johnson et al., 2014).

(iii) Expertise of personnel

Endoscopic training requires supervised education and proctoring (Adler et al., 2012; Sedlack et al., 2014). Substantial data exist on performance and training for both physician and non-physician endoscopists (Stephens et al., 2015). Competency standards have evolved from a minimum number of completed procedures to the documentation of a reliable ability to complete specific tasks (Sedlack et al., 2014; Rutter et al., 2016). Different skill levels are required for different procedures, and skill levels vary substantially. Sigmoidoscopies and colonoscopies can be completed within in-hospital settings, dedicated outpatient procedure units, and office-based settings; sigmoidoscopies, in particular, can be performed as high-volume activities. For CRC screening programmes in developed medical systems, it has been suggested that different levels of competency are required

for different procedures; at least level 1 competency is recommended to avoid otherwise unnecessary follow-up procedures to remove small polyps (Table 3.3.1) (Valori et al., 2012). Endoscopic examinations can be safely and effectively performed by both physician and non-physician endoscopists (Day et al., 2014). However, the lower direct costs of non-physician endoscopists may be offset by greater requirements for repeat examinations, specialty follow-up, and additional consultations (Stephens et al., 2015).

Requirements for endoscopy room personnel vary by the procedure performed, governmental regulations, and local practices (Dumonceau et al., 2013, 2015). At a minimum, the endoscopist should be assisted by one additional medical professional, typically a nurse or similarly certified member of personnel, responsible for patient monitoring and assisting with interruptible tasks such as biopsies. In some settings, a second assistant is routinely used, although guidelines suggest that this is required only if sustained additional technical assistance is required (Calderwood et al., 2014). Minimum competencies indicate that unlicensed personnel with sufficient initial and current training can assist with biopsies and similar procedures (Calderwood et al., 2014).

(iv) Infection control

Guidelines exist for endoscope processing, infection control, and administration of prophylactic antibiotics during procedures (Petersen et al., 2011; Jover et al., 2012; Hookey et al., 2013; Calderwood et al., 2014; SGNA Practice Committee 2013–14, 2015; Herrin et al., 2016; Son et al., 2017). These include recommendations for routine hand hygiene before patient contact; use of personal protective equipment, such as gloves, facial protection, and impervious gowns; administration of medication; and methods for handling potentially contaminated equipment (Petersen et al., 2011; Jover et al., 2012; Hookey et al., 2013; Calderwood et al., 2014; SGNA Practice Committee 2013–14, 2015; Herrin et al., 2016; Son et al., 2017).

(v) Sedation

Many colonoscopies and some sigmoidoscopies use conscious sedation according to patient preference, tolerance, and local practice (Bretthauer et al., 2016; Rees et al., 2016). Data on sedation are mainly for colonoscopies. Guidelines and training curricula exist for sedation and monitoring, although their evidence base is weak on whether routine compliance improves patient-related outcomes (Vargo et al., 2012; Dietrich et al., 2013; Calderwood et al., 2014); commonly used agents include midazolam, fentanyl, meperidine, and propofol (Dumonceau et al., 2015; Obara et al., 2015). Guidelines recommend pre-procedure evaluations of each patient's physical status, such as with the criteria established by the American Society of Anesthesiologists; the Mallampati airway classification and risk factors for sedation; intraprocedural monitoring by qualified personnel of blood pressure, respiratory rate, heart rate, and pulse oximetry; availability of medication reversal agents; and post-procedure monitoring until the patient is stabilized (Calderwood et al., 2014).

(d) Technical quality control

Several performance standards and quality measures are recommended for lower gastrointestinal endoscopy (Minoli et al., 1999; Ball et al., 2004; Rex et al., 2006, 2015; Rembacken et al., 2012; Valori et al., 2012; Rutter et al., 2016; Kaminski et al., 2017a). A recent European guideline noted 44 different performance measures, many of which evaluate processes (e.g. documentation of certain findings) rather than evidence-based factors that influence outcomes (Rees et al., 2016). Additional recommendations exist for particular techniques, such as endoscopic polypectomy and endoscopic mucosal resection (Ferlitsch et al., 2017).

Table 3.3.1 Levels of operator ability required to perform endoscopy procedures for colorectal cancer screening

Competency level	Skills required	Comments
Level 0	Operator does not remove any lesions, but refers all patients with detected lesions; lesion biopsies can be performed, with pathological results informing referral decisions.	Basic competency level for diagnostic sigmoidoscopy; not recommended for screening.
Level 1	Operator can remove lesions < 10 mm in diameter at sigmoidoscopy. Larger lesions are removed at colonoscopy. Tissue biopsy is required to decide whether colonoscopy is necessary.	People performing screening sigmoidoscopy should have this competency level.
Level 2	Operator can remove polypoid and sessile lesions < 25 mm provided the lesion is endoscopically accessible.	All colonoscopists should have this competency level.
Level 3	Operator can remove most smaller flat lesions (< 20 mm), larger sessile and polypoid lesions, and small lesions with difficult endoscopic access.	Any colonoscopists completing follow-up for positive screening results require this competency level.
Level 4	Operator can remove large flat lesions or challenging polypoid lesions that otherwise might require surgery. These lesions would not be removed at the first colonoscopy, because of time constraints or because of the need for discussion of surgical options.	This competency level is expected only among a small number of referral, regionally-based colonoscopists.

Adapted with permission from © Georg Thieme Verlag KG (Valori et al., 2012).

The three main measures of endoscopy quality that are clearly associated with patient outcomes are completion of the examination to the minimum desired extent, thoroughness of the endoscopic inspection, and adequacy of bowel preparation (see also Section 3.3.1(f)) (Minoli et al., 1999; Ball et al., 2004; Rex et al., 2006, 2015; Rembacken et al., 2012; Valori et al., 2012; Rutter et al., 2016; Kaminski et al., 2017a). The minimum desired extent of the examination is the junction of the sigmoid and the descending colon for sigmoidoscopy (Atkin et al., 2002), and the caecum for colonoscopy. The actual proximal extent achieved for most sigmoidoscopies is not precisely defined, given the ambiguity of landmarks, and is often considered the maximum tolerated scope insertion distance, or approximately 60 cm of scope length (Painter et al., 1999; Weissfeld et al., 2000). The caecum is identified using the appendiceal orifice, ileocecal valve, and caecal sling fold (a combination of muscular folds around the appendix) (Rex et al., 2015).

The most validated measurement of the thoroughness of endoscopic inspection is the adenoma detection rate (ADR) of the physician. The physician ADR is the percentage of the physician's examinations in which one or more adenomas are detected (Rex et al., 2006). Reported ADRs varied from less than 10% to more than 60% among reports from both academic and community-based colonoscopy providers (Hixson et al., 1990; Rex et al., 1997, 2006; Bretthauer et al., 2003; Hosokawa et al., 2003; Schoen et al., 2003; Atkin et al., 2004; Bressler et al., 2004; Leaper et al., 2004; Pickhardt et al., 2004; Sanchez et al., 2004; Barclay et al., 2006; Chen & Rex, 2007; Corley et al., 2011, 2014; Jensen et al., 2015) and from 8.6% to 15.9% for sigmoidoscopy in the United Kingdom Flexible Sigmoidoscopy Screening Trial (UKFSST) (Atkin et al., 2004). The prevalence of adenomas is higher with increasing patient age and is higher in men than in women, but no large differences in prevalence exist between racial or ethnic groups (Corley et al., 2013). Adjusting for differences in patient demographics only modestly influenced the overall variability in physician ADRs in a large community-based setting (Jensen et al.,

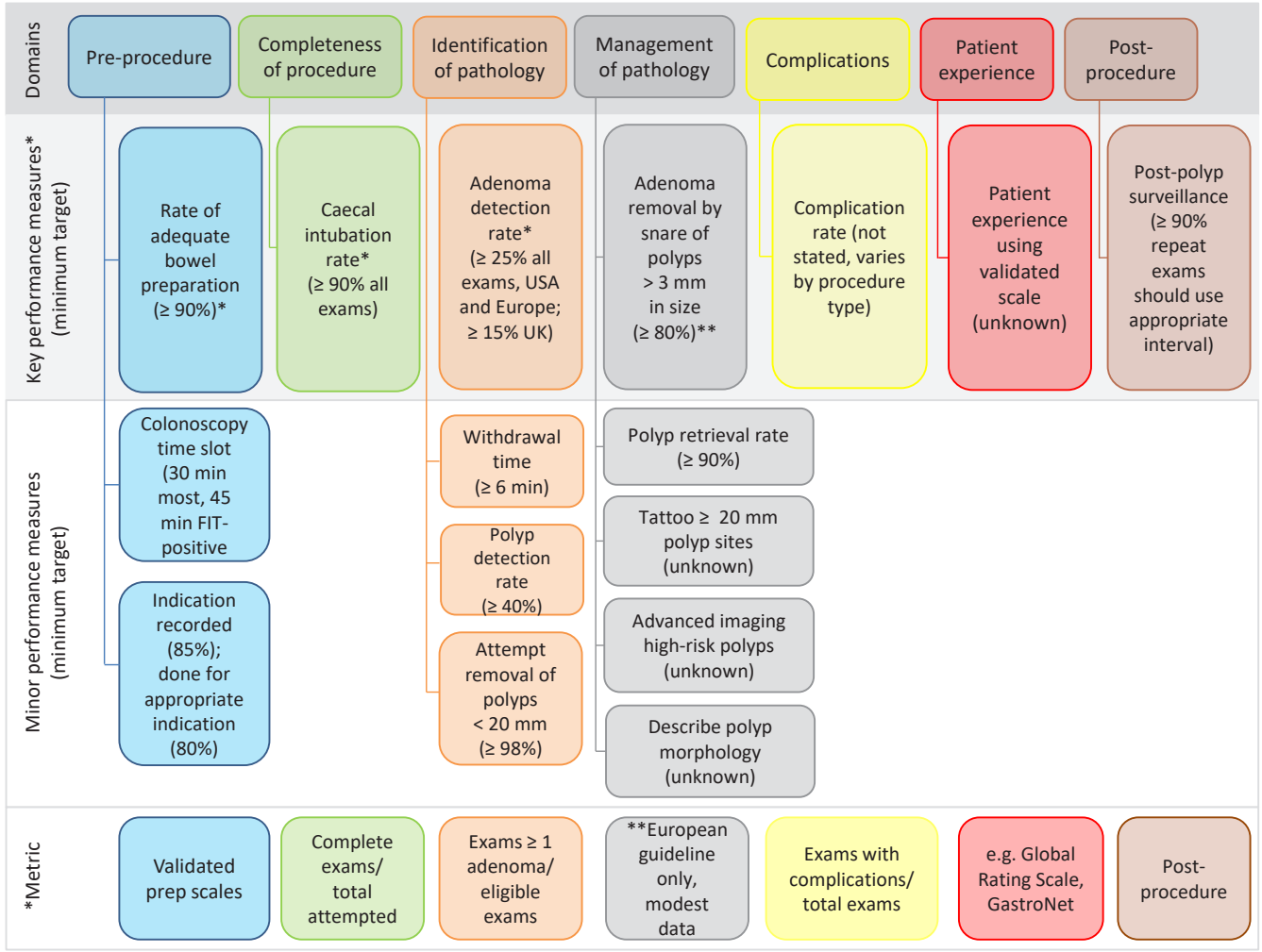
2015). Therefore, physician ADR appears to vary with physician-related factors during endoscopic inspection, rather than patient-related factors.

Variation in physician ADR is strongly inversely associated with patients' subsequent CRC outcomes for both colonoscopy and sigmoidoscopy. Studies in large populations in Europe and the USA demonstrated substantially lower future risks of post-colonoscopy CRC and death from CRC in patients of physicians with higher ADRs than in patients of those with lower ADRs (Kaminski et al., 2010; Rogal et al., 2013; Corley et al., 2014); a similar analysis for sigmoidoscopy demonstrated higher risks of post-sigmoidoscopy distal CRCs in patients of providers with lower ADRs. A community-based study demonstrated that each absolute increase of 1% in a physician's ADR was associated with 3% and 5% decreases in their patients' risks of future CRC (HR, 0.97; 95% CI, 0.96–0.98) and death from CRC (HR, 0.95; 95% CI, 0.94–0.97), respectively (Corley et al., 2014). A complementary modelling study estimated that lifetime risks of CRC incidence and mortality decreased by 11–13% for every 5% increase in ADR, translating to 53–60% lifetime differences between the lowest and the highest ADR quintiles (Meester et al., 2015). Variation in ADR could be associated with approximately one third of the total estimated mortality benefit from screening, compared with no screening (Meester et al., 2015). Improvements in ADR over time have also been associated with fewer deaths from CRC (Kaminski et al., 2017b). The physician ADR may have a comparably large influence on FIT-based screening programmes, because colonoscopy is required for follow-up after a positive FIT result. In response to these collective findings, minimum target ADRs recommended in quality guidelines for screening colonoscopy were recently increased to 25% (or from 15% to 20% for women and from 25% to 30% for men) (Rex et al., 2015), and ADR was adopted by the United States Centers for Medicare & Medicaid Services as a quality measure (Centers for Medicare & Medicaid Services, 2017). The polyp detection rate can be a surrogate for ADR if pathology data are not readily available (Williams et al., 2012; Patel et al., 2013). Fewer data exist on ADR guidelines for sigmoidoscopy; the United Kingdom Joint Advisory Group recommends a minimum ADR of 10% for sigmoidoscopy (Valori & Barton, 2007). The relative paucity of recommendations for sigmoidoscopy is partly due to the fact that sigmoidoscopy has a less standardized extent of examination, which influences polyp detection rate (Segnan et al., 2007; Fracchia et al., 2010). Cumulatively, these findings and recommendations indicate that measures to increase ADR at either the patient level (e.g. adequate bowel preparation) or the provider level are appropriate targets for ADR interventions for both sigmoidoscopy and colonoscopy providers.

Incomplete resection of precancerous polyps is also likely to influence patients' risk of post-colonoscopy CRC, although it is difficult to calculate the effect magnitude versus such cancers arising from undetected or new polyps (Erichsen et al., 2013; Pohl et al., 2013; Samadder et al., 2014; Pullens et al., 2015). In one recent study, approximately one third of post-colonoscopy cancers were in the same colorectal segment (e.g. ascending colon or transverse colon) as a previously resected adenoma (Belderbos et al., 2017). To decrease the risk of incomplete removal, a guideline recommends snare removal (instead of biopsy forceps) for polyps larger than 3 mm, although the recommendation's evidence base is modest, particularly for relatively small polyps such as those 4–6 mm in size (Lee et al., 2013; Kim et al., 2015).

Although this was not explicitly stated by the guidelines, many of the listed metric methods are readily adaptable to measuring the quality of sigmoidoscopy, but few data are available to support metrics for sigmoidoscopy (Fig. 3.3.1). Performance guidelines for sigmoidoscopy focus primarily on technical skills, such as threshold limit of complications (Rees et al., 2016) and

Fig. 3.3.1 Recommended quality and performance measures for colonoscopy



FIT, faecal immunochemical test; min, minutes.
Data from the European working group (Valori et al., 2012; Kaminski et al., 2017a), United States (Levin et al., 2005), and United Kingdom guidelines (Rees et al., 2016), and with reference scales/metrics for bowel preparation (Aronchick et al., 1999; Rostom & Jolicoeur, 2004), procedure indication (American Society for Gastrointestinal Endoscopy, 2000; Juillerat et al., 2009), and patient experience (Breivik et al., 2000; Skovlund et al., 2005).

completion of a minimum number of examinations to a depth of at least 50 cm (JAG, 2004; Enns et al., 2008), although even the definition of a complete sigmoidoscopy, based on clinically important outcomes, was not fully specified by an international working group (Levin et al., 2005).

(e) Performance of screening endoscopy

The goals of screening are to detect CRC (early detection) and to remove precancerous polyps (cancer prevention). Therefore, the performance of screening endoscopy is the ability of the examination to detect CRC and to remove precancerous polyps.

The performance of sigmoidoscopy, particularly for proximal colon cancer, depends in part on the threshold for referral to colonoscopy, as regards polyp characteristics. Colonoscopy referral criteria used by some recent RCTs included (i) any polyp or mass (Prostate, Lung, Colorectal, and Ovarian [PLCO] Cancer Screening Trial in the USA; biopsies not routinely performed); (ii) any CRC, polyp > 5 mm in diameter, ≥ 3 adenomas, or any adenoma with high-grade dysplasia or villous histology (Screening for Colon and Rectum [SCORE] trial in Italy); (iii) any CRC, any adenoma, or any polyp > 10 mm (Norwegian Colorectal Cancer Prevention [NORCCAP] trial); and (iv) any CRC, any polyp > 10 mm, any polyp with tubulovillous or villous histology, or ≥ 3 adenomas (UKFSST) (Castells et al., 2013; Holme et al., 2017). A comparison of the latter three strategies suggested that for the goal of detecting an advanced adenoma or an invasive cancer of the proximal colon with colonoscopy, the NORCCAP trial criteria provided the greatest sensitivity, whereas the UKFSST criteria provided the lowest number of people needed to refer to colonoscopy per advanced proximal neoplasm detected (Castells et al., 2013).

Comprehensive summaries estimated that the sensitivity of endoscopy, within the examined segments, was approximately 95% for the detection of CRC; these estimates are derived mainly from tandem colonoscopy studies, in which a patient underwent two examinations. The estimated sensitivity of endoscopy for the detection of adenomas varied by polyp size: 95% for adenomas ≥ 10 mm, 85% for adenomas of 6–9 mm, and 75% for adenomas of 1–5 mm (van Rijn et al., 2006). The sensitivity of colonoscopy for the detection of proximal colorectal polyps may be somewhat lower, although the absence of a reference standard for identifying difficult-to-see sessile lesions complicates these sensitivity calculations. An RCT of a standard inspection of the proximal colon followed by either an additional inspection in retroflexion or a second forward-view examination demonstrated overall ADRs of 47% and 47%, respectively, and found that at least one additional adenoma was detected on second withdrawal in similar proportions (7.5% with retroflex and 10.5% with repeat forward view) (Kushnir et al., 2015). Sigmoidoscopy has similar assumed performance characteristics for lesions within reach of the examination (e.g. within 50 cm) (Knudsen et al., 2016).

Direct comparisons of the yields of sigmoidoscopy and colonoscopy are difficult, given that the typical sigmoidoscopy can inspect from the rectum up to the mid-sigmoid colon or, less commonly, the distal transverse colon. A multicentre colonoscopy trial estimated that of 3121 people who underwent a colonoscopy, 37.5% had ≥ 1 neoplastic lesion anywhere in the colon, and 329 (10.5%) had an advanced neoplasia/adenoma (≥ 10 mm, villous histology, high-grade dysplasia, or cancer). Of the 329 patients with an advanced neoplasia, in 128 it was proximal to the splenic flexure (the typical maximum extent of a sigmoidoscopy) and in 228 it was distal to the splenic flexure. The likelihood that the advanced proximal neoplasia would have been detected if the patients were initially screened with sigmoidoscopy was estimated, using the assumption that a full colonoscopy would be performed for

any distal colon adenoma. Of the patients with an advanced proximal neoplasia, 48.4% (62 of 128) had ≥ 1 distal colon adenoma (Lieberman et al., 2000). Therefore, a sigmoidoscopy screening strategy would presumably detect a large majority of distal advanced adenomas and, when a distal advanced adenoma is detected, lead to a colonoscopic examination of the proximal colon. However, these results may be due to the fact that most of the study population in the trial were men (n = 3021), in whom the prevalence of advanced adenoma and invasive cancer of the colon and the rectum was higher than that in adults at average risk (Heitman et al., 2009). The relative effects of sigmoidoscopy versus colonoscopy on small adenomas and sessile adenomas were less clear.

The ability of sigmoidoscopy and colonoscopy to distinguish between cancerous and non-cancerous lesions depends largely on pathology, which has moderate interobserver variability for villous, dysplastic (Costantini et al., 2003; Mahajan et al., 2013; Osmond et al., 2014), and malignant features, and for identifying serrated polyps and adenomas versus non-adenomas (Turner et al., 2013; Schachschal et al., 2016); interobserver variability includes differences between pathologists within the same country and differences in interpretation between countries (Schlemper et al., 1998). Classification methods based solely on the endoscopic appearance of polyps have been proposed to enable more selective pathological confirmation, but these are currently not widely used.

(f) Host factors that affect screening performance

The primary host factors that influence screening performance are the patient's ability to complete the examination and the quality of the bowel preparation. Patient factors associated with inadequate bowel cleansing include a history of constipation, inability to complete the bowel preparation (primarily because of nausea), and use of neuroleptic or antidepressant medications (Hautefeuille et al., 2014). Other factors related to incomplete sigmoidoscopy and colonoscopy include older patient age, female sex, and previous abdominal or pelvic surgery (Ramakrishnan & Scheid, 2003; Shah et al., 2007; Laiyemo et al., 2012).

Bowel preparation is central to screening performance for both sigmoidoscopy and colonoscopy. For colonoscopy, adenoma detection is substantially reduced among patients with inadequate bowel preparations, for both non-advanced adenomas (OR, 0.53; 95% CI, 0.46–0.62) and advanced adenomas (OR, 0.74; 95% CI, 0.62–0.87) (Sulz et al., 2016). However, bowel preparation represents a continuum, and how different levels of preparation influence adenoma detection is less certain. A recent data synthesis of different levels of bowel preparation found, when comparing low-, intermediate-, and high-quality bowel preparations, an absolute increase of 5% in colonoscopy ADRs for both intermediate- and high-quality preparations, compared with low-quality preparation (OR, 1.39; 95% CI, 1.08–1.79 for intermediate quality; OR, 1.41; 95% CI, 1.21–1.64 for high quality), but no large differences were found between intermediate- and high-quality preparations (Clark et al., 2014). Therefore, for patients who undergo routine screening or surveillance examinations with "inadequate" preparations, it is recommended that the examination should be repeated within 1 year (Johnson et al., 2014).

Patient education may improve the quality of the bowel preparation. A meta-analysis of RCTs of patient education measures suggested that a brief information or counselling session significantly improved the adequacy of bowel preparation (RR, 1.22; 95% CI, 1.10–1.36), with a marginal trend towards decreasing the likelihood of needing a repeat colonoscopy (RR, 0.52, CI, 0.25–1.04) (Chang et al., 2015). Similar findings were noted for a greater likelihood of an adequate bowel preparation among those receiving "enhanced" instructions, consisting

of both verbal and written information, versus written information alone (OR, 2.35; 95% CI, 1.65–3.35) (Guo et al., 2017).

3.3.2 Randomized controlled trials

(a) RCTs of sigmoidoscopy

Four RCTs of sigmoidoscopy with CRC mortality and/or CRC incidence as end-points have been published. Note that this excludes one very small trial with 799 total subjects randomized (Thiis-Evensen et al., 1999a). Table 3.3.2, Table 3.3.3, Table 3.3.4, and Table 3.3.5 describe the design and findings of the four RCTs.

(b) Descriptions of RCTs

(i) PLCO trial

The PLCO trial in the USA examined screening for four different cancers (Schoen et al., 2012). In 1993–2001 at 10 screening centres, subjects aged 55–74 years were individually randomized to either an intervention arm or a usual-care arm. All subjects provided informed consent, with consent generally before randomization. Subjects in the intervention arm were offered screening for CRC, lung cancer, and either prostate cancer (men) or ovarian cancer (women). For the CRC screening component, subjects were offered sigmoidoscopy at baseline and either at 3 years (for those who were randomized before April 1995) or at 5 years. A positive sigmoidoscopy screening result was defined as the detection of a polyp or mass. Subjects with a positive screening result were referred to their health-care providers for follow-up; the PLCO trial did not dictate or perform follow-up. By trial protocol, polyps were not removed at the screening sigmoidoscopy. Subjects with adenomas (or CRC) detected on follow-up endoscopy after a positive screening result were advised not to return for the subsequent screening; they received surveillance colonoscopy in accordance with community standards.

Exclusion criteria for the PLCO trial included a history of prostate cancer, lung cancer, ovarian cancer, or CRC and current treatment for cancer. Starting in April 1995, subjects who had undergone a colonoscopy or sigmoidoscopy in the previous 3 years were also ineligible for the trial.

The primary outcome of the CRC screening component was CRC-specific mortality, with CRC incidence as a secondary outcome. Planned follow-up was for 13 years or until 31 December 2009, whichever came first.

A total of 77 445 individuals were randomized to the intervention arm and 77 455 to the usual-care arm; 50.5% of the subjects in each arm were women. In the intervention arm, 83.5% of subjects received the baseline sigmoidoscopy screen and 54.0% received the second-round screen; 86.6% of subjects received at least one sigmoidoscopy screen. The rates of positive screening results were 23.4% at the baseline screen and 23.5% at the subsequent screen. Of those with a positive screening result, 80.5% received some diagnostic follow-up within 1 year, of whom 95.6% received colonoscopy. Of all subjects in the intervention arm, 21.9% received a colonoscopy follow-up of a positive sigmoidoscopy screening result.

The use of sigmoidoscopy and colonoscopy in the usual-care arm was monitored on a sampling basis. The estimated rates of endoscopic examination during the screening phase of the trial (the first 6 years of the study) were 25.8% for sigmoidoscopy, 34.4% for colonoscopy, and 46.5% for either sigmoidoscopy or colonoscopy. An ancillary study was performed to examine the use of surveillance colonoscopy in subjects in the intervention arm who had a positive baseline screening result and had adenomas removed on the subsequent colonoscopy. After a median follow-up of 8.9 years, 79.3% of subjects with advanced adenomas, 81.9% of subjects with ≥ 3 non-advanced adenomas, and 74.2% of subjects with 1 or 2 non-advanced adenomas had received at least one post-baseline colonoscopy.

Table 3.3.2 Characteristics of randomized controlled trials on colorectal cancer screening with sigmoidoscopy

Trial Country	Randomization	Number of subjects Intervention arm/ control arm	Accrual period	Age at entry (years)	Referral protocol
PLCO USA	Individual	154 900 77 445/77 455	1993–2001	55–74	Contingent on personal physician and medical care
UKFSST United Kingdom	Individual	170 038 57 099/112 939	1994–1999	55–64	≥ 10 mm polyp, ≥ 3 adenomas, tubulovillous or villous change, severe dysplasia, malignancy
NORCCAP Norway	Individual	98 792 20 572/78 220	1999–2001	50–64	≥ 10 mm polyp, any adenoma or malignancy
SCORE Italy	Individual/ cluster[a]	34 292 17 136/17 136	1995–1999	55–64	≥ 5 mm polyp, ≥ 3 adenomas, tubulovillous or villous change, severe dysplasia, malignancy

NORCCAP, Norwegian Colorectal Cancer Prevention trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCORE, Screening for Colon and Rectum trial; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial.

[a] Cluster randomization was adopted for 3 out of 6 centres, and the unit of randomization was the physician.

(ii) UKFSST

The UKFSST was an RCT of once-only screening with sigmoidoscopy (Atkin et al., 2010). Men and women aged 55–64 years who were registered with participating general practices in the United Kingdom were eligible for the trial, provided they had no history of CRC, adenomas, or inflammatory bowel disease, had a life expectancy of at least 5 years, and had not received a colonoscopy or sigmoidoscopy in the previous 3 years. Eligible subjects (368 142) were first sent a questionnaire asking whether they would participate in an RCT of CRC screening. Those who agreed to participate were then randomized in a 2:1 ratio to the control arm or the intervention arm of the trial.

Subjects in the intervention arm underwent baseline sigmoidoscopy with polypectomy. Those with polyps meeting any of the following criteria were referred for colonoscopy: ≥ 10 mm in diameter, ≥ 3 adenomas, tubulovillous or villous histology, high-grade dysplasia, malignancy, or ≥ 20 hyperplastic polyps above the distal rectum.

Trial enrolment began in November 1994 and was completed in March 1999. A total of 170 432 individuals were randomized, and after exclusions for deaths and previous CRC, 170 038 were included in the analysis (112 939 in the control arm and 57 099 in the intervention arm); 50.0% were women. The participation rate in the baseline screening was 71%; of those screened, 5% underwent follow-up colonoscopy, of whom 85% subsequently entered a surveillance programme.

(iii) NORCCAP trial

The NORCCAP trial was an RCT of once-only screening with sigmoidoscopy (Holme et al., 2014). Men and women aged 55–64 years living in the city of Oslo or in Telemark County, Norway, were identified through population registers. In 1998, birth cohorts were randomly sampled to be invited to the screening arm or included in the control arm; subjects in the control arm were not contacted. In 2000, the trial was extended to include individuals aged 50–54 years. The ratios of subjects aged 55–64 years to those aged 50–54 years differed between the screening arm and the control arm; subjects in the control arm were younger than those in the screening arm. Subjects in the screening arm were further randomized in a 1:1 ratio to receive either

Table 3.3.3 Designs of randomized controlled trials on colorectal cancer screening with sigmoidoscopy

Trial	Intervention	Number of screening rounds	Screening interval	Compliance with first round (%)	Determination of end-point (for mortality)	Median duration of follow-up (years)
PLCO	Sigmoidoscopy at baseline and after 3 or 5 years	2	3 or 5 years[a]	84	Independent death review	11.9 (incidence) 12.1 (mortality)
UKFSST	Once-only sigmoidoscopy	1	N/A	71	Independent death review	17.1 (mortality)
NORCCAP	Once-only sigmoidoscopy, with or without a single FIT	1	N/A	63	Official statistics	11.2 screened (incidence) 10.9 controls (incidence)
SCORE	Once-only sigmoidoscopy	1	N/A	58	Independent death review	10.5 (incidence) 11.4 (mortality)

FIT, faecal immunochemical test; N/A, not applicable. NORCCAP, Norwegian Colorectal Cancer Prevention trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCORE, Screening for Colon and Rectum trial; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial.

[a] The screening interval was 3 years for participants randomized before April 1995 and 5 years for other participants.

Table 3.3.4 Results of randomized controlled trials on colorectal cancer screening with sigmoidoscopy (intention-to-treat analyses)

Trial	Incidence			Mortality		
	Rate per 100 000 person-years		RR or HR (95% CI)	Rate per 100 000 person-years		RR or HR (95% CI)
	Intervention arm	Control arm		Intervention arm	Control arm	
PLCO	119	152	0.79 (0.72–0.85)	29	39	0.74 (0.63–0.87)
UKFSST[a]	114	149	0.77 (0.70–0.84)	30	44	0.69 (0.59–0.82)
UKFSST[b]	137	184	0.74 (0.70–0.80)	39	56	0.70 (0.62–0.79)
NORCCAP	112.6	141.0	0.80 (0.70–0.92)	31.4	43.1	0.73 (0.56–0.94)
SCORE	144.1	176.4	0.82 (0.69–0.96)	34.7	44.5	0.78 (0.56–1.08)

CI, confidence interval; HR, hazard ratio; NORCCAP, Norwegian Colorectal Cancer Prevention trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RR, relative risk; SCORE, Screening for Colon and Rectum trial; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial.

[a] Based on initial report; median follow-up, 11.2 years.

[b] Based on extended follow-up analysis; median follow-up, 17.1 years.

Table 3.3.5 Results of randomized controlled trials on colorectal cancer screening with sigmoidoscopy (per-protocol analyses)

Trial	RR or HR (95% CI)	
	Incidence	Mortality
PLCO	–	–
UKFSST[a]	0.67 (0.60–0.76)	0.57 (0.45–0.72)
UKFSST[b]	0.65 (0.59–0.71)	0.59 (0.49–0.70)
NORCCAP	0.68 (0.56–0.86)	0.63 (0.40–1.40)
SCORE	0.69 (0.56–0.86)	0.62 (0.40–0.96)

CI, confidence interval; HR, hazard ratio; NORCCAP, Norwegian Colorectal Cancer Prevention trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RR, relative risk; SCORE, Screening for Colon and Rectum trial; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial.

[a] Based on initial report; median follow-up, 11.2 years.

[b] Based on extended follow-up analysis; median follow-up, 17.1 years.

sigmoidoscopy plus FIT at baseline or only a baseline sigmoidoscopy. All visible lesions were removed at sigmoidoscopy and subjected to histopathology; subjects with a polyp ≥ 10 mm, any adenoma or suspected CRC, or a positive FIT result were referred for colonoscopy, at which time all polyps were removed.

A total of 20 780 subjects were randomized to the screening arm and 79 430 to the control arm. After exclusions for deaths and previous CRC, 20 572 subjects were analysed in the screening arm and 78 220 in the control arm; 50.1% were women. The participation rate for screening sigmoidoscopy was 63.0%; of those screened, 19.5% attended follow-up colonoscopy and 9.8% were recommended for surveillance colonoscopy.

(iv) SCORE trial

The SCORE trial in Italy was an RCT of once-only screening with sigmoidoscopy (Segnan et al., 2002). Ineligibility criteria included a personal history of CRC, adenoma, or inflammatory bowel disease, having undergone a lower gastrointestinal endoscopy in the previous 2 years, having two or more first-degree relatives with CRC, or having a medical condition that precluded a benefit from screening. Individuals aged 55–64 years who responded to a mailed questionnaire that they certainly or probably would attend screening if offered were randomized to an intervention arm (17 148) or a control arm (17 144); 50.0% were women. In three centres (Biella, Genoa, and Milan), with 16 690 subjects, randomization was at the individual level; in the three other centres (Arezzo, Rimini, and Turin), with 17 602 subjects, cluster randomization was used, and the unit of randomization was the general practitioner. Subjects in the control arm were not contacted further. The data set for the final analysis excluded 12 subjects in the intervention arm and 8 subjects in the control arm, because of death or CRC diagnosis before randomization; therefore, it included 17 136 subjects in each arm.

Diminutive polyps (≤ 5 mm) were removed at sigmoidoscopy. Subjects with larger polyps (> 5 mm), 3 or more adenomas, adenomas with more than 20% villous component, severe dysplasia, or CRC and subjects with inadequate bowel preparation and at least one polyp were referred for colonoscopy.

Of the 17 148 individuals in the screening arm, 9999 (58.3%) attended the screening and 9911 (57.8%) were actually screened (the remaining 88 were referred for later screening because of inadequate bowel preparation but did not return for screening). After screening,

20 (0.2%) were immediately referred to surgery and 775 (8%) attended colonoscopy. Subsequent surveillance colonoscopy was indicated for 395 subjects.

(c) Effects on CRC incidence and mortality and all-cause mortality

This section summarizes findings from the RCTs on the effects of sigmoidoscopy on CRC mortality, CRC incidence, and all-cause mortality. All relative risks and hazard ratios are from intention-to-treat analyses, unless otherwise stated. For per-protocol analyses, the UKFSST and the SCORE trial reported adjusted relative risks derived using the Cuzick method (Cuzick et al., 1997). The NORCCAP trial reported per-protocol 10-year risk differences using an instrumental variable approach; these were converted to relative risks to obtain a comparable metric to that reported for the other trials. The PLCO trial did not report per-protocol analyses.

[For the SCORE trial, in the statistical methods section of the final outcome publication (Segnan et al., 2011), there is no indication that the statistical analysis took into account the cluster randomization of the three centres; the computed 95% confidence intervals seem to have been calculated from only person-years and the number of reported events.]

(i) CRC mortality

In the PLCO trial, after a median follow-up of 12.1 years, the relative risk of CRC-specific mortality was 0.74 (95% CI, 0.63–0.87) (Schoen et al., 2012). The relative risk was 0.50 (95% CI, 0.38–0.64) for distal CRC and 0.97 (95% CI, 0.77–1.22) for proximal CRC. Stratified analyses showed that the relative risk of CRC-specific mortality was 0.84 (95% CI, 0.67–1.06) for those aged 55–64 years and 0.65 (95% CI, 0.52–0.82) for those aged 65–74 years ($P_{\text{interaction}}$ = 0.11). By sex, the relative risk was 0.66 (95% CI, 0.53–0.81) for men and 0.87 (95% CI, 0.68–1.12) for women ($P_{\text{interaction}}$ = 0.10).

In the UKFSST, an initial analysis of the primary end-points, published in 2010, with a median follow-up of 11.2 years, showed a hazard ratio for CRC mortality of 0.69 (95% CI, 0.59–0.82) (Atkin et al., 2010). By anatomical location, the mortality rate ratio was 0.58 (95% CI, 0.46–0.74) for distal CRC and 0.87 (95% CI, 0.68–1.12) for proximal CRC (Lin et al., 2016b). An extended follow-up analysis was published in 2017, with a median follow-up of 17.1 years (Atkin et al., 2017). The hazard ratio for CRC mortality was 0.70 (95% CI, 0.62–0.79). The hazard ratio for CRC mortality was also reported by anatomical location: 0.54 (95% CI, 0.45–0.65) for distal CRC and 0.91 (95% CI, 0.76–1.08) for proximal CRC. The hazard ratio for CRC mortality (in the extended follow-up analysis) by age was 0.67 (95% CI, 0.55–0.81) for those aged 55–59 years and 0.72 (95% CI, 0.62–0.84) for those aged 60–64 years ($P_{\text{interaction}}$ = 0.519). By sex, the hazard ratio was 0.67 (95% CI, 0.57–0.79) for men and 0.74 (95% CI, 0.61–0.90) for women ($P_{\text{interaction}}$ = 0.417). In the per-protocol analysis (extended follow-up), the relative risk was 0.59 (95% CI, 0.49–0.70) for overall CRC mortality and 0.34 (95% CI, 0.26–0.46) for distal CRC mortality.

In the NORCCAP trial, the (age-adjusted) hazard ratio for CRC mortality was 0.73 (95% CI, 0.56–0.94) (Holme et al., 2014). The hazard ratio was 0.79 (95% CI, 0.55–1.11) for distal CRC mortality and 0.73 (95% CI, 0.49–1.09) for proximal CRC mortality. The hazard ratio for mortality did not differ significantly by subgroup of the screening arm; the hazard ratio was 0.62 for sigmoidoscopy plus FOBT and 0.84 for sigmoidoscopy alone ($P_{\text{heterogeneity}}$ = 0.20). By age group, the hazard ratios were similar for those aged 50–54 years (HR, 0.74; 95% CI, 0.40–1.35) and those aged 55–64 years (HR, 0.73; 95% CI, 0.55–0.97). By sex, the hazard ratio was 0.58 (95% CI, 0.40–0.85) for men and 0.91 (95% CI, 0.64–1.30) for women ($P_{\text{interaction}}$ = 0.10). In

the per-protocol analysis, the relative risk was 0.63 (95% CI, 0.40–1.40). [After the Working Group meeting, updated results (with a median follow-up of 14.8 years) were reported (Holme et al., 2018).]

In the SCORE trial, the median follow-up was 11.4 years for CRC mortality (Segnan et al., 2011). The relative risk of CRC mortality was 0.78 (95% CI, 0.56–1.08). The relative risk was 0.73 (95% CI, 0.47–1.12) for distal CRC and 0.85 (95% CI, 0.52–1.39) for proximal CRC. In the per-protocol analysis, the relative risk was 0.62 (95% CI, 0.40–0.96) for overall CRC mortality and 0.48 (95% CI, 0.24–0.94) for distal CRC mortality.

(ii) CRC incidence

In the PLCO trial, the relative risk of CRC incidence was 0.79 (95% CI, 0.72–0.85) (Schoen et al., 2012). The relative risk was 0.71 (95% CI, 0.64–0.80) for distal CRC incidence and 0.86 (95% CI, 0.76–0.97) for proximal CRC incidence. The relative risk of CRC incidence was similar by age: 0.78 (05% CI, 0.69–0.87) for those aged 55–64 years and 0.79 (95% CI, 0.71–0.89) for those aged 65–74 years. By sex, the relative risk was 0.73 (95% CI, 0.66–0.82) for men and 0.86 (95% CI, 0.76–0.98) for women, indicating a borderline significant interaction ($P_{\text{interaction}}$ = 0.052).

In the UKFSST, the hazard ratio for CRC incidence was 0.77 (95% CI, 0.70–0.84) in the earlier analysis (Atkin et al., 2010). The hazard ratio was 0.64 (95% CI, 0.57–0.72) for distal CRC incidence and 0.98 (95% CI, 0.85–1.12) for proximal CRC incidence (Lin et al., 2016b). In the extended follow-up analysis, the hazard ratio for CRC incidence was 0.74 (95% CI, 0.70–0.80); the hazard ratio was 0.59 (95% CI, 0.54–0.64) for distal CRC incidence and 0.96 (95% CI, 0.87–1.06) proximal CRC incidence (Atkin et al., 2017); the hazard ratios for CRC incidence were similar for those aged 55–59 years (HR, 0.74; 95% CI, 0.67–0.82) and those aged 60–64 years (HR, 0.75; 95% CI, 0.69–0.82). By sex, the hazard ratio was 0.70 (95% CI, 0.65–0.77) for men and 0.81 (95% CI, 0.73–0.89) for women ($P_{\text{interaction}}$ = 0.047). In the per-protocol analysis (extended follow-up), the relative risk was 0.65 (95% CI, 0.59–0.71) for overall CRC incidence and 0.44 (95% CI, 0.38–0.50) for distal CRC incidence.

In the NORCCAP trial, the median follow-up was 11.2 years in the screening arm and 10.9 years in the control arm (Holme et al., 2014). The (age-adjusted) hazard ratio for CRC incidence was 0.80 (95% CI, 0.70–0.92). The hazard ratio was 0.76 (95% CI, 0.63–0.92) for distal CRC incidence and 0.90 (95% CI, 0.73–1.10) for proximal CRC incidence. The hazard ratio for CRC incidence did not differ significantly by subgroup of the screening arm; the hazard ratio was 0.88 for sigmoidoscopy plus FIT and 0.72 for sigmoidoscopy alone ($P_{\text{heterogeneity}}$ = 0.11). By age group, the hazard ratio for CRC incidence was 0.68 (95% CI, 0.49–0.94) for those aged 50–54 years and 0.83 (95% CI, 0.71–0.96) for those aged 55–64 years ($P_{\text{interaction}}$ = 0.27). By sex, the hazard ratio was 0.73 (95% CI, 0.60–0.89) for men and 0.87 (95% CI, 0.72–1.06) for women ($P_{\text{interaction}}$ = 0.26). In the per-protocol analysis, the relative risk of CRC incidence was 0.68 (95% CI, 0.56–0.86). [After the Working Group meeting, updated results (with a median follow-up of 14.8 years) were reported (Holme et al., 2018).]

In the SCORE trial, the median follow-up was 10.5 years for CRC incidence (Segnan et al., 2011). The relative risk of CRC incidence was 0.82 (95% CI, 0.69–0.96). The relative risk was 0.76 (95% CI, 0.62–0.94) for distal CRC incidence and 0.91 (95% CI, 0.69–1.20) for proximal CRC incidence. By age group, the relative risk was 0.84 (95% CI, 0.67–1.06) for those aged 55–59 years and 0.79 (95% CI, 0.62–1.00) for those aged 60–64 years. By sex, the relative risk was 0.88 (95% CI, 0.71–1.09) for men and 0.72 (95% CI, 0.55–0.96) for women. In the per-protocol analysis, the relative risk was 0.69 (95% CI, 0.56–0.86) for overall CRC incidence and 0.60 (95% CI, 0.46–0.80) for distal CRC incidence.

(iii) All-cause mortality

In the UKFSST, the hazard ratio for all-cause mortality was 0.97 (95% CI, 0.94–1.00) in the earlier analysis and 0.99 (95% CI, 0.97–1.01) in the extended follow-up analysis (Atkin et al., 2010, 2017).

In the NORCCAP trial, the relative risk of all-cause mortality was 0.97 (95% CI, 0.93–1.02) (Holme et al., 2014).

In the SCORE trial, all-cause mortality rates were reported as 660.26 per 100 000 person-years in the control arm and 640.96 per 100 000 person-years in the intervention arm, based on 1233 deaths in the control arm and 1202 deaths in the intervention arm (Segnan et al., 2011). [From these mortality rates and numbers of deaths, the relative risk is 0.75 (95% CI, 0.55–1.02).]

In the PLCO trial, the numbers of deaths from all causes excluding cancers of the colorectum, prostate, ovary, and lung were reported as 9138 in the intervention arm and 9286 in the control arm (Schoen et al., 2012). [Using the number of deaths from CRC (252 in the intervention arm and 341 in the control arm) and the total person-years for mortality, the relative risk of mortality from all causes excluding cancers of the lung, ovary, and prostate is 0.98 (95% CI, 0.95–1.01).]

(iv) Meta-analyses and pooled analyses of RCTs of sigmoidoscopy

Several meta-analyses of RCTs of sigmoidoscopy have been performed using the results from the four RCTs described above (PLCO, UKFSST, NORCCAP, and SCORE) (Fitzpatrick-Lewis et al., 2016; Lin et al., 2016a, b; Tinmouth et al., 2016). None of these included the updated findings of the UKFSST. Another meta-analysis, performed as a Cochrane systematic review (Holme et al., 2013), included only preliminary findings from the NORCCAP trial, with 7 years of follow-up, compared with the 11 years of follow-up used in the later NORCCAP publication; therefore, quantitative estimates from that meta-analysis are not included here. However, the trial ratings from Holme et al. (2013), as well as those from Lin et al. (2016a), are summarized below.

The Cochrane review (Holme et al., 2013) examined six potential factors related to risk of bias in the trials: random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. For three of the four RCTs (UKFSST, NORCCAP, and SCORE), the risk of bias was rated as low for all factors; for the PLCO trial, the risk of bias was rated as low for all factors except selective reporting, which was rated as unclear risk. Lin et al. (2016a) evaluated each trial for overall quality using criteria developed by the USPSTF. All four trials were rated as of fair quality.

The meta-analyses differed quantitatively with respect to several minor factors (Table 3.3.6). In addition, two (Fitzpatrick-Lewis et al., 2016; Lin et al., 2016b) of the three analyses did not adjust for age in the NORCCAP trial (i.e. they used the unadjusted instead of the adjusted relative risks). This had a relatively small effect on the final relative risk estimates for CRC incidence and mortality but a larger relative effect on all-cause mortality. [Because subjects in the screening arm were (by design) older than subjects in the control arm in the NORCCAP trial, not adjusting for age in the NORCCAP trial in a meta-analysis severely biased the overall relative risk estimate against finding an overall mortality reduction in the screening arm versus the control arm. Therefore, the results for all-cause mortality in the meta-analyses that did not adjust for age in the NORCCAP trial are not valid.]

For CRC mortality, the results for the three meta-analyses were similar, with combined relative risk estimates ranging from 0.72 (95% CI, 0.65–0.80) to 0.74 (95% CI, 0.67–0.83). Two of the meta-analyses (Lin et al., 2016b; Tinmouth et al., 2016) examined CRC incidence, with combined

Table 3.3.6 Meta-analyses of randomized controlled trials on colorectal cancer screening with sigmoidoscopy, by outcome

Outcome measure	Reference	Number of trials included[a]	Control arm		Screening arm		RR (95% CI)
			Population (PYs)	Number of events	Population (PYs)	Number of events	
CRC incidence	Tinmouth et al. (2016)	4	285 758 (3 067 081)	4579	172 264 (1 860 990)	2218	0.78 (0.74–0.83)
CRC incidence	Lin et al. (2016b)[b]	4	(3 067 081)	4497	(1 860 990)	2222	0.79 (0.75–0.85)
Distal CRC incidence	Lin et al. (2016b)[b]	4	(3 068 922)	2680	(1 862 062)	1154	0.71 (0.64–0.82)
Proximal CRC incidence	Lin et al. (2016b)[b]	4	(3 071 386)	1755	(1 862 971)	1034	0.92 (0.84-1.02)
CRC mortality	Tinmouth et al. (2016)	4	285 758 (3 114 546)	1321	172 264 (1 902 184)	576	0.72 (0.65–0.80)
CRC mortality	Lin et al. (2016a)[b]	4	(3 114 546)	1391	(1 902 184)	609	0.73 (0.66–0.82)
CRC mortality	Fitzpatrick-Lewis et al. (2016)[b,c]	4	285 752	1292	161 963	547	0.74 (0.67–0.83)
Distal CRC mortality	Lin et al. (2016b)[b]	4	(3 114 546)	702	(1 902 184)	253	0.63 (0.49–0.84)
Proximal CRC mortality	Lin et al. (2016b)[b]	4	(3 114 546)	529	(1 902 184)	295	0.90 (0.77–1.04)
All-cause mortality[d]	Tinmouth et al. (2016)	4	285 758 (3 114 546)	32 903	172 264 (1 902 184)	19 525	0.97 (0.96–0.99)
All-cause mortality[d]	Lin et al. (2016a)[b]	3	(2 243 271)	22 774	(1 030 254)	10 166	1.00 (0.94–1.06)
All-cause mortality[d]	Fitzpatrick-Lewis et al. (2016)[b,c]	4	285 752	33 865	161 963	19 971	1.00 (0.96–1.04)

CI, confidence interval; CRC, colorectal cancer; NORCCAP, Norwegian Colorectal Cancer Prevention trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PYs, person-years; RR, relative risk; SCORE, Screening for Colon and Rectum trial; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial.

[a] Trials included were PLCO, UKFSST, NORCCAP, and SCORE.

[b] Did not adjust for age in the NORCCAP trial.

[c] Excluded the sigmoidoscopy plus FIT subgroup in the NORCCAP trial.

[d] For PLCO, deaths from lung, ovarian, and prostate cancers were not reported; Lin et al. excluded the PLCO trial for this reason.

relative risk estimates of 0.79 (95% CI, 0.75–0.85) and 0.78 (95% CI, 0.74–0.83), respectively. With respect to all-cause mortality, the one meta-analysis that adjusted for age in the NORCCAP trial (Tinmouth et al., 2016) found a significant reduction with sigmoidoscopy in all-cause mortality, with a relative risk of 0.97 (95% CI, 0.96–0.99) (Table 3.3.6).

A pooled analysis of the PLCO, NORCCAP, and SCORE trials estimated the relative risk of CRC incidence and mortality in men and women (Holme et al., 2017). For CRC incidence, the relative risks were 0.76 (95% CI, 0.70–0.83) for men and 0.83 (95% CI, 0.75–0.92) for women. No difference in the effect of screening was seen between men younger than 60 years and those aged 60 years or older. In contrast, screening reduced the incidence of CRC in women younger than 60 years (RR, 0.71; 95% CI, 0.59–0.84) but not significantly in those aged 60 years or older (RR, 0.90; 95% CI, 0.80–1.02). For CRC mortality, the relative risks were 0.67 (95% CI, 0.57–0.80) for men and 0.82 (95% CI, 0.67–1.00) for women. Screening reduced CRC mortality significantly in both younger and older men as well as in women younger than 60 years.

(d) Colonoscopy

There are currently four trials under way of screening colonoscopy versus FIT and/or no screening: one in Spain; one in Sweden; one in the Netherlands, Norway, and Poland; and one in the USA (Robertson et al., 2015). To date, there are no reported results on CRC incidence or mortality from these trials.

3.3.3 Observational studies on preventive effects of endoscopy

The observational studies that fulfilled the two Working Group criteria (see Section 3.1) and were included in the cited systematic review (Brenner et al., 2014a) and/or found separately in the literature search are described in detail under cohort and case–control studies below.

(a) Sigmoidoscopy

(i) Meta-analyses

The most recent systematic review of observational studies of endoscopy (Brenner et al., 2014a) included a total of two cohort studies and seven case–control studies (published in 1992–2013) in a meta-analysis of the effectiveness of sigmoidoscopy screening. [All nine studies met the Working Group criteria except Nishihara et al. (2013), which excluded prevalent cancers at baseline (the study is reported in the tables because it is included in the meta-analysis of mortality, but it is otherwise not highlighted in the text). There was heterogeneity among the included studies, for example in the designs, in the study populations (seven in the USA, one in Canada, and one in Sweden), and in adjustment for confounders (from only sex and age up to 16 variables) in the analyses, potentially biasing the effectiveness and maximum time frames of sigmoidoscopy before CRC diagnosis or mortality from 8–25 years.] The included studies are presented in Table 3.3.7 and Table 3.3.8.

The estimated meta-risk reduction for CRC incidence (five studies) was 49% (RR, 0.51; 95% CI, 0.39–0.65), with an incidence reduction of 64% (RR, 0.36; 95% CI, 0.26–0.50) for distal CRC, compared with 24% (RR, 0.76; 95% CI, 0.65–0.90) for proximal CRC. Mortality reduction was evaluated by pooling the results from four studies including Nishihara et al. (2013). The estimated overall risk reduction for CRC mortality was 47% (RR, 0.53; 95% CI, 0.30–0.97), with a mortality reduction of 66% (RR, 0.34; 95% CI, 0.19–0.62) for distal CRC, but with no mortality reduction for proximal CRC (RR, 0.96; 95% CI, 0.74–1.23). The heterogeneity in the meta-analysis of distal CRC mortality (and overall CRC mortality) was mostly caused by the large risk reduction (79%) demonstrated in the small case–control study

Table 3.3.7 Cohort studies of colorectal cancer incidence and mortality with screening sigmoidoscopy

Reference Country	Study population	Recruitment	Age (years)	Follow-up (years)	Total number of CRCs	Adjustment	RR or HR (95% CI)
Incidence							
Blom et al. (2008)[a] Sweden	1986	Randomly from population register	59–61	9	21	Sex	RR, 0.5 (0.2–1.3)[b]
Nishihara et al. (2013)[c] USA	88 902	Nurses' Health Study and Health Professionals Follow-up Study	W, 30–55 M, 40–75	25	1512	Age, BMI, heredity, smoking, physical activity, intake of red meat, folate, calcium, total energy intake, alcohol consumption, multivitamin use, aspirin use, use of cholesterol-lowering drugs, HRT use	HR, 0.60 (0.53–0.68) after negative sigmoidoscopy D: HR, 0.44 (0.36–0.53) P: HR, 0.92 (0.77–1.11)
Mortality							
Nishihara et al. (2013)[a] USA	88 902	Nurses' Health Study and Health Professionals Follow-up Study	W, 30–55 M, 40–75	25	1512	Age, BMI, heredity, smoking, physical activity, intake of red meat, folate, calcium, total energy intake, alcohol consumption, multivitamin use, aspirin use, use of cholesterol-lowering drugs, HRT use	HR, 0.59 (0.45–0.76) D: HR, 0.31 (0.20–0.49) P: HR, 1.04 (0.73–1.48)

BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; D, distal; HR, hazard ratio; HRT, hormone replacement therapy; M, men; P, proximal; RR, relative risk; W, women.

[a] Included in meta-analyses of CRC incidence and mortality of sigmoidoscopy by Brenner et al. (2014a).

[b] Data retrieved by Brenner et al. (2014a).

[c] Not fulfilling the Working Group criteria, and the data on incidence are not included in the meta-analysis by Brenner et al. (2014a). [Included here for completeness.]

Table 3.3.8 Case–control studies of colorectal cancer incidence and mortality with screening sigmoidoscopy

Reference Country	Study population	Recruitment	Age of cases (number < 50 years)	Retrospective follow-up (years)	Total number of CRCs	Adjustments in analysis in addition to matching	Risk OR (95% CI)
Incidence							
Slattery et al. (2000)[a] USA	2257	Kaiser Permanente Medical Care Program and Utah	30–79 (80)	10	1048	Age, BMI, total energy intake, physical activity, aspirin use, NSAID use, heredity, dietary fibre, calcium, and cholesterol	M, overall: 0.6 (0.4–0.8) M, D: 0.5 (0.3–0.7) M, P: 0.7 (0.5–1.1) W, overall: 0.5 (0.3–0.8) W, D: 0.5 (0.3–0.9) W, P: 0.5 (0.3–0.9)
Newcomb et al. (2003)[a] USA	2962	Cases from SEER registry and community-based controls	20–75	16	1668	Age, sex, heredity, HRT use (women), education level, smoking, BMI, number of previous tests	D: 0.24 (0.17–0.33) P: 0.89 (0.68–1.16)
Cotterchio et al. (2005)[a] Canada	2915	Ontario Familial Colorectal Cancer Registry and population-based controls	20–74 (120)[b]	≥ 5	971	Age, sex, NSAID use, education level, BMI, heredity	0.52 (0.34–0.80) D: 0.41 (0.30–0.56) P: 0.72 (0.51–1.01)
Doubeni et al. (2013)[a] USA	980	Managed care organizations with electronic patient data	55–85	≥ 5	471	CRC tests, number of preventive health-care visits, Charlson Comorbidity Index score, socioeconomic status, heredity	0.51 (0.36–0.71) D: 0.26 (0.14–0.49) P: 0.80 (0.52–1.25)
Kahi et al. (2014) USA	2492	The VA Center for Integrated Healthcare system	Mean, 81 SD, ± 3.9	10	623	Race, NSAID use, Charlson Comorbidity Index score	0.91 (0.68–1.23) (10 yr) 0.75 (0.46–1.24) (5 yr) D and P: non-significant
Mortality							
Newcomb et al. (1992)[a] USA	262	Medical records of the Greater Marshfield Community Health Plan	< 50 – ≥ 80	10	66	Heredity, other screening tests, duration of health plan enrolment	0.21 (0.08–0.52) D: 0.05 (0.08–0.52) P: 0.36 (0.11–1.20)
Selby et al. (1992)[a] USA	1129	Kaiser Permanente Medical Care Program of Northern California	45–91	10	261	History of CRC/polyp, heredity, number of periodic health check-ups	D: 0.41 (0.25–0.69) P: 0.96 (0.61–1.50)
Scheitel et al. (1999)[a] USA	653	Mayo Clinic and Olmstead Medical Center medical record systems	45–95	10	218	Number of hospitalizations, periodic health examinations, history of polyps, heredity	1.04 (0.21–5.13)

Table 3.3.8 (continued)

Reference Country	Study population	Recruitment	Age of cases (number < 50 years)	Retrospective follow-up (years)	Total number of CRCs	Adjustments in analysis in addition to matching	Risk OR (95% CI)
Doubeni et al. (2018) USA	5207	Kaiser Permanente Northern and Southern California health-care systems	50–89	10	1747	Age, sex, race, family history, education level, health plan enrolment duration, geographical region, Charlson Comorbidity Index score, number of primary care visits, faecal occult blood testing	0.64 (0.56–0.75) D: 0.52 (0.41–0.66) P: 0.75 (0.62–0.92)

BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; D, distal; HR, hazard ratio; HRT, hormone replacement therapy; M, men; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; P, proximal; RR, relative risk; SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results Program; W, women; yr, year or years.

[a] Included in meta-analyses of CRC incidence and mortality reduction of sigmoidoscopy by Brenner et al. (2014a).

[b] Of all screening modalities evaluated, not sigmoidoscopy specifically.

by Newcomb et al. (1992); when that study was excluded, the mortality reduction was 63% for distal CRC (compared with 66% reported earlier) and 35% for overall CRC mortality (compared with 47% reported earlier).

(ii) Cohort studies

There were only two cohort studies performed in a screening setting: the study by Nishihara et al. (2013), which did not fulfil the inclusion criteria because it excluded prevalent cancers at baseline and only reported outcome measures after a negative endoscopy, and a smaller study by Blom et al. (2008) (Table 3.3.7). The study by Blom et al. (2008) was a prospective pilot study of screening sigmoidoscopy in the population at average risk. Approximately 2000 individuals aged 59–61 years were randomly selected and invited for a sigmoidoscopy examination. During follow-up, only 5 CRCs were diagnosed among participants and 16 among non-participants; the reduction in incidence was a non-significant 50%.

(iii) Case–control studies

With respect to the effect of screening sigmoidoscopy on CRC incidence, four case–control studies have been performed, all in North America (Table 3.3.8). In three of the studies (Slattery et al., 2000; Newcomb et al., 2003; Cotterchio et al., 2005), the participants were asked to report – in questionnaires or interviews – background factors and any screening examination (check-up). [The use of questionnaires adds recall bias to the bias of self-selection to screening. Another limitation of the generalizability of the three studies is that the CRC cases and controls had a wide range of ages, including relatively young individuals who did not represent an eligible screening population at average risk.]

Slattery et al. (2000) stratified by sex and demonstrated a reduction in overall CRC incidence of 40% (OR, 0.6; 95% CI, 0.4–0.8) in men and 50% (OR, 0.5; 95% CI, 0.3–0.8) in women. There was a significant reduction in incidence in men for distal CRC (OR, 0.5; 95% CI, 0.3–0.7) but not for proximal CRC (OR, 0.7; 95% CI, 0.5–1.1). In women, the reduction in CRC incidence was 50% for both distal CRC and proximal CRC (OR, 0.5; 95% CI, 0.3–0.9 for both) (Table 3.3.8).

In the population-based case–control study by Newcomb et al. (2003), screening with sigmoidoscopy was associated with a significant reduction in incidence (OR, 0.24; 95% CI, 0.17–0.33) for distal CRC, but not for proximal CRC (OR, 0.89; 95% CI, 0.68–1.16), up to 16 years of follow-up.

The study by Cotterchio et al. (2005) reported an overall incidence reduction with sigmoidoscopy of close to 50% (OR, 0.52; 95% CI, 0.34–0.80), with a strong reduction for distal CRC (OR, 0.41; 95% CI, 0.30–0.56) and a non-significant reduction for proximal CRC (OR, 0.72; 95% 0.51–1.01).

Doubeni et al. (2013) performed a case–control study of adults at average risk enrolled for at least 5 years in one of different health plans. CRC screening ascertainment was done by auditing electronic patient data files. In a population of just more than 1000 individuals, 92 case patients and 173 controls had undergone a screening sigmoidoscopy, resulting in an incidence reduction of 49% (OR, 0.51; 95% CI, 0.36–0.71) for overall CRC and of 74% (OR, 0.26; 95% CI, 0.14–0.49) for distal CRC, but no incidence reduction was found for proximal CRC (OR, 0.80; 95 CI, 0.52–1.25).

No protective effect was observed in the study by Kahi et al. (2014). The study of Kahi et al. (2014) primarily evaluated the protective effects of colonoscopy but reported non-significant associations between sigmoidoscopy and CRC incidence reduction after 5 years (OR, 0.75; 95% CI, 0.46–1.24) and 10 years (OR, 0.91; 95% CI, 0.68–1.23) of follow-up. [The figures were relatively small: only seven patients with distal CRC had undergone sigmoidoscopy in the 5-year window.]

With respect to the effect of sigmoidoscopy on CRC mortality, two relatively small, older case–control studies (with a total of 327 cases and 1064 controls) by Newcomb et al. (1992) and Selby et al. (1992) reported an association of having had a sigmoidoscopy screening examination with a decreased risk of CRC mortality, by approximately 80% (OR, 0.21; 95% CI, 0.08–0.52) for overall CRC (Newcomb et al., 1992) and by 59% (OR, 0.41; 95% CI, 0.25–0.69) for distal CRC (Selby et al., 1992). [The exposure was screening with rigid sigmoidoscopy in Selby et al. (1992).]

The association of a decreased risk of CRC mortality with sigmoidoscopy was not observed in the smaller study in the USA (Scheitel et al., 1999) (OR, 1.04; 95% CI, 0.21–5.13). Scheitel et al. (1999) found the same frequency of having had a sigmoidoscopy within 10 years of diagnosis in 218 cases (10.6%) and 435 controls (9.9%) and speculated that the low frequency could be the reason for a lack of a protective effect. In the study by Newcomb et al. (1992), the frequency of screening sigmoidoscopy was 10.6% in cases and 29.1% in controls, and in the study by Selby et al. (1992), the frequency was 8.8% in cases and 24.2% in controls.

A recently published case–control study of the effectiveness of endoscopy in a screening-eligible population in the USA (with 1747 cases and 3460 controls) (Doubeni et al., 2018) reported an overall CRC mortality reduction of 36% (OR, 0.64; 95% CI, 0.56–0.75) with sigmoidoscopy after extensive adjustment for potential confounders (e.g. matching and adjustments), with a strong preventive effect for CRC on both the distal and the proximal side of the colon (OR, 0.52; 95% CI, 0.41–0.66 for distal CRC and OR, 0.75; 95% CI, 0.62–0.92 for proximal CRC).

(b) Colonoscopy

There are few high-quality observational studies that have evaluated the preventive effects of colonoscopy screening in the population at average risk and even fewer that have evaluated incidence and mortality outcomes in current colonoscopy screening programmes. Most of the studies retrospectively evaluated colonoscopy by any indication or the quality indicators of the procedure (e.g. the ADR, which is a prerequisite for a screening programme to be effective but will not be highlighted in this section).

(i) Meta-analyses

The systematic review of observational studies of endoscopy (Brenner et al., 2014a) included three cohort studies and three case–control studies of colonoscopy (published in 2005–2014) in a meta-analysis of the effectiveness of colonoscopy screening. [All of the studies met the Working Group criteria except Nishihara et al. (2013) and Manser et al. (2012), both of which excluded prevalent cancers at baseline (included in Table 3.3.9). There was heterogeneity among the included studies, for example in the designs, in the study populations (four in the USA, one in Switzerland, and one in Germany), and in adjustment for confounders (from only 3 up to 14 variables) in the analyses, potentially biasing the effectiveness and maximum time frames of sigmoidoscopy before CRC diagnosis or mortality from 6–22 years.] The included studies are presented in Table 3.3.9 and Table 3.3.10.

The meta-estimates demonstrated a reduction of 69% (RR, 0.31; 95% CI, 0.12–0.77) in CRC incidence (five studies) and of 68% (RR, 0.32; 95% CI, 0.23–0.43) in CRC mortality (three studies) at any site. When stratified by anatomical location, the incidence reduction disappeared for either distal CRC or proximal CRC (RR, 0.21; 95% CI, 0.03–1.53 for distal CRC; RR, 0.44; 95% CI, 0.15–1.31 for proximal CRC). However, there was a mortality reduction of 82% (RR, 0.18; 95% CI, 0.10–0.31) for distal CRC and of 53% (RR, 0.47; 95% CI, 0.29–0.76) for proximal CRC.

(ii) Cohort studies

See Table 3.3.9.

Table 3.3.9 Cohort studies of colorectal cancer incidence and mortality with screening colonoscopy

Reference Country	Study population	Recruitment	Age (years)	Follow-up (years)	Total number of CRCs	Adjustment	Risk RR/absolute risk difference/ HR/SIR/SMR/OR (95% CI)
Incidence							
Kahi et al. (2009)[a] USA	715	Health-care personnel and spouses and SEER data	50–86	Median, 8	12	Age, sex, calendar year	SIR, 0.33 (0.10–0.62)
Manser et al. (2012)[a] Switzerland	22 686	Population-based colon cancer screening programme	50–80	6	214 (excluding 11 at screen)	"Baseline risk profiles" (e.g. comorbidity, BMI, family tumour history, lifestyle factors, smoking, medication, profession, symptoms)	OR, 0.31 (0.16–0.59)
Nishihara et al. (2013)[a] USA	88 902	Nurses' Health Study and Health Professionals Follow-up Study	30–75	25	1385	Age, BMI, heredity, smoking, physical activity, intake of red meat, folate, calcium, total energy intake, alcohol consumption, multivitamin use, aspirin use, use of cholesterol-lowering drugs, HRT use	HR, 0.44 (0.38–0.52) after negative colonoscopy D: HR, 0.24 (0.18–0.32) P: HR, 0.73 (0.57–0.92)
García-Albéniz et al. (2017) USA	1 355 692	Medicare beneficiaries	70–79	8	46 812	Sex, race, age, original reason for entitlement, comprehensive preventive evaluative in previous 2 yr, use of 3 preventive services in previous 2 yr, United States Census Bureau division, combined comorbidity score, chronic condition, warehouse condition, calendar month	Absolute risk difference: Age 70–74 yr: −0.42% (−0.24% to −0.63%) Age 75–79 yr: −0.14% (−0.41% to 0.16%)[b] RR[c]: [Age 70–74 yr: 0.84 (0.76–0.91)] [Age 75–79 yr: 0.95 (0.87–1.05)]
Mortality							
Kahi et al. (2009)[a] USA	715	Health-care personnel and spouses and SEER data	50–86	Median, 8	12	Age, sex, calendar year	SMR, 0.35 (0.00–1.06)
Manser et al. (2012)[a] Switzerland	22 686	Population-based colon cancer screening programme	50–80	6	214 (excluding 11 at screen)	"Baseline risk profiles" (e.g. comorbidity, BMI, family tumour history, lifestyle factors, smoking, medication, profession, symptoms)	OR, 0.12 (0.01–0.93)

Table 3.3.9 (continued)

Reference Country	Study population	Recruitment	Age (years)	Follow-up (years)	Total number of CRCs	Adjustment	Risk RR/absolute risk difference/ HR/SIR/SMR/OR (95% CI)
Eldridge et al. (2013) USA	68 531	NIH-AARP Diet and Health Study	50–71	Mean, 11	602	Age, sex, HRT use, education level, race, diabetes, heredity	RR, 0.40 (0.30–0.55)
Nishihara et al. (2013)[a] USA	88 902	Nurses' Health Study and Health Professionals Follow-up Study	30–75	25	1385	Age, BMI, heredity, smoking, physical activity, intake of red meat, folate, calcium, total energy intake, alcohol consumption, multivitamin use, aspirin use, use of cholesterol-lowering drugs, HRT use	HR, 0.32 (0.24–0.45) D: HR, 0.18 (0.10–0.31) P: HR, 0.47 (0.29–0.76)

BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; D, distal; HR, hazard ratio; HRT, hormone replacement therapy; NIH-AARP, National Institutes of Health-American Association of Retired Persons; OR, odds ratio; P, proximal; RR, relative risk; SEER, Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio; SMR, standardized mortality ratio; yr, year or years.

[a] Included in meta-analyses of CRC incidence and mortality reduction of sigmoidoscopy by Brenner et al. (2014a).

[b] Absolute 8-year risk difference of screening colonoscopy group versus no-screening group.

[c] Retrieved by personal communication.

Table 3.3.10 Case–control studies of colorectal cancer incidence and mortality with screening colonoscopy

Reference Country	Study population	Recruitment	Age of cases (number < 50 years)	Retrospective follow-up (years)	Total number of CRCs	Adjustments in analysis in addition to matching	Risk OR (95% CI)
Incidence							
Cotterchio et al. (2005)[a] Canada	2915	Ontario Familial Colorectal Cancer Registry and population-based controls	20–74 (120)[b]	≥ 5	971	Age, sex, NSAID use, education level, BMI, heredity	0.69 (0.44–1.07) D: 0.68 (0.49–0.94) P: 1.02 (0.72–1.45)
Doubeni et al. (2013)[a] USA	980	Managed care organizations with electronic patient data	55–85	≥ 5	471	CRC tests, number of preventive health-care visits, Charlson Comorbidity Index score, socioeconomic status, heredity	0.30 (0.15–0.59) D: 0.26 (0.06–1.11) P: 0.37 (0.16–0.82) 0.69 (0.44–1.07) D: 0.68 (0.49–0.94) P: 1.02 (0.72–1.45)
Brenner et al. (2014b)[a] Germany	318	Cases from hospitals and controls from population registries	50– > 80	10	43	Age, sex, county of residence, education level, heredity, smoking, BMI, NSAID use, HRT use, health screening examination	0.09 (0.07–0.13) M: 0.07 (0.05–0.12) W: 0.14 (0.08–0.23) Age ≥ 70 yr: 0.08 (0.05–0.13) Age < 70 yr: 0.11 (0.07–0.18)
Kahi et al. (2014) USA	2492	The VA Center for Integrated Healthcare system	Mean, 81.2 SD, ± 3.9	10	623	Race, NSAID use, Charlson Comorbidity Index score	0.57 (0.47–0.70) (10 yr) D: 0.45 (0.32–0.62) (10 yr) P: 0.65 (0.46–0.92) (10 yr) 0.49 (0.39–0.61) (5 yr) D: 0.36 (0.25–0.53) (5 yr) P: 0.51 (0.35–0.76) (5 yr)
Mortality							
Doubeni et al. (2018) USA	5207	Kaiser Permanente Northern and Southern California health-care systems	50–89	10	1747	Age, sex, race, family history, education level, health plan enrolment duration, geographical region, Charlson Comorbidity Index score, number of primary care visits, faecal occult blood testing	0.33 (0.21–0.52) D: 0.25 (0.12–0.53) P: 0.35 (0.18–0.65)

CI, confidence interval; CRC, colorectal cancer; D, distal; HRT, hormone replacement therapy; M, men; OR, odds ratio; P, proximal; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; W, women; y, year or years.

[a] Included in meta-analyses of CRC incidence and mortality reduction of sigmoidoscopy by Brenner et al. (2014a).

[b] Of all screening modalities evaluated, not colonoscopy specifically.

In a population-based cohort study that estimated the preventive effects of colonoscopy in elderly people [study not included in the systematic review by Brenner et al. (2014a)], approximately 1 355 000 Medicare beneficiaries in the USA were prospectively followed up for 8 years (García-Albéniz et al., 2017). In the age group 70–74 years, the risk of CRC was 2.19% (95% CI, 2.00–2.37%) in those who had a screening colonoscopy, compared with 2.62% (CI, 2.56–2.67%) in the non-colonoscopy group, i.e. an absolute risk reduction of 0.42% (CI, 0.24–0.63%) for those who had a screening colonoscopy. In the age group 75–79 years, the risk of CRC was 2.84% in the colonoscopy group and 2.97% in the non-colonoscopy group (risk difference, −0.14%; CI, −0.41% to 0.16%). [The strength of the study is the large study population and the use of Medicare data to identify screening colonoscopies. Potential confounding factors are not adjusted for, but sensitivity analyses have been performed. Only one quarter of the individuals were followed up for longer than 5.5 years; this may be insufficient to adequately evaluate the protective effects of colonoscopy screening, but it could be valid for the older population studied.]

In another cohort study in the USA, the study population was generated from a diet and health study by the National Institutes of Health that sent questionnaires to people aged 50–71 years (Eldridge et al., 2013). The primary objective was to estimate the magnitude of uncontrolled confounding in observational studies by using medical records. Colonoscopy screening demonstrated a reduction in risk of CRC mortality of 60% (RR, 0.40; 95% CI, 0.30–0.55) after a mean follow-up of 11 years (Table 3.3.9).

In a smaller follow-up study of a previous study that evaluated colonic neoplasia after a negative FOBT result (Rex et al., 1993), Kahi et al. (2009) followed up a population of approximately 700 individuals at average risk (mean age, 61 years); after a median follow-up of 8 years, 12 CRCs were diagnosed. Having had a screening colonoscopy decreased the risk of CRC incidence by 67% (SIR, 0.33; 95% CI, 0.10–0.62) and, statistically non-significantly, the risk of CRC mortality by 65% (SMR, 0.35; 95% CI, 0.00–1.06). [The study cohort did not have a concurrent control group, and observed rates of CRC incidence and mortality were compared with the expected rates from the Surveillance, Epidemiology, and End Results Program.]

(iii) Case–control studies

See Table 3.3.10.

In the study by Kahi et al. (2014) [study not included in the meta-analysis by Brenner et al. (2014a)], the protective effect of colonoscopy in reducing CRC incidence was observed for both the distal colon and the proximal colon. Kahi et al. (2014) demonstrated a 55% reduction in the incidence of distal CRC (OR, 0.45; 95% CI, 0.32–0.62) and a 35% reduction for proximal CRC (OR, 0.65; 95% CI, 0.46–0.92) in older United States veterans who had undergone a colonoscopy in the previous 10 years. The reduction in overall CRC incidence was 43% (OR, 0.57; 95% CI, 0.47–0.70). [The majority of colonoscopies were for diagnostic indications in a population of 99% men with an average age of > 80 years at diagnosis.] When estimated at 5 years, the point estimates were even lower (OR, 0.49; 95% CI, 0.39–0.61 for overall CRC; OR, 0.36; 95% CI, 0.25–0.53 for distal CRC; OR, 0.51; 95% CI, 0.35–0.76 for proximal CRC).

The study by Cotterchio et al. (2005), previously referred to among the case–control studies of sigmoidoscopy, also reported a reduction in CRC incidence in those who had undergone a screening colonoscopy. Cotterchio et al. (2005) did not observe any significant reduction in overall CRC incidence (OR, 0.69; 95% CI, 0.44–1.07) or proximal CRC incidence (OR, 1.02; 95% CI, 0.72–1.45), but observed a significant reduction (OR, 0.68; 95% CI, 0.49–0.94) in distal CRC incidence. [The study population was

relatively young (20–74 years), with few screening colonoscopies (4% in both groups).]

In a case–control study by Brenner et al. (2014b), cases were recruited from 22 hospitals in the study region of Germany and matched with controls from population registries. Standardized personal interviews were used to retrieve information on previous colonoscopy and potential confounding factors. Having had a screening colonoscopy was associated with a reduction in CRC incidence by 91% (OR, 0.09; 95% CI, 0.07–0.13). Brenner et al. (2014b) stratified by sex and age and observed an association in both men (OR, 0.07; 95% CI, 0.05–0.12) and women (OR, 0.14; 95% CI, 0.08–0.23) and in both older individuals (≥ 70 years) (OR, 0.08; 95% CI, 0.05–0.13) and younger individuals (< 70 years) (OR, 0.11; 95% CI, 0.07–0.18). [The self-reported colonoscopies and their indications were validated by medical record audits, which varied in quality, and some misclassification of indication could be present.]

In the case–control study of screening-eligible members of the Kaiser Permanente Medical Care Program in the USA, a preventive effect of colonoscopy on CRC mortality was observed for both distal CRC and proximal CRC (Doubeni et al., 2018). For the association of having had a colonoscopy within 10 years and reduced CRC mortality, the odds ratio was 0.25 (95% CI, 0.12–0.53) for distal CRC and 0.35 (95% CI, 0.18–0.65) for proximal CRC. For the association of having had a colonoscopy within 10 years and reduced overall CRC mortality, the odds ratio was 0.33 (95% CI, 0.21–0.52) (Table 3.3.10).

(c) Other measures of performance

A decreased incidence of late-stage CRC is an intermediate measure of screening effectiveness. One case–control study of the population at average risk (471 cases, 509 controls) by Doubeni et al. (2013), previously referred to, evaluated the association between colonoscopy screening and the risk of late-stage CRC. For having undergone a screening colonoscopy up to 10 years before the reference date, the odds ratio was 0.30 (95% CI, 0.15–0.59) for late-stage CRC (stage IIB–IV). Sigmoidoscopy screening was performed in 19.5% of the cases and in 34.0% of the controls, with an associated reduction in the risk of late-stage distal CRC (OR, 0.26; 95% CI, 0.14–0.49) but not of late-stage proximal CRC (OR, 0.80; 95% CI, 0.52–1.25). [The generalizability of the result of the study is limited because of its case–control design. Screening colonoscopies were relatively uncommon at the beginning of the study, and there is potential for unmeasured and unadjusted residual confounders.]

3.3.4 Adverse effects

(a) False-positive results

Screening techniques are intended for the screening of large numbers of asymptomatic individuals at average risk, and the ultimate goal is further stratification, not final diagnosis. As a result, identifying a small number of cases of cancers and/or precancerous lesions in a large population may, by necessity, result in large numbers of false-positive results.

(i) Sigmoidoscopy

The criteria for referral to colonoscopy vary widely among sigmoidoscopy-based screening strategies, because of a lack of consensus about which features of distal lesions predict the risk of advanced proximal neoplasms (Castells et al., 2013). A proportion of individuals who undergo a screening sigmoidoscopy that results in a follow-up colonoscopy will ultimately not be diagnosed with any cancerous or precancerous lesions. [Such false-positive results are not well reported in studies. Therefore, the total number and/or percentage of referrals in these studies are reported here.] The proportion of patients referred for colonoscopy ranged from 5.2% to 23.4% in the RCTs of sigmoidoscopy (Table 3.3.11).

Table 3.3.11 False-positive results[a] in randomized controlled trials on colorectal cancer screening with sigmoidoscopy

Characteristic	Trial			
	UKFSST	SCORE	NORCCAP	PLCO
Number of subjects screened	40 674	9911	12 960	64 658
Definition of positive screens	Biopsy at screen or referral for colonoscopy or surgery	Biopsy at screen or referral for colonoscopy or surgery	Referral for colonoscopy	Polyp or mass at screen
Positive screen, *n* (%)	11 268 (27.7)	1745 (17.6)	2639 (20.4)	15 150 (23.4)
Criteria for colonoscopy	≥ 10 mm polyp, ≥ 3 adenomas, tubulovillous or villous change, severe dysplasia, malignancy	≥ 5 mm polyp, ≥ 3 adenomas, tubulovillous or villous change, severe dysplasia, malignancy	≥ 10 mm polyp, any adenoma or malignancy	Contingent on personal physician and medical care
Colonoscopy referral, *n* (%)	2131 (5.2)	832 (8.3)	2639 (20.4)	15 150 (23.4)
Colonoscopy follow-up	2051 (5.0)	775 (7.8)	2524 (19.5)	11 241 (17.4)
Any distal adenoma, *n* (%)[b]	4931 (12.1)	1070 (10.8)	[2208] (17.0)[e]	4656 (7.2)
Advanced distal lesions, *n* (%)[b,c,d]	1905 (4.7)	341 (3.4)	[545] (4.2)[e]	1746 (2.7)
Distal cancer, *n* (%)	131 (0.3)	47 (0.5)	[41] (0.3)[e]	139 (0.2)
True-positives (any distal adenoma or cancer), *n*[f]	5062	1117	2249	4795
True-positives (advanced neoplasia), *n*[f]	1905	388	586	1885

NORCCAP, Norwegian Colorectal Cancer Prevention trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PPV, positive predictive value; SCORE, Screening for Colon and Rectum trial; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial.

[a] False-positive rate can be calculated as (1 – PPV)*100.

[b] For PLCO in subjects without distal cancer.

[c] For UKFSST, advanced distal lesions defined as a ≥ 10 mm polyp, ≥ 3 adenomas, tubulovillous or villous adenoma, severe dysplasia, malignancy, or ≥ 20 hyperplastic polyps above the distal rectum, as determined by screening sigmoidoscopy and associated biopsies; for SCORE, advanced distal lesions defined as a ≥ 10 mm adenoma, tubulovillous or villous adenoma, or severe dysplasia, as determined by screening sigmoidoscopy and associated biopsies; for PLCO, advanced distal lesions defined as a ≥ 10 mm adenoma, tubulovillous or villous adenoma, or severe dysplasia in rectum, sigmoid colon, or descending colon or within 50 cm of anal verge (if segment not specified), as determined by diagnostic follow-up procedures completed within 1 year of screening.

[d] For UKFSST, proximal to sigmoid colon; for SCORE, proximal to the descending colon or in the descending colon, if not detected at screening sigmoidoscopy; for PLCO, segment proximal to descending colon or more than 50 cm from anal verge (if segment not specified).

[e] For NORCCAP, proximal lesions were included.

[f] The denominator to calculate the percentage of true-positives were individuals with a positive screen regardless of whether they underwent a colonoscopy.

Adapted from Weissfel et al., Flexible sigmoidoscopy in the PLCO cancer screening trial: results from the baseline screening examination of a randomized trial, *JCNI: Journal of the National Cancer Institute*, 2005, volume 97, issue 13, pages 989–997, adapted by permission of Oxford University Press (Weissfeld et al., 2005).

Results are available online from population-based programmes in Italy (Osservatorio Nazionale Screening, 2017) and the United Kingdom (Bowel Cancer Screening Southern Programme Hub; National Health Service, 2015). In Italy, approximately 50 000 individuals aged 55 years were offered sigmoidoscopy for CRC screening for 2014, and the percentage of patients who met the criteria for referral for colonoscopy was 10.9%. The roll-out of the sigmoidoscopy programme in the United Kingdom started in 2013. In 2014, 12 of 18 screening centres of the Bowel Cancer Screening Southern Programme Hub invited individuals older than 55 years for a single sigmoidoscopy (n = 8433). On average, 5.2% of those screened were referred for colonoscopy, although some variability was observed between centres, with referral rates ranging from 2.8% to 11.5%.

(ii) Colonoscopy

False-positive results are not an issue for primary colonoscopy screening, in which, if it is appropriate, polyps can be removed during the screening procedure and no further assessment is required.

(b) Overdiagnosis

Overdiagnosis refers to the detection of cancerous or precancerous lesions that would not, in the absence of screening, have caused symptoms or death in the individual's lifetime (Esserman et al., 2014).

(i) Sigmoidoscopy

There are no publications that address overdiagnosis of CRC via sigmoidoscopy screening.

(ii) Colonoscopy

Brenner et al. (2015) estimated the probabilities of prevention of CRC, early detection of CRC, or overdiagnosis of CRC according to sex and age at screening colonoscopy. This was the first and only attempt to date to estimate overdiagnosis from a national CRC screening programme. In the analysis of Brenner et al. (2015), the proportion of overdiagnosis among CRCs detected with screening colonoscopy was 11% in men and 8% in women overall, and 7% in men and 4% in women for screening colonoscopies in individuals younger than 70 years. [The Working Group noted that the validity of their calculations depends on the validity of the assumed transition rates from adenomas to CRCs. Even a small change in these rates would result in a large change in the estimated proportion of overdiagnosis. Therefore, the Working Group considered that the level of overdiagnosis is uncertain.]

Yang et al. (2014) calculated the difference between the observed CRC incidence and an expected baseline incidence for each year from 1979 to 2009. Then, for each year, they multiplied the difference in incidence by the number of individuals aged 50 years and older in the same year. Finally, they summed the results for each year from 1979 to 2009. This was similar to the approach used by Bleyer & Welch (2012) to estimate the number of breast cancers overdiagnosed because of mammography screening. Yang et al. (2014) concluded that there is probably little overdiagnosis of CRC. [The Working Group noted that this study has little validity, because (i) it only demonstrates that the preventive effect of CRC screening is higher than the rate of overdiagnosis and (ii) it is of ecological design.]

(c) Endoscopy-related complications

Endoscopy-related complications can occur immediately or several days after the procedure. Although endoscopy services must have processes in place to identify and record adverse outcomes that occur after the patient leaves the endoscopy unit, the accurate identification of those events that occur after the patient is dismissed from the endoscopy unit is still a challenge. Late complications may still be underestimated because of underreporting.

The following complications in CRC screening with sigmoidoscopy or colonoscopy are

defined as serious: death within 30 days or hospitalization within 30 days (because of serious haemorrhage involving transfusion, or because of perforation, vagal syndrome, or peritonitis-like syndrome as a consequence of primary screening with endoscopic techniques) (Segnan et al., 2010). [Because serious harms from endoscopy other than perforation and bleeding are not routinely reported or defined, the reported rates of serious harms are of limited value.] On the basis of a few large-scale studies, the mortality rate within 30 days associated with endoscopic procedures was estimated to be 1 in 15 000 (Bacchus et al., 2016).

(i) Sigmoidoscopy

Compared with colonoscopy, sigmoidoscopy has fewer adverse effects, requires less bowel preparation, and poses a lower risk of bowel perforation (Lin et al., 2016a). Physical adverse effects of the screening procedure and of colonoscopy follow-up were reported in all the RCTs of CRC screening with sigmoidoscopy (Table 3.3.12 and Table 3.3.13, respectively) but only partly in the PLCO trial in the USA (Schoen et al., 2012). There was incomplete reporting of deaths related to the follow-up colonoscopy and surgery (Holme et al., 2013).

Lin et al. (2016a) reported harms from different CRC screening methods in pooled analysis using observational studies and RCTs. In a population at average risk, perforations from sigmoidoscopy were relatively uncommon (0.1 per 1000 procedures; I^2 = 18.4%), as were episodes of major bleeding (0.2 per 1000 procedures; I^2 = 52.2%). The risk of complications increased markedly in examinations where a polypectomy was performed. In a large prospective, multicentre study that focused on colonoscopy polypectomy, major bleeding complications occurred in 1.6% of the examinations, and the perforation rate was 1.1%. Large polyp size and distal polyp location were found to be significant risk factors for major complications (OR, 31.01; 95% CI, 7.53–128.1 for large polyp size; OR, 2.40; 95% CI, 1.34–4.28 for distal polyp location) (Heldwein et al., 2005).

Recent studies in sigmoidoscopy screening settings showed that the procedure was well tolerated by most participants (Blom et al., 2004; Viiala & Olynyk, 2007; Robb et al., 2012; Bevan et al., 2015). Robb et al. (2012) reported that the most common side-effect that reached moderate or severe levels was wind (16%); abdominal pains and cramps were the next most commonly reported side-effect (7%). Compared with men, women found the procedure more uncomfortable and had a smaller average depth of insertion, which is determined mainly by patient tolerance (Eloubeidi et al., 2003; Viiala & Olynyk, 2008).

(ii) Colonoscopy

Major complications were reported in two of the four trials of colonoscopy screening currently under way. In the Nordic-European Initiative on Colorectal Cancer (NordICC) trial (Bretthauer et al., 2016), 1 screened individual had a colonoscopy perforation at the baseline screen (0.08 per 1000 procedures), and 18 individuals developed bleeding due to polypectomy (1.5 per 1000 procedures). No deaths or other major complications related to the screening intervention occurred within 30 days after screening. A total of 51 screened individuals experienced minor vasovagal reactions during colonoscopy (4.1 per 1000 procedures). However, all complications were short-term, and none required extra measures for the patient after the procedure.

Of the major complications reported at baseline in the COLONPREV trial (Quintero et al., 2012), 12 individuals developed bleeding (2.4 per 1000 procedures) and 1 individual had a colonoscopy perforation (0.2 per 1000 procedures). Other serious adverse events were reported: 10 individuals experienced hypotension or bradycardia (2.0 per 1000 procedures), and 1 individual had desaturation (0.2 per 1000 procedures).

Three meta-analyses of population-based studies aimed at estimating complications and

risk factors for colonoscopy have been published recently (Lin et al., 2016a; Reumkens et al., 2016; Vermeer et al., 2017). In two of them, major bleeding occurred in 0.8 per 1000 procedures (Lin et al., 2016a; Vermeer et al., 2017). In contrast, Reumkens et al. (2016) reported overall post-colonoscopy bleeding in 2.4 per 1000 procedures. The perforation rate for screening or surveillance colonoscopies ranged from 0.07 per 1000 procedures to 0.4 per 1000 procedures (Lin et al., 2016a; Reumkens et al., 2016; Vermeer et al., 2017). Reumkens et al. (2016) found that perforation rates for screening or surveillance colonoscopies were about one quarter those for diagnostic examinations in symptomatic patients (0.3 per 1000 procedures vs 1.3 per 1000 procedures; $P < 0.001$), because of a population at average risk with fewer findings that required diagnostic or therapeutic interventions.

Other severe complications that require hospitalization are not consistently reported. Two studies that evaluated harms in people who received colonoscopy versus those who did not found no increased risk of myocardial infarction, cerebrovascular accident, or other cardiovascular events as a result of colonoscopy (Warren et al., 2009; Stock et al., 2013).

The risks of less serious complications, such as self-limited bleeding or abdominal pain, are less well documented than major complications after colonoscopy. One third of individuals who undergo a colonoscopy may report some gastrointestinal symptoms after the procedure (Zubarik et al., 1999; Bini et al., 2003; Ko et al., 2007). Reported symptoms include abdominal pain (10.5%), bloating (25%), self-limited gastrointestinal bleeding (3.8%), diarrhoea (6.3%), and nausea (4.0%). These symptoms generally are mild and resolve within 2 days after colonoscopy (Ko & Dominitz, 2010). Screening colonoscopy performed with conscious sedation is associated with less patient-reported abdominal discomfort compared with screening sigmoidoscopy without conscious sedation (Zubarik et al., 2002).

Findings from systematic reviews suggested similar tolerability, based on the number of minor adverse events, no difference in efficacy of bowel preparation, and no differences in the number and type of clinically significant adverse events between colon cleansing regimens (such as polyethylene glycol solution, oral sodium phosphate solution, sodium picosulfate or magnesium citrate, and enemas) (Tan & Tjandra, 2006; Belsey et al., 2007).

Complications from conscious sedation for colonoscopy are also uncommon but include respiratory depression, hypoxia, chest pain, cardiac arrhythmias, hypotension or hypertension, and vasovagal reactions (Ko & Dominitz, 2010). Sharma et al. (2007) found an overall risk of cardiopulmonary complications after colonoscopy of 1.1%.

(d) Psychosocial harms

Short-term or long-term adverse psychosocial consequences of factors related to cancer screening can occur in any phase of the screening programme. Most of the evidence about the psychological effects of being screened was derived from RCTs and was reported according to the individuals' screening results.

(i) Sigmoidoscopy

False-positive results have the potential to cause symptoms of anxiety, distress, and depression as well as changes in the overall perception of one's health status (Kirkøen et al., 2016), and therefore individuals who have had a false-positive result may be more reluctant to undergo successive screening. In results from RCTs, the psychological consequences in individuals who were found not to have advanced neoplasia have been reported to be transient (Wardle et al., 2003; Taylor et al., 2004; Miles et al., 2009; Kapidzic et al., 2012). Furthermore, the pilot study of a national screening programme for CRC in Norway showed that a positive screening result did not increase participants' levels of anxiety

Table 3.3.12 Serious adverse events from sigmoidoscopy in randomized controlled trials on colorectal cancer screening with sigmoidoscopy

Reference	Trial	Follow-up	Sigmoidoscopies *n*	Perforation *n* (%)	Bleeding *n* (%)	Mortality *n* (%)	Other serious events *n* (%)
Atkin et al. (2002)	UKFSST	30 days	40 332	1 (0.002)	12 (0.03)	6 (0.01)	Hospitalization: 12 Myocardial infarction: 2 Syncope: 95 Other 1 (pulmonary embolism)
Segnan et al. (2002)	SCORE	30 days	9911	1 (0.01)	0 (0)	NR	Other: 4 (colitis, seizure)
Gondal et al. (2003)	NORCCAP	NR	12 960	0 (0)	0 (0)	NR	Syncope: 26 Other: 1 (pulmonary embolism)
Segnan et al. (2005)	SCORE	NR	4466	NR	0 (0)	NR	Syncope: 1
Senore et al. (2011)	SCORE	30 days	1502	0 (0)	12 (0.8)	NR	Hospitalization:16 Emergency department: 2 Other: 18 (cardiovascular disease, hernia, severe pain, hypotension)
Schoen et al. (2012)	PLCO	NR	67 071	3 (0.004)	NR	NR	NR

NORCCAP, Norwegian Colorectal Cancer Prevention trial; NR, not reported; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCORE, Screening for Colon and Rectum trial; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial.
Adapted from Lin et al. (2016b).

Table 3.3.13 Serious adverse events from follow-up colonoscopy in randomized controlled trials on colorectal cancer screening with sigmoidoscopy

Reference	Trial	Recruited population	Follow-up	Colonoscopies *n*	Perforation *n* (%)	Bleeding *n* (%)	Mortality *n* (%)	Other serious events *n* (%)
Atkin et al. (2002)	UKFSST	Patients with polyps meeting high-risk criteria	30 days	2051	4 (0.2)	9 (0.4)	1 (0.05)	Hospitalization[a]: 9
Segnan et al. (2002)	SCORE	Sigmoidoscopy-positives	30 days	775	1 (0.1)	1 (0.1)	NR	0 (0)
Segnan et al. (2005)	SCORE	Sigmoidoscopy-positives	NR	332	NR	1 (0.3)	NR	Hospitalization[a]: 1
Gondal et al. (2003); Hoff et al. (2009)	NORCCAP	Sigmoidoscopy- or sigmoidoscopy/FIT-positives	NR	2 524	6 (0.2)	4 (0.2)	NR	Hospitalization[a]: 4 (0.2) Syncope: 24 (1.0)
Schoen et al. (2012)	PLCO	Sigmoidoscopy-positives	NR	17 672	19 (0.1)	NR	NR	NR
Rasmussen et al. (1999)	–	Sigmoidoscopy- or gFOBT-positives	NR	502	0 (0)	0 (0)	0 (0)	0 (0)

FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; NORCCAP, Norwegian Colorectal Cancer Prevention trial; NR, not reported; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCORE, Screening for Colon and Rectum trial; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial.

[a] Hospitalizations are not mutually exclusive from the patients with perforation and serious bleeding.

Adapted from Lin et al. (2016b).

or depression, or decrease participants' levels of health-related quality of life (Kirkøen et al., 2016).

Psychological distress derived from a true-positive screening result (i.e. being labelled as sick or at risk) should not be dismissed. Nevertheless, among participants with a positive sigmoidoscopy result, Kapidzic et al. (2012) found similar quality of life scores in those with negative or positive colonoscopy results. Possible explanations for these mainly positive effects of CRC screening in participants with a true-positive result could be that although the participants were worried about the possibility of having CRC, when polyps were detected they were also relieved that the polyps were detected early and that they would be screened regularly to prevent CRC, or when CRC was detected they were reassured because they soon underwent treatment. In the case of a false-positive screening result, the authors hypothesized that the participants were relieved because no abnormalities were found during further investigations.

Robb et al. (2012) examined changes in anxiety levels and self-rated health from before screening to follow-up among participants in a population-based sigmoidoscopy screening programme. No significant changes were found for either anxiety levels or self-reported health. Results did not differ by sex, deprivation index, ethnicity, or screening outcome, and satisfaction with the screening process was high.

In contrast, another study reported that the level of anxiety was directly correlated with levels of pain and discomfort after the procedure and was inversely related to the level of satisfaction. Better management of anxiety may lead to higher procedural comfort in procedures performed without sedation (Carter et al., 2013).

(ii) Colonoscopy

There is little evidence about adverse psychological effects of colonoscopy among the screened population as a whole (Thiis-Evensen et al., 1999b; Taupin et al., 2006).

(e) False reassurance

It has been suggested that receiving a negative screening result may cause false reassurance or have a "certificate of health" effect. False reassurance in participants who receive a negative screening result may cause them to wrongly believe that they are at lower risk of the disease, and they may therefore be less likely to engage in health-related behaviours that would lower their risk and/or be less alert to symptoms that may appear or to the need for further evaluation.

(i) Sigmoidoscopy

Short-term effects on lifestyle and health attitudes were addressed in two reports from the trial in the United Kingdom (Miles et al., 2003; Wardle et al., 2003), and no negative effects were detected. Adverse effects on lifestyle were evaluated prospectively in a randomized controlled study within the NORCCAP trial (Larsen et al., 2007). After 3 years, those who had been screened reduced their intake of fruit, berries, and vegetables, did not follow the trend of increased frequency of physical exercise seen for controls, gained more weight than controls, and did not improve their smoking habits as successfully as did the controls not invited for screening. Also, normal findings at screening (i.e. no neoplasia) were associated with a subsequent statistically significant gain in body weight compared with subjects with positive screening results. These findings persisted after adjustment for confounding factors.

(ii) Colonoscopy

No studies are available on false reassurance in colonoscopy screening.

The extent to which false reassurance plays a role in CRC screening with endoscopy remains unclear. There are no known studies that have examined the phenomenon of delayed presentation of symptoms after endoscopy screening for CRC.

(f) Time/effort and opportunity costs

For all aspects of participation in the screening process, depending on the health-care system, there are time/effort and opportunity costs (non-financial harms) for the participant, as well as potential financial harms to the participant or family or psychological harm from anticipation of future financial costs related to screening (PDQ Screening and Prevention Editorial Board, 2017).

(i) Sigmoidoscopy

There are no studies available that have aimed to address time/effort and opportunity costs derived from participating in a sigmoidoscopy screening programme.

(ii) Colonoscopy

Two small studies have examined time off from work among asymptomatic individuals undergoing colonoscopy. Ko et al. (2007) reported that 69.3% of individuals who underwent colonoscopy for CRC screening, surveillance, or follow-up of another abnormal screening result lost at least 1 day from their normal activities for the colonoscopy preparation, procedure, or recovery. About 25% of individuals reported that their family or friends lost at least 1 day from their normal activities because of the procedure. Dong et al. (2011) observed that one third of the participants who worked and who underwent midweek screening colonoscopy missed work on days in addition to the day of the procedure. Unanticipated time missed from work could increase the indirect costs of screening colonoscopy.

3.3.5 Benefit–harm ratio

In this section, the benefit–harm ratio of endoscopy screening is described. Endoscopy screening, like all other forms of screening, is associated with both benefits and harms (see Section 3.3.2, Section 3.3.3, and Section 3.3.4). It is the balance between these benefits and harms that determines whether a particular form of screening is worthwhile (see Section 3.1).

(a) Systematic review and decision modelling for USPSTF

In 2016, a systematic review (Lin et al., 2016a, b) and decision analysis (Knudsen et al., 2016) of benefits and harms of screening were published alongside the USPSTF recommendations for CRC screening. These studies provide a way to initially assess the benefit–harm ratio of endoscopy screening. The systematic review demonstrated that harms of colonoscopy were greater than those of sigmoidoscopy and may also include harms from bowel preparation and sedation (Lin et al., 2016a, b). Reported harms were mostly proportional to the number of colonoscopies performed with screening. Therefore, in the USPSTF decision analysis, the benefit–harm ratio of screening was expressed as the number of colonoscopies that needed to be performed for every life year gained. This decision analysis showed that repeated colonoscopy at ages 50 years, 60 years, and 70 years could result in 250–275 life years gained per 1000 individuals aged 40 years requiring an average of just more than four colonoscopies in a lifetime (including surveillance colonoscopies). These numbers correspond to 14.5–16.5 colonoscopies per life year gained. The efficiency ratio (i.e. the ratio of incremental colonoscopies per additional life year gained compared with a less intensive colonoscopy strategy) varied between 39 and 65 colonoscopies per life year gained.

(b) QALYs and DALYs from modelling studies

[The Working Group noted that the estimates described in this section are based on Markov models, which mostly assume that the additional adenomas detected by colonoscopy have similar progressive potential to those detected by sigmoidoscopy, and that colonoscopy screening will therefore be more effective than sigmoidoscopy screening. Therefore, all results in the following section should be interpreted with caution.]

Seventeen studies evaluated the impact of endoscopy screening on QALYs or life expectancy (Table 3.3.14). [Most of these studies were conducted in settings characterized by high background cancer incidence rate. As described in Section 3.1.5, benefit–harm ratios depend heavily on this background cancer incidence rate. Therefore, the results of these studies may not easily be transferable to settings characterized by low cancer incidence rate.] All of the studies concluded that screening influenced QALYs positively and resulted in a net gain in QALYs (Table 3.3.14). The QALYs gained for colonoscopy varied substantially, from 17 QALYs per 1000 individuals in a study in Singapore (Dan et al., 2012) to 611 QALYs per 1000 individuals in a study in Hong Kong Special Administrative Region, China (Wong et al., 2015). [The Working Group raised some doubts about the validity of this value.] For sigmoidoscopy, the net benefit of screening was slightly lower than that for colonoscopy, varying from 5 QALYs gained per 1000 individuals (Dan et al., 2012) to 124 QALYs gained per 1000 individuals (Lam et al., 2015). The wide variability in estimates can be explained partly by the age of the population to which the estimates were standardized and partly by variation in disease risk. When studies with questionable validity or young and mixed-age populations were excluded, the reported range in QALYs gained narrowed considerably, to 50–125 QALYs per 1000 individuals for colonoscopy and 65–125 QALYs per 1000 individuals for sigmoidoscopy. All of the studies consistently showed a net gain in QALYs, indicating a favourable balance between benefits and harms of CRC screening. [The Working Group placed an important caveat on these estimates: 11 studies only took the impact of CRC diagnosis on quality of life into account. The impacts of other harms of screening, such as adverse events, false-positive results, and anxiety, were not considered. Three studies did consider some other harms of screening, such as the disutility of knowledge of being an adenoma patient (Lam et al., 2015; Wong et al., 2015) or the disutility of undergoing colonoscopy and experiencing adverse effects (van Hees et al., 2014b). None of the studies considered in their estimates of QALYs the anxiety associated with screening and diagnostic follow-up or the potential negative impact of a negative screening result on an increased risk of adopting an unhealthy lifestyle.]

Of the studies that evaluated 10-yearly colonoscopy and 5-yearly sigmoidoscopy, four found higher QALYs with colonoscopy than with sigmoidoscopy (Heitman et al., 2010; Dan et al., 2012; Sharaf & Ladabaum, 2013; Kingsley et al., 2016). [As noted before, these results should be interpreted with caution because all of these models would have assumed a higher effectiveness of colonoscopy screening compared with sigmoidoscopy screening.]

Only two studies evaluated the impact of endoscopy screening on DALYs (Woo et al., 2007; Ginsberg et al., 2012) (Table 3.3.15). Both studies found endoscopy screening to result in a net decrease in DALYs, ranging from 0.3 to 10 DALYs averted for sigmoidoscopy and from 0.6 to 9 DALYs averted for colonoscopy. [However, again, only one study considered the negative impact of screening on DALYs, taking into account years of life lost because of complications of screening. Disability from adverse effects, anxiety, false-positive results, and adenoma diagnosis could not be taken into account, because disability coefficients for such events have not been established.]

Table 3.3.14 Studies measuring quality-adjusted life years gained from endoscopy screening compared with no screening

Reference	Country	Population simulated[a]	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	QALYs gained per 1000 individuals[b]	Considered disutility from screening?[c]	Comments
Ness et al. (2000)	USA	Cohort age 40 yr	100	Single colonoscopy	61–64/65–68	65–66	No	–
Tappenden et al. (2007)	United Kingdom	Cohort age 30 yr	60	Single sigmoidoscopy	20/23	27	No	Low effectiveness estimates, because young cohort at start of simulation
Heitman et al. (2010)	Canada	Cohort age 50–75 yr	68	10-yearly colonoscopy 5-yearly sigmoidoscopy	62/65 58/61	41 36	No	Low effectiveness estimates, because mixed-age cohort
Telford et al. (2010)	Canada	Cohort age 50 yr	73	10-yearly colonoscopy	81/83	120	No	Uncertain whether reported incidence/ mortality reductions pertain to 100% participation
Dan et al. (2012)	Singapore	Cohort age 50–75 yr	NR	10-yearly colonoscopy 5-yearly sigmoidoscopy	35/38 28/30	17 5	No	Low effectiveness estimates, because mixed-age cohort
Sharp et al. (2012)	Ireland	Cohort age 30 yr	39	Single sigmoidoscopy at age 60 years	4.9/7.5	6	No	Low effectiveness estimates, because young cohort at start of simulation
Barouni et al. (2012)	Islamic Republic of Iran	Cohort age 50 yr	68	10-yearly colonoscopy	76/78	119	NR	–
Dinh et al. (2013)	USA	Cohort age 50–75 yr	100	10-yearly colonoscopy	76/77	115	No	–
Sharaf & Ladabaum (2013)	USA	Cohort age 50 yr	100	10-yearly colonoscopy 5-yearly sigmoidoscopy	73/80 68/75	76 69	No	–
Ladabaum et al. (2014)	Germany	Cohort age 50 yr	100	Colonoscopy at ages 55 and 65 years	62/67	90	NR	–
van Hees et al. (2014b)	USA	Cohort age 65 yr	100	10-yearly colonoscopy	NR/NR	65	Yes	–

Table 3.3.14 (continued)

Reference	Country	Population simulated[a]	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	QALYs gained per 1000 individuals[b]	Considered disutility from screening?[c]	Comments
Lam et al. (2015)	Hong Kong SAR, China	Cohort age 50 yr	NR	10-yearly colonoscopy 5-yearly sigmoidoscopy	NR/NR	109 124	Only for being diagnosed with polyps	–
Wong et al. (2015)	Hong Kong SAR, China	Cohort age 50 yr	60	10-yearly colonoscopy	NR/NR	611	Only for being diagnosed with polyps	High QALYs, because assumed positive impact of adenoma diagnosis on quality of life
Kingsley et al. (2016)	USA	Cohort age 50 yr	38	10-yearly colonoscopy 5-yearly sigmoidoscopy	NR/60[d]	100 62	No	–
Ladabaum & Mannalithara (2016)	USA	Cohort age 50 yr	100	10-yearly colonoscopy	73/81	77	No	–
Sekiguchi et al. (2016)	Japan	Cohort age 40 yr	60	10-yearly colonoscopy	69/NR	219	NR	Questionable model validity, because incidence reduction higher than participation
Aronsson et al. (2017)	Sweden	Cohort age 60 yr	38	Single colonoscopy 10-yearly colonoscopy	NR/NR	49 56	No	–

NR, not reported; QALYs, quality-adjusted life years; SAR, Special Administrative Region; yr, year or years.

[a] Signifies the population at the start of the simulation, i.e. cohort age 50 years signifies a population of people aged 50 years that are followed up until death or a certain age, and cohort age 50–75 years signifies a population of people aged 50–75 years that are followed up until death or for a certain period.

[b] Estimates for QALYs gained depend on background cancer incidence. Therefore, estimates may not easily be transferable to low-incidence settings.

[c] "No" indicates that the studies that only incorporated the disutility of having a CRC diagnosis on quality of life; disutility of harms of screening, such as adverse events, false-positive results, and anxiety, was not considered. "Only for being diagnosed with polyps" indicates that apart from the disutility of CRC diagnosis, studies also incorporated the disutility of knowledge of being an adenoma patient. "Yes" indicates that the study also included the disutility of undergoing colonoscopy and experiencing adverse effects. None of the studies considered in their estimates of QALYs the anxiety associated with screening and diagnostic follow-up or the potential negative impact of a negative screening result on an increased risk of adopting an unhealthy lifestyle.

[d] Reported mortality reduction for 100% participation.

Table 3.3.15 Studies measuring disability-adjusted life-years averted from endoscopy screening compared with no screening

Reference	Country[a]	Population simulated[b]	Participation rate (%)	Strategy evaluated	Mortality reduction (%)	DALYs averted per 1000 individuals	Considered disability from screening?
Ginsberg et al. (2012)	South-East Asia Sub-Saharan Africa South-East Asia Sub-Saharan Africa	Population in 2005	95	10-yearly colonoscopy 10-yearly colonoscopy Sigmoidoscopy + FOBT Sigmoidoscopy + FOBT	NR	8 9 10 9	No
Woo et al. (2007)	Hong Kong Special Administrative Region, China	Female population in 2001	100	10-yearly colonoscopy 5-yearly sigmoidoscopy	41 23	0.6 0.3	Only for deaths from screening

DALYs, disability-adjusted life years; FOBT, faecal occult blood test; NR, not reported.

[a] In the WHO classification, sub-Saharan Africa and South-East Asia, including those countries with very high adult mortality and high child mortality, are referred to as AfrE and SearD, respectively.

[b] Signifies the population at the start of the simulation, i.e. cohort age 50 years signifies a population of people aged 50 years that are followed up until death or a certain age, and cohort age 50–75 years signifies a population of people aged 50–75 years that are followed up until death or for a certain period.

[The lack of consideration of disability and disutility of the harms of screening itself in the above-mentioned studies probably reflects the lack of studies assessing the impact of the screening process on quality of life. The one study that included burden of screening and diagnostic follow-up in QALYs estimates used disutility values obtained by making assumptions because estimated values are lacking.] Only one study has directly assessed the burden of colonoscopy in a time-trade-off analysis. That study suggested that the number of days of life that individuals are willing to give up to avoid having to undergo screening depends on screening status (Dominitz & Provenzale, 1997). Those who had not been screened were willing to give up a median of 91 days to avoid screening sigmoidoscopy and 183 days to avoid screening colonoscopy. However, those who had already been screened were not willing to give up any time to avoid screening, indicating that the impact of the screening examination on quality of life was negligible for those individuals. A study in Hong Kong Special Administrative Region, China, evaluated health-related quality of life after diagnosis with colorectal neoplasia (Lam et al., 2015). Interestingly, quality of life was higher in patients with adenomas than in the Hong Kong reference population. [The better quality of life in this patient group probably reflects a "healthy screenee effect": those who participate in screening are on average healthier than the average population and therefore experience better health-related quality of life.]

[The outcomes of these studies indicate the difficulty of obtaining reliable estimates of the impact of screening on quality of life, and therefore of weighing the benefits of screening against its harms.]

3.3.6 Cost–effectiveness studies

(a) Background

[Like estimates of QALYs and DALYs, cost–effectiveness estimates are based mostly on Markov models, assuming that the benefits of colonoscopy screening are larger than those of sigmoidoscopy screening. Therefore, comparative results should be interpreted with caution. Several studies have been published that assessed the cost–effectiveness of CRC screening. The majority of these studies have been conducted in high-income countries, which are often characterized by high background cancer incidence rate. As described in Section 3.1.5, cost–effectiveness estimates depend heavily on this background cancer incidence rate and local costs. Therefore, the results of these studies may not easily be transferable to other settings, such as low- and middle-income countries.]

(b) Cost–effectiveness studies and systematic reviews

The literature on this topic has been summarized in three systematic reviews that used similar methodology, in 2002, 2011, and 2015 (Table 3.3.16) (Pignone et al., 2002; Lansdorp-Vogelaar et al., 2011; Patel & Kilgore, 2015). The reviews followed a similar methodology except that the review by Lansdorp-Vogelaar et al. (2011) also included studies outside the USA. This description of the cost–effectiveness of CRC screening is based on these reviews and supplemented with individual studies published since then.

Pignone et al. (2002) included seven studies in the USA that evaluated cost–effectiveness of CRC screening with endoscopy. Six studies considered life years gained as the outcome without adjustment for quality of life. Only the study by Ness et al. (2000) considered quality of life, but it did not include disutility for the burden of screening, adverse events, and false-positive results. All of the studies found endoscopy screening to cost

Table 3.3.16 Reviews of cost–effectiveness of endoscopy screening compared with no screening

Reference	Country	Studies included	Range in cost–effectiveness ratios[a] (US$)	Cost–effectiveness analysis of COL vs SIG
Pignone et al. (2002)	USA	5 studies evaluating COL and SIG 1 study evaluating COL only 1 study evaluating SIG only	COL: 9038–22 012 SIG: cost savings, 39 359	COL dominated in 3 studies COL and SIG both cost-effective in 1 study FOBT + SIG dominated COL in 1 study
Lansdorp-Vogelaar et al. (2011)	All	12 studies evaluating COL and SIG 3 studies evaluating COL only	COL: cost savings, 31 700 SIG: cost savings, 56 600	COL dominated in 6 studies COL < US$ 100 000 per LYG compared with SIG in all studies
Patel & Kilgore (2015)	USA	6 studies evaluating COL and SIG 5 studies evaluating COL only	COL: cost savings, 27 328 SIG: cost savings, 30 671	COL dominated in 4 simulations COL < US$ 50 000 per LYG compared with SIG in 9 simulations COL > US$ 50 000 per LYG compared with SIG in 2 simulations

COL, colonoscopy; FOBT, faecal occult blood test; LYG, life year grained; SIG, sigmoidoscopy.

[a] Estimates for cost–effectiveness depend on background cancer incidence. Therefore, estimates may not easily be transferable to low-incidence settings.

less than US$ 50 000 per life year gained. One study showed that sigmoidoscopy screening could potentially even be cost saving in a dedicated screening setting (Loeve et al., 2000). For the remainder of studies, costs per life year gained varied between less than US$ 5000 and US$ 40 000 per life year gained. Three of five studies that evaluated both strategies found that colonoscopy dominated sigmoidoscopy (i.e. it was both more effective and had lower costs per life year gained). One study found both strategies to be cost-effective, and one study found that colonoscopy was dominated by the combination of sigmoidoscopy plus FOBT.

The systematic review by Lansdorp-Vogelaar et al. (2011) included 16 studies that evaluated the cost–effectiveness of sigmoidoscopy and/or colonoscopy screening. The review found wide variability in the estimated cost–effectiveness of endoscopy screening across studies. Twelve studies estimated cost–effectiveness of sigmoidoscopy compared with no screening. In two studies, sigmoidoscopy screening was found to be cost saving, whereas in one study, costs per QALY gained were as high as US$ 56 600. Sixteen studies assessed the cost–effectiveness of colonoscopy screening compared with no screening; five of the studies found colonoscopy screening to be cost saving. At a willingness-to-pay threshold of US$ 100 000 per QALY gained, all of the studies found sigmoidoscopy screening and/or colonoscopy screening to be cost-effective compared with no screening. At a threshold of US$ 50 000 per QALY gained, only one study found sigmoidoscopy screening not to be cost-effective. As expected, all of the studies that evaluated both strategies found that colonoscopy screening was more effective than sigmoidoscopy screening. Approximately half of the studies also found that colonoscopy screening cost less per QALY gained and therefore dominated sigmoidoscopy screening. For the other half of the studies, the incremental costs per life year gained for colonoscopy screening compared with sigmoidoscopy screening varied between US$ 1000 and US$ 85 000, and at a willingness-to-pay threshold of US$ 100 000 per life year gained, colonoscopy screening would be considered cost-effective.

The review by Patel & Kilgore (2015) identified 13 studies in the USA in addition to the studies included in the review of Lansdorp-Vogelaar et al. (2011). [It must be noted that there was overlap in the models used between different studies.] Six independent models evaluated 5-yearly sigmoidoscopy screening. Four concluded that this strategy was less costly and more effective than no screening. In the other two models, costs were less than US$ 31 000 per life year gained. Eleven independent models evaluated 10-yearly colonoscopy screening. Three models found this strategy to be cost saving, whereas the cost–effectiveness ratio was less than US$ 30 000 per life year gained for the remainder of the strategies. In the comparison across these sigmoidoscopy and colonoscopy strategies, only two of seven models concluded that the incremental costs per life year gained for colonoscopy screening compared with sigmoidoscopy screening exceeded US$ 50 000.

Since the review by Patel & Kilgore (2015), two new models have been published on the cost–effectiveness of CRC screening in the USA (Kingsley et al., 2016; Barzi et al., 2017), and two models have published updated results (Hassan & Gralnek, 2015; Ladabaum & Mannalithara, 2016) (Table 3.3.17). The findings of these studies were consistent with those of Patel & Kilgore (2015) and demonstrated cost–effectiveness ratios of both sigmoidoscopy screening and colonoscopy screening not exceeding US$ 15 000 per QALY gained. Kingsley et al. (2016) and Barzi et al. (2017) provided estimates for both sigmoidoscopy screening and colonoscopy screening and showed that colonoscopy screening was more effective than sigmoidoscopy screening. Kingsley et al. (2016) found colonoscopy also to be more costly, with an incremental cost–effectiveness ratio of less than US$ 50 000 per QALY gained,

Table 3.3.17 Studies of cost–effectiveness of endoscopy screening compared with no screening[a]

Reference Country	Population simulated[b]	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	QALYs or LYs gained per 1000 individuals[c]	Costs (×1000) (US$)	Cost per QALY or LY gained[c]	Comments
Heitman et al. (2010) Canada	Cohort age 50–75 yr	68	10-yearly colonoscopy 5-yearly sigmoidoscopy	62/65 58/61	41 36	154 280	3800 7800	Low effectiveness estimates, because of mixed-age cohort
Telford et al. (2010) Canada	Cohort age 50 yr	73	10-yearly colonoscopy	81/83	120	578	4800	Uncertain whether reported incidence/ mortality reductions pertain to 100% participation
Barouni et al. (2012) Islamic Republic of Iran	Cohort age 50 yr	68	10-yearly colonoscopy	76/78	119	746	5000	
Dan et al. (2012) Singapore	Cohort age 50–75 yr	NR	10-yearly colonoscopy 5-yearly sigmoidoscopy	35/38 28/30	17 5	573 163	33 700 38 300	Low effectiveness estimates, because of mixed-age cohort
Sharp et al. (2012) Ireland	Cohort age 30 yr	39	Single sigmoidoscopy at age 60 yr	4.9/7.5	7	21 726	3000	Low effectiveness estimates, because of young cohort at start of simulation
Wang et al. (2012) China	Cohort age 50–80 yr	90	Single colonoscopy 10-yearly colonoscopy	67/73 66/71	1336 1394	10 000 93 245	7 70	Questionable model validity, because single endoscopy more effective than repeat endoscopy
Whyte et al. (2012) United Kingdom	Cohort age 50 yr	85	Sigmoidoscopy at ages 55 yr and 65 yr	18/22	33	51	1500	
Ladabaum et al. (2014) Germany	Cohort age 50 yr	100	Colonoscopy at ages 55 yr and 65 yr	62/67	90	–1300	Cost savings	
Hassan & Gralnek (2015) USA	Cohort age 50 yr	100	10-yearly colonoscopy	75/73	150	663	4400	

Table 3.3.17 (continued)

Reference Country	Population simulated[b]	Participation rate (%)	Strategy evaluated	Reduction in incidence/ mortality (%)	QALYs or LYs gained per 1000 individuals[c]	Costs (×1000) (US$)	Cost per QALY or LY gained[c]	Comments
Lam et al. (2015) Hong Kong SAR, China	Cohort age 50 yr	NR	10-yearly colonoscopy 5-yearly sigmoidoscopy	NR/NR	124 109	1610 2286	14 800 18 500	
Wong et al. (2015) Hong Kong SAR, China	Cohort age 50 yr	60	10-yearly colonoscopy	NR/NR	QALY, 611 LY, 97	2212	3600	Adjustment for quality of life seems invalid
Kingsley et al. (2016) USA	Cohort age 50 yr	38	10-yearly colonoscopy 5-yearly sigmoidoscopy	NR/60[d] NR/NR	100 62	327 –189	3300 Cost savings	
Ladabaum & Mannalithara (2016) USA	Cohort age 50 yr	100	10-yearly colonoscopy	73/81	77	1153	15 000	
Sekiguchi et al. (2016) Japan	Cohort age 40 yr	60	10-yearly colonoscopy	69/NR	219	–495	Cost savings	Questionable model validity, because incidence reduction higher than participation
Aronsson et al. (2017) Sweden	Cohort age 60 yr	38	Single colonoscopy 10-yearly colonoscopy	NR/NR	49 56	–74 142	Cost savings 2500	
Barzi et al. (2017) USA	Cohort age 50–75 yr	63	10-yearly colonoscopy 5-yearly sigmoidoscopy	23/34 11/21	22 16	–554 –270	Cost savings Cost savings	

LYG, life year gained; LYs, life years; NR, not reported; QALYs, quality-adjusted life years; SAR, Special Administrative Region; yr, year or years.

[a] Includes studies published after Patel & Kilgore (2015) (for studies in the USA) or published after Lansdorp-Vogelaar et al. (2011) (for studies outside the USA).

[b] Signifies the population at the start of the simulation, i.e. cohort age 50 years signifies a population of people aged 50 years that are followed up until death or a certain age, and cohort age 50–75 years signifies a population of people aged 50–75 years that are followed up until death or for a certain period.

[c] Estimates for QALYs gained and cost–effectiveness depend on background cancer incidence. Therefore, estimates may not easily be transferable to low-incidence settings.

[d] Reported mortality reduction for 100% participation.

whereas Barzi et al. (2017) found colonoscopy to be more cost saving than sigmoidoscopy.

Since the review by Lansdorp-Vogelaar et al. (2011), 12 new studies have been published that evaluated the cost–effectiveness of endoscopy screening outside the USA: two in Canada (Heitman et al., 2010; Telford et al., 2010), four in Europe (Sharp et al., 2012; Whyte et al., 2012; Ladabaum et al., 2014; Aronsson et al., 2017), and six in Asia (including the Middle East) (Barouni et al., 2012; Dan et al., 2012; Wang et al., 2012; Lam et al., 2015; Wong et al., 2015; Sekiguchi et al., 2016). Sigmoidoscopy screening was evaluated in seven studies, and colonoscopy screening was evaluated in 10 studies. All of the studies found cost–effectiveness ratios of less than US$ 35 000 per QALY gained. Five studies evaluated both sigmoidoscopy screening and colonoscopy screening, and all of them found that 10-yearly colonoscopy was more effective than 5-yearly sigmoidoscopy (Heitman et al., 2010; Dan et al., 2012; Lam et al., 2015; Kingsley et al., 2016; Barzi et al., 2017). In the other studies, the incremental costs per life year gained moving from sigmoidoscopy screening to colonoscopy screening were less than US$ 35 000.

[Overall, there is high variability in the estimates for cost–effectiveness across these studies. The reviews tried to standardize as much as they could across the studies, either by including only studies in the USA (Pignone et al., 2002; Patel & Kilgore, 2015) or by converting all currencies into United States dollars (Lansdorp-Vogelaar et al., 2011). However, the variability is high even between studies in the USA. All of the authors of the cost–effectiveness reviews mentioned differences in assumptions about natural history, screening characteristics, and screening participation as potential reasons for differences in model outcomes (Pignone et al., 2002; Lansdorp-Vogelaar et al., 2011; Patel & Kilgore, 2015). Limited empirical evidence hinders the assessment of which set of assumptions is the most plausible. In addition, despite recommendations from the Panel on Cost-Effectiveness in Health and Medicine (Weinstein et al. 1996), the studies still differ widely with respect to perspective, population, time horizon, and discount rate, introducing another reason for differences between the studies (Lansdorp-Vogelaar et al. 2011).]

[Although the majority of the studies indicate that colonoscopy screening is more effective and less costly than sigmoidoscopy screening, these results may be biased in favour of colonoscopy. As explained previously, the models estimated a higher effectiveness of colonoscopy by assumptions, and the lower costs may result from higher savings due to treatment avoided because of higher effectiveness as well as from the shorter interval for screening sigmoidoscopy than for screening colonoscopy in the modelling studies. As shown in RCTs, the interval for sigmoidoscopy can be safely extended to at least 10 years without attenuation of its protective effect (Atkin et al., 2010; Segnan et al., 2011; Schoen et al., 2012; Holme et al., 2014).]

(c) Additional cost–effectiveness considerations

(i) Lower age limit of screening

Very few studies have assessed the optimal age at which to start CRC screening. Two studies have assessed the optimal timing for a single endoscopy to gain the most QALYs. The first study (Ness et al., 2000) found that a single colonoscopy between age 50 years and age 54 years was cost-effective both compared with no screening and compared with colonoscopy at older ages. For men, colonoscopy between age 45 years and age 49 years may also be cost-effective for a willingness-to-pay threshold exceeding US$ 69 000 per QALY gained. The second study (Whyte et al., 2012) assessed the optimal age for a single sigmoidoscopy and found that sigmoidoscopy at age 55 years was associated with the greatest gain in QALYs compared with sigmoidoscopy at older

ages. However, results for a single sigmoidoscopy at any age between 52 years and 58 years resulted in very similar QALYs gained. The results for a single sigmoidoscopy at ages younger than 52 years and older than 58 years showed that the QALYs gained decreased, and these alternatives were not found to be cost-effective.

The Cancer Intervention and Surveillance Modeling Network (CISNET) performed a decision analysis for the USPSTF to determine the optimal age at which to start, the optimal age at which to stop, and the optimal interval for CRC screening (Knudsen et al., 2016). The models suggested that starting CRC screening at age 45 years, rather than at age 50 years, yielded a modest increase in life years gained and had a more favourable balance between life years gained and the clinical burden of colonoscopies. For colonoscopy screening, two of the three models found that performing colonoscopy every 15 years from age 45 years resulted in slightly more life years gained compared with colonoscopy every 10 years from age 50 years without increasing the lifetime number of colonoscopies. However, one model estimated a slight loss in life years gained with a longer screening interval and an earlier age to start screening. On the basis of these discordant findings, the USPSTF concluded that there was insufficient evidence to support a starting age of 45 years for the general population, especially given the lack of empirical evidence of screening in the younger population.

Finally, one study assessed whether the optimal age at which to start colonoscopy screening varied by race and sex (Lansdorp-Vogelaar et al., 2009). This study showed that although the risks of CRC incidence and mortality in women reach levels comparable to those in men 4–8 years later in life, the optimal age at which to start screening does not differ by sex. This finding can be explained by the longer life expectancy in women: the number needed to screen to detect one advanced adenoma may be higher in women than in men, but the number of detected advanced adenomas needed to prevent one case of CRC is lower in women than in men. This makes the number needed to screen to prevent one CRC case similar for men and women. However, the study did show that the optimal age at which to start screening was approximately 5 years earlier for African Americans (age 47 years) than for Whites (age 53 years) for both men and women.

(ii) Upper age limit of screening

Few studies have assessed the optimal age at which to stop screening. Maheshwari et al. (2008) performed a life-table analysis to estimate the impact of prematurely stopping screening compared with the maximal potential benefit from lifelong screening. They concluded that stopping screening at approximately age 82 years would retain 80% of the maximal clinical benefit of screening. However, this analysis was based on the risk of dying from CRC among older people and did not take into account the impact of previous screening on this risk.

In the decision analysis for the USPSTF, the CISNET models also evaluated the optimal age at which to stop screening. Screening strategies were compared, with stopping ages varying between 75 years, 80 years, and 85 years (Knudsen et al., 2016). The models showed that in individuals who were consistently screened from age 50 years onwards, the life years gained associated with extending the age at which to stop screening beyond age 75 years were generally small relative to the number of additional colonoscopies required. Therefore, it was concluded that age 75 years would be a reasonable age to stop screening.

Two studies evaluated the age to stop colonoscopy screening in the light of previous screening history, background risk, and comorbidity (van Hees et al., 2014a, 2015). The study by van Hees et al. compared the balance between benefits and harms of screening in elderly individuals for unscreened cohorts of people with and

without comorbidities (van Hees et al., 2014a). For these individuals, the benefits of screening at a later age are much greater than those for previously screened individuals, whereas the harms are relatively similar. Consequently, the modelling suggested that individuals without previous screening can be screened until a much later age and may still have a favourable balance between benefits and harms: up to age 83 years, 80 years, and 77 years for no, moderate, and severe comorbidities, respectively. Ideally, the age at which to stop screening should be based on personal risk, previous screening history, and comorbidity (van Hees et al., 2015). The current recommendation of continuing screening up to age 75 years could result in a loss, rather than a gain, of QALYs in some populations at low risk (e.g. for White women aged 74 years with moderate comorbidities, half the average background risk of CRC, and negative findings from a screening colonoscopy 10 years previously). For other groups, continuing screening was found to be highly cost-effective (e.g. for Black men aged 81 years with no comorbidities, an average background risk of CRC, and no previous screening). According to this study, the optimal age at which to stop screening varies between 66 years and 88 years, depending on individual risk, comorbidity, and previous screening history.

(iii) Screening interval

In the decision analysis for the USPSTF, the CISNET models also addressed the optimal interval for CRC screening (Knudsen et al., 2016). Two of the three models suggested that colonoscopy screening with a 15-year interval starting at age 45 years yielded a modest increase in life years gained and had a more favourable balance between life years gained and the clinical burden of colonoscopies, compared with colonoscopy every 10 years from age 50 years, without increasing the lifetime number of colonoscopies. However, one model estimated a slight loss in life years gained with this longer screening interval. Sigmoidoscopy screening was not found to be a sufficiently effective strategy compared with colonoscopy screening, and therefore no optimal interval was identified for this modality.

Six cost–effectiveness analyses also addressed endoscopy screening at different intervals, often comparing a single endoscopy, endoscopy every 10 years, and/or endoscopy every 5 years. One study even assessed a 3-yearly interval for colonoscopy (Table 3.3.18). The outcomes of the analyses varied widely, and no conclusions could be drawn about the optimal interval for endoscopy screening on the basis of these studies.

Table 3.3.18 Cost–effectiveness studies assessing different intervals for endoscopy screening

Reference Country	Population simulated[a]	Strategy evaluated	Reduction in incidence/ mortality (%)	QALYs gained per 1000 individuals[b]	Costs (×1000) (US$)	Optimal interval	Comments
Aronsson et al. (2017) Sweden	Cohort age 60 yr	Single colonoscopy 10-yearly colonoscopy	NR/NR	49 56	–74 142	WTP < US$ 30 000 WTP > US$ 30 000	
Lam et al. (2015) Hong Kong SAR, China	Cohort age 50 yr	10-yearly colonoscopy 5-yearly colonoscopy 10-yearly sigmoidoscopy 5-yearly sigmoidoscopy	NR/NR	124 172 70 109	1610 2897 1244 2286	WTP < US$ 26 000 WTP > US$ 26 000 WTP < US$ 26 000 WTP > US$ 26 000	
van Hees et al. (2014b) USA	Cohort age 65 yr	10-yearly colonoscopy 5-yearly colonoscopy 3-yearly colonoscopy	NR/NR	65 68 66	922 1495 2151	WTP < US$ 179 000 WTP > US$ 179 000	
Whyte et al. (2012) United Kingdom	Cohort age 50 yr	Single sigmoidoscopy at age 55 yr Sigmoidoscopy at ages 55 yr and 65 yr	9/11 18/22	21 33	33 51	WTP < US$ 2250 WTP > US$ 2250	
Wang et al. (2012) China	Cohort age 50–80 yr	Single colonoscopy 10-yearly colonoscopy	67/73 66/71	1336 1394	10 000 93 245	Repeat 10-yearly colonoscopy not cost-effective compared with single colonoscopy within reasonable WTP values	Questionable model validity, because single endoscopy more effective than repeat endoscopy
Dan et al. (2012) Singapore	Cohort age 50–75 yr	Single sigmoidoscopy 5-yearly sigmoidoscopy	19/16 28/30	3 5	56 163	WTP < US$ 53 500 WTP > US$ 53 500	Low effectiveness estimates, because mixed-age cohort

NR, not reported; QALYs, quality-adjusted life years; SAR, Special Administrative Region; WTP, willingness to pay; yr, year or years.

[a] Signifies the population at the start of the simulation, i.e. cohort age 50 years signifies a population of people aged 50 years that are followed up until death or a certain age, and cohort aged 50–75 years signifies a population of people aged 50–75 years that are followed until death or for a certain period.

[b] Estimates for QALYs gained depend on background risk of cancer. Therefore, estimates may not easily be transferable to low-incidence settings.

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3.4 Comparison of the preventive effects of endoscopic methods and stool-based tests for blood

To date, only two methods have been assessed in RCTs to investigate reductions in CRC incidence or mortality: gFOBT and sigmoidoscopy. This section deals with comparisons between major endoscopic and stool-based CRC screening methods (i.e. sigmoidoscopy or colonoscopy vs gFOBT or FIT) in terms of mortality or incidence outcomes, ADRs, and cost–effectiveness. Comparisons of the established screening methods (colonoscopy, sigmoidoscopy, gFOBT, and FIT) in terms of participation are described in Section 3.6.

3.4.1 Reduction in colorectal cancer incidence or mortality

No RCT is available that directly compares two or more CRC screening tests. Evidence comes from indirect comparisons of observational studies and from indirect meta-analyses, so-called network meta-analyses using Bayesian statistics. Results from network meta-analyses are considered here, in the absence of direct comparison studies. [The Working Group highlighted as weaknesses of network meta-analyses the risk of non-comparability of control groups, the different screening participation rates across trials, and the heterogeneity in study designs available for the different screening methods compared (i.e. no trials available for colonoscopy or FIT). In conclusion, results from these studies were interpreted as lower-quality evidence.]

Of the five network meta-analyses identified, two focused exclusively on RCTs and thus included only gFOBT and sigmoidoscopy (Holme et al., 2013; updated by Emilsson et al., 2017), whereas the remaining three included observational studies as well but acknowledged that comparative estimates may be biased towards superiority of colonoscopy (Brenner et al., 2014; Elmunzer et al., 2015; Zhang et al., 2017).

The meta-analysis by Emilsson et al. (2017) included nine RCTs with 338 467 individuals randomized to screening and 405 919 individuals randomized to the control groups (Table 3.4.1). An indirect comparison of the primary analyses showed that sigmoidoscopy was superior to gFOBT in reducing CRC incidence (RR, 0.84; 95% predictive interval [PrI], 0.72–0.97). For CRC mortality, the relative risk for sigmoidoscopy versus gFOBT was 0.89 (95% PrI, 0.68–1.17). No heterogeneity was observed among the sigmoidoscopy trials, and moderate heterogeneity was reported among the gFOBT trials (I^2 = 51.5%).

The remaining meta-analyses conducted indirect comparisons including both RCTs and observational studies. [Brenner et al. (2014) and Zhang et al. (2017) did not perform analyses restricted to studies in CRC screening settings as opposed to clinical settings, and therefore these network meta-analyses are not included in this evaluation.] With analyses restricted to studies in a screening setting, Elmunzer et al. (2015) reported improved effectiveness of colonoscopy in reducing CRC mortality compared with both sigmoidoscopy (RR, 0.56; 95% CI, 0.32–0.94) and gFOBT (RR, 0.49; 95% CI, 0.30–0.76). [There was significant heterogeneity among the studies included. However, when outlier studies were removed, the results were strengthened.]

3.4.2 Detection rates of adenoma and colorectal cancer

(a) Meta-analyses

Hassan et al. (2012) assessed participation in screening and compared the detection rates of advanced neoplasia between endoscopic methods and stool-based tests for blood, as well as within stool-based tests for blood (gFOBT vs FIT). Littlejohn et al. (2012) compared sigmoidoscopy either with no screening (not reported

Table 3.4.1 Network meta-analyses comparing incidence and/or mortality reduction from screening with endoscopic methods and stool-based tests for blood

Reference	Study design Population	Screening exposure; age of included subjects	Linkage or use of screening, cancer registry, death databases; data items available	CRC incidence and mortality, absolute effects	Indirect comparison RR (95% CI/95% PrI)	Adjustments/ comments
Elmunzer et al. (2015)	Meta-analysis with indirect comparison of 4 RCTs on FS, 4 RCTs on gFOBT, and 8 observational studies on colonoscopy, 3 on FS, and 13 on gFOBT Average-risk population 1 290 544 individuals in the colonoscopy observational studies, 21 950 in the FS observational studies, 414 966 in the FS RCTs, 900 843 in the gFOBT RCTs, 4 329 642 in the gFOBT observational studies	Colonoscopy: Once-only colonoscopy in all studies Age at inclusion, 50–90 yr FS: Once-only FS in all but one RCT (which used 2 rounds of screening) Age at inclusion, 55–74 yr for RCTs and 69 yr mean for 1 observational study gFOBT: Annual or biennial Age at inclusion, 45–80 yr for RCTs and 40–80 yr for observational study Test intervals not given	End-point ascertainment registries, survey, and end-point committees. No details given per study.	Absolute effects not reported	Colonoscopy vs gFOBT: Mortality: 0.49 (0.30–0.76)	No studies on FIT included Mixtures of ITT analyses from RCTs and observational studies with imbalance for design between the 3 tests
Emilsson et al. (2017)	Meta-analysis with indirect comparison of 5 RCTs on FS and 4 RCTs on gFOBT Average-risk population 338 467 individuals randomized to screening and 405 919 individuals randomized to the control groups	FS: 4 RCTs with 1 round, 1 RCT with 2 rounds Age at inclusion, 50–74 yr gFOBT: 2 RCTs with biennial screening, 1 RCT with biennial or annual screening, and 1 RCT with a mixture of different intervals Age at inclusion, 45–80 yr	End-point ascertainment through national, regional, or local registries, or survey. Some studies had end-point committee, others did not	FS: Mortality: No screening, 8 per 1000 Screening, 6 per 1000 Incidence: No screening, 20 per 1000 Screening, 16 per 1000 gFOBT: Mortality: No screening, 8 per 1000 Screening, 7 per 1000 Incidence: No screening, 20 per 1000 Screening, 19 per 1000	FS vs gFOBT: Mortality: 0.89 (0.68–1.17) Incidence: 0.84 (0.72–0.97)	The study is an update of Holme et al. (2013)

CI, confidence interval; CRC, colorectal cancer; FIT, faecal immunochemical test; FS, flexible sigmoidoscopy; gFOBT, guaiac faecal occult blood test; ITT, intention-to-treat; PrI, predictive interval; RCTs, randomized controlled trials; RR, relative risk; vs, versus; yr, year or years.

here) or with alternative screening methods. All individual studies included in these meta-analyses are summarized in Table 3.4.2.

Both meta-analyses included RCTs or controlled studies, and they overlapped in seven studies (Berry et al., 1997; Verne et al., 1998; Rasmussen et al., 1999; Segnan et al., 2005, 2007; Multicentre Australian Colorectal-neoplasia Screening (MACS) Group, 2006; Hol et al., 2010).

The meta-analysis by Hassan et al. (2012) included several comparisons of screening methods in relation to detection of advanced neoplasia, advanced adenoma, and CRC. The study found that endoscopic techniques (sigmoidoscopy and colonoscopy) were more likely than stool-based tests for blood (gFOBT or FIT) to detect advanced neoplasia (RR, 3.21; 95% CI, 2.38–4.32) and CRC (RR, 1.58; 95% CI, 0.97–2.56). Separately, the detection rates of advanced neoplasia with both colonoscopy (RR, 3.56; 95% CI, 1.79–7.09) and sigmoidoscopy (RR, 3.2; 95% CI, 1.87–5.19) were significantly higher than those with gFOBT or FIT, whereas no significant differences were observed for the detection rates of CRC.

Littlejohn et al. (2012) included six studies that compared sigmoidoscopy with FOBT for the detection of advanced adenoma. Sigmoidoscopy (alone or in combination with FOBT) was more effective than FOBT alone in detecting advanced adenoma (sigmoidoscopy vs gFOBT: RR, 7.23; 95% CI, 4.86–10.75, comparing 4 studies; sigmoidoscopy vs FIT: RR, 3.74; 95% CI, 3.03–4.62, comparing 3 studies). Similar results were observed for the detection of CRC with sigmoidoscopy (alone or in combination with gFOBT) compared with gFOBT alone (RR, 3.34; 95% CI, 1.70–6.54) and with sigmoidoscopy (alone or in combination with FIT) compared with FIT alone (RR, 1.63; 95% CI, 0.67–3.97). [The Working Group noted that these comparisons were based on a small number of cases, and that the associations were weaker or non-significant for the CRC end-point.]

(b) Additional RCTs

Several additional RCTs published after 2012 have reported on the detection rates of advanced neoplasia, advanced adenoma, and/or CRC, comparing different screening modalities (see Table 3.4.2; Castells et al., 2014; Holme et al., 2014; Sali et al., 2016).

In a subanalysis of the population-based COLONPREV trial in Spain, which used FIT and colonoscopy in two study arms, the authors used the information from the colonoscopy up to the splenic flexure and interpreted it as sigmoidoscopy, with the aim of assessing how many colonic lesions sigmoidoscopy could detect. [The Working Group noted the possible limitation of simulating sigmoidoscopy by extrapolating from the colonoscopy results.] Simulated sigmoidoscopy was better than one-time FIT in detecting distal neoplasia (OR, 2.61; 95% CI, 2.20–3.10). Also, FIT and sigmoidoscopy did not differ significantly in their performance in detecting advanced proximal neoplasia (OR, 1.17; 95% CI, 0.78–1.76) (Castells et al., 2014).

In a trial in Norway of about 100 000 people, comparing sigmoidoscopy (n = 10 283) and the combination of FIT and sigmoidoscopy (n = 10 289), the detection rates of advanced adenoma and CRC were similar for the two modalities: the detection rates of advanced adenoma increased by 4.6% with sigmoidoscopy versus no screening and by 4.5% with combined FIT and sigmoidoscopy versus no screening, and the detection rate of CRC increased by 0.3% in both groups (Holme et al., 2014).

In a study of 9288 and 1036 residents of Florence, Italy, aged 54–65 years invited to participate in a CRC screening RCT with FIT or colonoscopy, respectively, Sali et al. (2016) reported that the detection rates of advanced neoplasia were 1.7% with first-round FIT and 7.2% with colonoscopy. The same study reported that colonoscopy was almost 5 times as likely as FIT to detect advanced neoplasia, in a model adjusted

Table 3.4.2 Individual studies included in the meta-analyses comparing detection rates of neoplastic lesions with endoscopic methods versus stool-based tests for blood

Reference Country	No. of subjects Age at entry	Intervention	Attendance at first round (%)	Detection rate of advanced adenoma/CRC (%)[a]	Comments
Berry et al. (1997)[b,c] United Kingdom	6371 50–74 yr	1. gFOBT 2. gFOBT+FS 2a. Returns the gFOBT test 2b. Goes to FS	1. 50 2a. 48.4 2b. 20.2	gFOBT: 0.1/0.1 gFOBT+FS: 0.8/0.1	
Brevinge et al. (1997)[c] Sweden	6367 55–56 yr	1. FS 2. gFOBT	1. FS: 42.5 2. gFOBT: 59.5	FS: 0.8/0.2 gFOBT: 0.3/0.03	
Verne et al. (1998)[b,c] United Kingdom	3744 50–75 yr	1. FS 2. gFOBT+FS 2a. Either gFOBT returned or FS accepted 2b. Both gFOBT returned and FS accepted 3. gFOBT alone	1. 46.6 2a. 39.5 2b. 30.1 3. 31.6	FS: 2.2/0.2 gFOBT+FS: 0.1/0.1 gFOBT: 0.1/0.1	
Rasmussen et al. (1999)[b,c] Denmark	10 978 50–75 yr	1. gFOBT 2. FS+gFOBT	1. gFOBT: 56 2. FS+gFOBT: 41	gFOBT: 1.3/0.2 FS+gFOBT: 0.3/0.07	
Gondal et al. (2003)[c] Norway	20 780 50–64 yr	1. FS 2. FIT+FS 2a. FIT returned and FS accepted 2b. FIT not returned but FS accepted	1. 66.9 2a. 54.4 2b. 8.3	FS: 2.9/0.2 FIT+FS: 2.6/0.2	
Segnan et al. (2005)[b,c] Italy	28 319 55–64 yr	1. Biennial FIT (delivered by mail) 2. Biennial FIT (delivered by GP or screening facility) 3. Once-only FS 4. FS+biennial FIT 5. Patient's choice of screening test 5a. Once-only FS 5b. FS, then biennial FIT	1. 30 2. 28 3. 28 4. 28 5a. 15 5b. 13	FIT (by mail or by GP): 1.5/0.3 FIT (patient's choice): 0.8/0.4 FS (once-only or FS+FIT): 5.3/0.3 FS (patient's choice): 3.6/0.9	

Table 3.4.2 (continued)

Reference Country	No. of subjects Age at entry	Intervention	Attendance at first round (%)	Detection rate of advanced adenoma/CRC (%)[a]	Comments
Federici et al. (2006)[b] Italy	2987 50–74 yr	1. FS (with further investigation with a colonoscopy if positive) 2. FIT (with further investigation with a colonoscopy if positive)	1. 7.0 2. 17.2	FIT: 0.0/0.8 FS: 0.0/2.8	There was a significant effect of socioeconomic status on the probability of participation; participation was too low to enable effects of FS to be evaluated
Multicentre Australian Colorectal-neoplasia Screening (MACS) Group (2006)[b,c] Australia	1679 50–54 yr and 65–59 yr	1. FIT 2. FIT+FS 3. Colonoscopy 4. Choice of screening test 4a. "FIT kit with letter" 4b. "FIT kit requested by phone"	1. 27 2. 14 3. 18 4a. 19 4b. 23	FIT: 0.4/0 FIT+FS: 0/0 OC: 2.3/0	The study group was rather small, and thus the results were statistically uncertain
Segnan et al. (2007)[b,c] Italy	18 116 55–64 yr	1. Biennial FIT 2. FS once 3. Colonoscopy once	1. FIT: 32.3 2. FS: 32.3 3. OC: 26.5	FIT: 0.3/0.03 FS: 1.5/0.2 OC: 1.7/0.2	
Hol et al. (2010)[b,c] The Netherlands	15 011 50–74 yr	1. gFOBT 2. FIT 3. FS (with further investigation with a colonoscopy if positive)	1. 49 2. 62 3. 32	gFOBT: 0.5/0.1 FIT: 1.2/0.3 FS: 2.2/0.2	
Lisi et al. (2010)[b] Italy	8378 55–64 yr	1. gFOBT 2. Colonoscopy	1. gFOBT: 27.1 2. OC: 10.0	gFOBT: 0.12/0.02 OC: 0.63/0.05	
Quintero et al. (2012)[b] Spain	40 453 50–69 yr	1. FIT 2 Colonoscopy	1. FIT: 33.8 2. OC: 18.5	FIT: 0.8/0.1 OC: 1.8/0.1	
Castells et al. (2014) Spain	57 404 50–69 yr	1. Colonoscopy 2. FIT	1. 21 2. 35	FS[d]: 5.9/0.4 FIT: 2.4/0.3	FS underperforms for women aged 50–59 yr Both FS and FIT were limited in the detection of advanced proximal neoplasia FS was better in the detection of distal neoplasia

Table 3.4.2 (continued)

Reference Country	No. of subjects Age at entry	Intervention	Attendance at first round (%)	Detection rate of advanced adenoma/CRC (%)[a]	Comments
Holme et al. (2014) Norway	100 210 50–64 yr	1. FS 2. FS+FIT (with further investigation with a colonoscopy if positive)	1. 65.1 2. 60.9	FS: 4.6/0.3 FS+FIT: 4.5/0.3	
Sali et al. (2016) Italy	16 087 54–65 yr	1. Biennial FIT 2. Colonoscopy	1. 50.4 2. 14.8	FIT: 1.6/0.1 OC: 7.2/0.0	

CRC, colorectal cancer; FIT, faecal immunochemical test; FS, flexible sigmoidoscopy; gFOBT, guaiac faecal occult blood test; GP, general practitioner; OC, optical colonoscopy; yr, year or years.

[a] Adjusted for attendance (intention-to-treat analysis).

[b] Included in meta-analysis by Hassan et al. (2012).

[c] Included in meta-analysis by Littlejohn et al. (2012).

[d] FS yield was estimated from the results obtained in the colonoscopy by considering lesions detected in the rectum and sigmoid colon and according to the criteria proposed in the United Kingdom Flexible Sigmoidoscopy Screening Trial.

for sex, age, randomization group, and socioeconomic status (RR, 4.72; 95% CI, 2.44–9.13).

3.4.3 Cost–effectiveness

In recent years, many modelling studies (some of them conducted as part of national or international practice guideline projects) have evaluated the effectiveness of different CRC screening methods. Many of these modelling studies investigated more than one screening method or strategy. For a detailed overview of the studies on cost–effectiveness, see Section 3.2.6 and Section 3.3.6. Of the three systematic reviews of cost–effectiveness analyses of CRC screening, the most recent review by Patel & Kilgore (2015) was the only one to systematically compare all combinations of screening tests. That review included nine simulations that directly compared the costs (in United States dollars) and LYG of 10-yearly colonoscopy with those of annual gFOBT screening (Table 3.4.3). In all of the simulations, colonoscopy was more effective than annual gFOBT, and in most (six of nine simulations) the additional costs were less than US$ 50 000 per LYG. Five simulations compared 10-yearly colonoscopy versus annual HSgFOBT. In all five simulations colonoscopy was more effective than HSgFOBT and the additional costs were less than US$ 50 000 per LYG. For the comparison of 10-yearly colonoscopy versus annual FIT, the results were less consistent. In six of nine simulations, colonoscopy was more effective than FIT and more cost-effective with additional costs of less than US$ 50 000 per LYG, whereas in the other three simulations FIT was more effective and less costly than colonoscopy.

Comparisons of 5-yearly sigmoidoscopy versus annual HSgFOBT and FIT were very consistent, with 10 and 13 simulations, respectively, showing that sigmoidoscopy was less effective and more costly than these types of stool-based tests for blood. 5-Yearly sigmoidoscopy was consistently found to be more effective than annual gFOBT, and in most of the simulations, its additional costs were less than US$ 50 000 per LYG.

For the purpose of comparing different tests with a high degree of transparency with regard to the model applied, the most comprehensive and up-to-date study is part of the work developed for the latest update of the USPSTF recommendations for CRC screening, published in 2016 (Knudsen et al., 2016). This modelling study involved three microsimulation models – Simulation Model of Colorectal Cancer (SimCRC), Microsimulation Screening Analysis (MISCAN), and Colorectal Cancer Simulated Population Model for Incidence and Natural History (CRC-SPIN) – and used a hypothetical cohort of individuals aged 45, 50, or 55 years at the start of screening and aged 75, 80, or 85 years at the end of screening. A 100% participation rate in screening was assumed for all scenarios.

The following seven screening strategies were compared: HSgFOBT, FIT, the multitarget stool DNA (mt-sDNA) test, sigmoidoscopy (alone or in combination with stool-based testing for blood), computed tomography (CT) colonography, or colonoscopy. Different screening intervals and age ranges were explored. The primary end-point for all modelling analyses was LYG computed with the assumption that all gain from CRC detection would translate into LYG. The average LYG per 1000 people were 175–212 for HSgFOBT, 176–260 for FIT, 193–250 for mt-sDNA, 200–227 for sigmoidoscopy alone, 231–262 for sigmoidoscopy and FOBT, 184–265 for CT colonography, and 264–285 for colonoscopy. Although the ranges in LYG overlap for the different screening strategies, the models consistently found the highest LYG with 10-yearly colonoscopy, followed by the stool-based tests for blood, and the lowest LYG for sigmoidoscopy, which improved when sigmoidoscopy was combined with FOBT (Table 3.4.4).

Table 3.4.3 Systematic comparison of cost–effectiveness of endoscopic methods versus stool-based tests for blood for colorectal cancer screening

Strategy (test 1 vs test 2)	No. of studies	No. of simulations	No. of simulations in which test 1 is more effective and less costly than test 2	No. of simulations in which test 1 is more effective than test 2 and its additional costs are < US$ 50 000 per LYG	No. of simulations in which test 1 is more effective than test 2 and its additional costs are > US$ 50 000 per LYG	No. of simulations in which test 1 is less effective and more costly than test 2
10-yearly colonoscopy vs annual gFOBT	6	9	0	6	3	0
10-yearly colonoscopy vs annual HSgFOBT	2	5	0	5	0	0
10-yearly colonoscopy vs annual FIT	6	9	0	6	0	3
5-yearly FS vs annual gFOBT	5	13	0	9	4	0
5-yearly FS vs annual HSgFOBT	2	10	0	0	0	10
5-yearly FS vs annual FIT	5	13	0	0	0	13

FIT, faecal immunochemical test; FS, flexible sigmoidoscopy; gFOBT, guaiac faecal occult blood test; HSgFOBT, high-sensitivity gFOBT; LYG, life year gained; vs, versus.

Table 3.4.4 Modelling studies comparing colorectal cancer incidence or mortality reduction or quality-adjusted life years gained for different screening strategies

Reference Country	Model type Validation	Screening strategies considered	Population (age, gender, risk factors), screening intervals, and time frame of effect	Assumed compliance with screening interventions and follow-up	Background risk of disease	Outcome
Telford et al. (2010) Canada	Probabilistic Markov model No validation	10 strategies; all included in Knudsen et al. (2016), and at different intervals and combinations	Population aged 50 yr at average risk for CRC	Not known	Not known	**Relative reductions in CRC incidence and mortality vs no screening:** annual gFOBT: 44%, 55% annual FIT: 65%, 74% 10-yearly colonoscopy: 81%, 83%
Knudsen et al. (2016) USA	3 microsimulation models: SimCRC, MISCAN, and CRC-SPIN Validated against UKFSST (2010 data)	HSgFOBT FIT with cut-off of 100 ng (Hb) per mL (20 µg Hb/g faeces) mt-sDNA Sigmoidoscopy alone Sigmoidoscopy with HSgFOBT or FIT CTC Colonoscopy	Previously unscreened people aged 40 yr with no known CRC For each screening modality, evaluated multiple ages to start screening (45, 50, 55 yr) and end screening (75, 80, 85 yr) and multiple screening intervals Lifetime risk	Assumed 100% adherence to all procedures for all scenarios	CRC incidence: lifetime risk for people aged 40 yr, 67–72 per 1000 CRC mortality: lifetime risk for people aged 40 yr, 27–28 per 1000	**Life years gained from CRC diagnosis per 1000[a]:** HSgFOBT: 175–212 FIT: 176–260 mt-sDNA: 193–250 Sigmoidoscopy alone: 200–227 Sigmoidoscopy with HSgFOBT or FIT: 231–262 CTC: 184–265 Colonoscopy: 264–285
Sekiguchi et al. (2016) Japan	Markov model No validation	Strategy 1: annual FIT Strategy 2: colonoscopy Strategy 3: colonoscopy+annual FIT	Population at average risk aged 40 yr at start of screening	60% for all strategies	Not given	**Incremental cost per QALY gained:** Strategy 1 was dominated by strategy 3 For strategy 2 vs strategies 1 and 3, ¥293 616 and ¥781 342, respectively
Aronsson et al. (2017) Sweden	Markov decision analysis model No validation	FIT, 2 rounds Colonoscopy once Biennial FIT 10-yearly colonoscopy	Swedish population, based on scenario in screening of CRC (age 60 yr at start of screening)	Colonoscopy: 38% FIT: 50%	Not given	**Life years gained from CRC diagnosis per 1000[a]:** FIT, 2 rounds: 28 Colonoscopy once: 52 Biennial FIT: 54 10-yearly colonoscopy: 59

CRC, colorectal cancer; CRC-SPIN, Colorectal Cancer Simulated Population Model for Incidence and Natural History; CTC, computed tomography colonography; FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; Hb, haemoglobin; HSgFOBT, high-sensitivity gFOBT; MISCAN, Microsimulation Screening Analysis; mt-sDNA, multitarget stool DNA; QALY, quality-adjusted life year; RCT, randomized controlled trial; SimCRC, Simulation Model of Colorectal Cancer; UKFSST, United Kingdom Flexible Sigmoidoscopy Screening Trial; yr, year or years.

[a] All-cause mortality or life years gained for all causes not assessed for each study.

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3.5 Computed tomography colonography

3.5.1 Technique

The initial description of the use of computerized radiology for colon assessment dates back to the 1980s (Coin et al., 1983). However, it was not until more than a decade later that its full potential was better understood, because images to simulate the colon via three-dimensional (3D) fly-through techniques had been refined (Vining, 1996). The technology of computed tomography (CT) colonography enables a structural examination of the entire colon to be performed with a non-invasive method.

(a) Equipment

(i) Hardware

During the initial development of this technology, single-row helical CT scanners were used (Fenlon et al., 1999). Over time, the refinement of multidetector (or multirow) scanners has enabled the development of increasingly detailed images, and imaging times have become progressively shorter. For example, when a 64-slice multidetector scanner is used, the examination can be completed within a single breath hold of about 6–8 seconds (Lefere & Gryspeerdt, 2006). With multidetector scanners of at least 16 rows, submillimetre collimations are possible, enabling highly detailed 3D reconstructions (Cody & Mahesh, 2007).

Improvements in scanning technology continue. Currently, dual-source CT with 320 detector rows is in place at some centres. Automatic exposure control is also available (Kumar & Cash, 2017). This technology adjusts tube current continuously during the examination. Iterative reconstruction techniques are also being used. These improvements shorten the examination time and reduce radiation exposure. Nowadays, submillisievert examinations are possible (Lubner et al., 2015; Lambert et al., 2016).

(ii) Software

Software uses the cross-sectional image information obtained from the scanner to develop reconstructions of the colon for evaluation. Numerous developments in this area have enabled the image data to be manipulated in both two-dimensional (2D) and 3D formats (Kumar & Cash, 2017). Various types of 3D reconstructions are possible to facilitate reading. Examples of 3D reconstruction modes are fly-through, unfolded cube, and virtual dissection. The fly-through view develops colonoscopy-like images that can be examined in both antegrade and retrograde fashion, but it tends to have examination blind spots. Other reconstructions, such as unfolded cube and virtual dissection, "flatten" the colon more effectively and remove blind spots, but they introduce some distortion.

Data storage for the images can be a challenge. The use of a picture archiving and communication system (PACS) can facilitate both the storage and the retrieval of images when comparing examinations performed at different times and/or in separate venues.

(b) Procedure

From the patient perspective, there are several important considerations to ensure the completion of a high-quality examination. For example, the colon needs to be prepared before the examination and distended during the examination. Some of the key elements to patient preparation are discussed here.

(i) Colon preparation

As is the case for colonoscopy, the performance of CT colonography relies on adequate colon preparation to clear the colon of residual stool. Generally, dietary restriction (i.e. low-fibre diet) for at least a 24-hour period before the examination is recommended (Woodbridge &

Wylie, 2016). Laxatives are often used to induce catharsis, although they are not mandatory (see below). Multiple laxatives are available for colon preparation. The polyethylene glycol preparations that are commonly used for colonoscopy are the safest, because they are least associated with fluid shifts and electrolyte imbalance (Neri et al., 2013b). However, a relative disadvantage of polyethylene glycol is the high-volume "wet" nature of the preparation. This can lead to retained fluid in the bowel (Macari et al., 2001), which can be easily suctioned during conventional colonoscopy but is not effectively managed with CT colonography. For this reason, lower-volume preparations are often used (Laghi, 2014). This includes the use of osmotically active compounds such as sodium phosphate and magnesium citrate; however, some toxicity concerns remain about the administration of these types of agents in frail or elderly individuals. Acute phosphate nephropathy and the deposition of calcium phosphate within the renal tubules are particular concerns with sodium phosphate (Markowitz et al., 2005).

A separate consideration in colon preparation is faecal tagging, which uses the ingestion of high-density contrast agents to differentiate residual colonic contents from polyps. Tagging improves specificity by enabling the digital subtraction of stool after image collection, to better highlight colonic polyps (Fletcher et al., 2013). Barium and iodine-based agents (ionic and non-ionic), either alone or in combination, have been used for this purpose. When a contrast agent is used, the patient is asked to ingest the agent with each meal the day before the CT colonography examination (Neri et al., 2013b). Importantly, the iodine-based agents are hyperosmolar and therefore have inherent cathartic effects. These agents have facilitated the development of colon preparation protocols with a reduced dose of a conventional cathartic agent (Lefere et al., 2002) or even without such an agent (Zalis et al., 2012; Zueco Zueco et al., 2012). Although the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus statement favours the use of faecal tagging (Neri et al., 2013a), there is no clear consensus about which agent to use. The American College of Radiology (ACR) also endorses tagging, recommending the use of soluble contrast, alone or combined with low-volume barium (American College of Radiology, 2014).

Adequate distension of the colon is a requirement for CT colonography. To accomplish this, the physician or technician performing the procedure inserts a small, flexible catheter. Options for insufflation of the colon include air and carbon dioxide. Carbon dioxide is absorbed through the bowel wall and exhaled, making overdistension and discomfort less likely. Carbon dioxide has been shown to be more effective in reducing abdominal pain, both for CT colonography (Shinners et al., 2006) and for colonoscopy (Memon et al., 2016).

(ii) Patient positioning

Generally, images are obtained in both the supine and the prone positions. Imaging in two positions has several advantages: it enables redistribution of fluid and stool and improves segmental distension (Tewari et al., 2013).

(iii) Image interpretation

There is no consensus about the best approach to image interpretation and whether starting with the 2D or 3D images affects the findings. Generally, a 2D read is considered to be faster than a primary 3D read (de Haan et al., 2015). The performance of the two approaches has been compared. A large study by Pickhardt et al. (2007a) demonstrated that for the detection of adenomas 6 mm or larger, primary 2D CT colonography was less sensitive (44.1%) than 3D CT colonography (85.7%). However, in the large (n = 2600) ACR Imaging Network (ACRIN) study, no significant difference was seen between the two approaches in the detection of large lesions (Johnson et al.,

2008). The ESGAR consensus statement included statements about this topic (Neri et al., 2013a). There was strong consensus that interpretation should include both 2D and 3D visualization, and that the choice of the primary approach should be based on factors such as personal preference.

The time it takes to read a scan varies greatly, depending on experience and technique. In the multicentre study by Pickhardt et al. (2003), reading times were, on average, about 20 minutes. In a large, multicentre European investigation, somewhat shorter interpretation times were observed (~14 minutes) (Burling et al., 2006). The technique used is an important factor here. Although the 2D images have shorter interpretation times, there are multiple 3D approaches, which can vary in terms of time required for evaluation.

A separate but related issue for reading times is the use of a second reader to evaluate the scans. Computer-aided detection may facilitate the reading process; it uses software algorithms to highlight potential abnormalities that can be reviewed by the radiologists (Kumar & Cash, 2017).

A standard reporting format for CT colonography is now available. The CT Colonography Reporting and Data System (C-RADS) (Zalis et al., 2005) places studies into one of five categories of findings (C0–C4), depending on the interpretability of the scan and the severity of the findings. The categorization also outlines a suggested follow-up for each category. For findings in the categories C2 (intermediate polyp or indeterminate finding) and C3 (polyp, possibly advanced adenoma), colonoscopy is often the follow-up recommendation, and ideally systems are in place to move the patient to colonoscopy on the same day, so that a separate colon preparation is not required (Pickhardt, 2005). In addition to standard reporting of target findings within the colon, the C-RADS document also outlines standard reporting for extracolonic findings using a similar system of five categories (E0–E4).

(c) Quality control, including training

There is no single national or international standard on the performance of CT colonography. ACR (American College of Radiology, 2014) and ESGAR (Neri et al., 2013a) have issued guidance statements that cover the practical application issues discussed above.

The ACR document includes statements that preparation and distension should be adequate to detect large (≥ 10 mm) polyps, and that the examination should be a complete anatomical coverage (colon and rectum), with luminal surface views of each segment of the colon. The determination of detection rates for polyps 10 mm or larger is encouraged, as is the use of a registry to track performance. Guidance about interpretation includes outlining the need to have access to both 2D and 3D representations of the bowel, and to report polyp measurement in the largest dimension. ACR endorses the reporting of all polyps 6 mm or larger, and considers that reporting polyps smaller than 6 mm is not necessary. Significant extracolonic findings should be reported, and a "balanced approach" should be taken to recommending further workup of extracolonic findings, considering a host of factors (e.g. the clinical importance of the finding, cost, and patient anxiety) (American College of Radiology, 2014).

The approach of ESGAR to developing recommendations is slightly different to that of ACR. A panel of nine delegates from six European Union countries used a modified Delphi process to establish consensus. The panel was asked to evaluate 86 statements about all aspects of the CT colonography procedure, including patient preparation, image acquisition, and interpretation. After four rounds, the panel reached full consensus on 82% of the statements (Neri et al., 2013a).

The ACR document also establishes some training parameters for CT colonography. For physicians with prior qualifications in reading

abdominal and pelvic CT scans, education and hands-on experience with at least 50 CT cases is generally recommended. For physicians without prior experience in interpreting abdominal and pelvic CT scans (e.g. non-radiologists, such as gastroenterologists), completion of more than 200 hours of continuing medical education in the performance and interpretation of abdominal and pelvic CT scans and supervised review of at least 500 CT cases are needed before addressing CT colonography-specific training (American College of Radiology, 2014).

The American Gastroenterological Association released its own set of standards for gastroenterologists performing CT colonography (Cash et al., 2011). The guidance suggests that non-radiologists could perform colon-only interpretation (i.e. avoiding extracolonic CT images) after a period of fairly extensive training including more than 200 case reads with close mentorship.

(d) Screening performance

Several meta-analyses and systematic reviews have been conducted on the screening performance of CT colonography in terms of sensitivity and specificity (Mulhall et al., 2005; Whitlock et al., 2008; Martín-López et al., 2011; Pickhardt et al., 2011; Martín-López et al., 2014).

Most recently, the USPSTF performed a detailed evidence review (Lin et al., 2016a,b). Nine studies (Pickhardt et al., 2003; Macari et al., 2004; Johnson et al., 2007, 2008; Kim et al., 2008; Graser et al., 2009; Zalis et al., 2012; Fletcher et al., 2013; Lefere et al., 2013) of fair or good quality (n = 6497) assessed the screening performance of CT colonography. In seven studies (Pickhardt et al., 2003; Macari et al., 2004; Johnson et al., 2007, 2008; Kim et al., 2008; Graser et al., 2009; Lefere et al., 2013) colon preparation was used, and in two studies (Zalis et al., 2012; Fletcher et al., 2013) it was not. Colonoscopy was the standard reference for the assessment of test characteristics. When the seven studies that used colon preparation were considered, the per-person sensitivity of CT colonography for lesions 10 mm or larger was 67–94% and the per-person specificity was 96–98%. When lesions 6 mm or larger were considered, the per-person sensitivity was 73–98% and the per-person specificity was 89–91%.

An earlier meta-analysis also summarized evidence on the sensitivity of CT colonography for the detection of polyps (de Haan et al., 2011). It included four studies (Pickhardt et al., 2003; Johnson et al., 2008; Kim et al., 2008; Graser et al., 2009) that reported the sensitivity of CT colonography for adenoma detection at the 6 mm threshold and the 10 mm threshold. The per-patient sensitivity of CT colonography was 82.9% for adenomas 6 mm or larger and 87.9% for adenomas 10 mm or larger. No cancers were missed in any of these studies.

(e) Host factors that affect performance

Although there are several contraindications to the performance of CT colonography, most are not relevant to screening examinations. For example, there is an increased risk of perforation with CT colonography in those who have had recent colonoscopy or deep mucosal biopsies (American College of Radiology, 2014) (see also Section 3.5.3). One patient-related factor of some concern may be obesity. Radiological imaging generally requires higher doses of radiation in such circumstances (Yanch et al., 2009), and therefore the risk of inducing secondary cancer may be incrementally higher in obese individuals.

3.5.2 Preventive effects

There are no RCTs or observational studies that have reported CRC incidence or mortality outcomes associated with screening with CT colonography. Early evaluation of the effectiveness of CT colonography for the detection of advanced neoplasia was typically measured by tandem studies of CT colonography and colonoscopy in

a single group of patients (i.e. one-time screening with CT colonography followed by colonoscopy as the reference standard). These studies often included both asymptomatic individuals and individuals at higher risk (because of symptoms, family history, or history of colonic lesions), and therefore could not be interpreted as providing evidence related to test performance in a screening cohort.

Current evidence of the effectiveness of CT colonography comes from tandem studies, RCTs, and modelling studies in which detection rates of adenomas and cancer with CT colonography are compared with those with an established CRC screening test.

(a) Tandem studies

The tandem studies of CT colonography screening in asymptomatic adults in which the ADR and cancer detection rate (CDR) were reported or could be calculated are presented in Table 3.5.1. In 2003, Pickhardt et al. (2003) evaluated a cohort of 1233 asymptomatic adults who underwent same-day CT colonography and colonoscopy and observed slightly better performance with CT colonography in the detection rate of adenomas 10 mm or larger and of cancer compared with colonoscopy. The ADR for colonoscopy was superior to that for CT colonography for adenomas 6 mm or larger, but this was principally due to the subset of adenomas 6 mm in size. Kim et al. (2007) compared the performance of CT colonography and colonoscopy in two separate groups of consecutive adults undergoing screening with each test and observed similar detection rates for advanced neoplasia.

The first prospective, tandem study of significant size comparing CT colonography and colonoscopy in asymptomatic adults was the National CT Colonography Trial (ACRIN 6664), reported in 2008 (Johnson et al., 2008). The trial recruited about 2600 asymptomatic adults 50 years or older who underwent CT colonography followed by colonoscopy, which served as the reference standard. The primary end-point was detection by colonoscopy of large adenomas (≥ 10 mm) and adenocarcinomas, although radiologists reported all detected lesions 5 mm or larger, which enabled comparative measures of sensitivity per millimetre of size of adenomas and cancers. Per-polyp sensitivity was expressed as the proportion of lesions detected by colonoscopy that were also detected by CT colonography, which increased with increasing lesion size, from 0.59 for polyps 5 mm or larger to 0.84 for polyps 10 mm or larger (Johnson et al., 2008) Separate per-patient ADR and CDR were not reported. Graser et al. (2009) evaluated the performance of gFOBT, FIT, sigmoidoscopy, CT colonography, and colonoscopy in a group of 307 asymptomatic adults who underwent each of these tests consecutively, with colonoscopy as the reference standard. CT colonography and colonoscopy had a nearly equivalent performance in the detection of advanced adenomas (7.5% vs 8.1%) and of advanced neoplasia (9.4% vs 9.8%), and both CT colonography and colonoscopy identified the one case of cancer in the study group.

(b) Randomized controlled trials

In the Netherlands, the Colonoscopy or Colonography for Screening (COCOS) trial was initiated in 2009 to compare the participation rate and the detection rates between a CT colonography arm (n = 982 of 2920 CT colonography invitees) and a colonoscopy arm (n = 1276 of 5924 colonoscopy invitees) and to eventually link participants to the national cancer registry 10 years after invitation, for follow-up on CRC incidence and mortality (de Wijkerslooth et al., 2010; Stoop et al., 2012). Participants in the CT colonography arm who had one or more lesions 10 mm or larger were offered immediate colonoscopy; participants with three or more lesions of 6–9 mm were scheduled for colonoscopy in 1.5 years, and participants with one to two lesions of 6–9 mm were offered surveillance CT colonography in 3 years. The two primary outcomes were

Table 3.5.1 Detection rates of neoplastic lesions with CT colonography and colonoscopy in randomized controlled trials and tandem studies of colorectal cancer screening in asymptomatic adults

Study	Study type	Age at enrolment (years)	No. of participants	Detection rate of adenomas ≥ 10 mm (%) CTC/OC	Detection rate of cancer (%) CTC/OC	Detection rate of advanced neoplasia[a] (%) CTC/OC	Comments
Pickhardt et al. (2003)	Single cohort, TS	40–79	1233	3.6/3.4[b]	0.16/0.08[b]	4.1/4.0[c]	All patients underwent same-day CTC and OC
Kim et al. (2007)	Parallel CTC and OC studies of consecutive adults undergoing screening	CTC: 57 (7.2)[d] OC: 58 (7.8)[d]	CTC: 3120 OC: 3163	3.3/3.3[c]	0.45/0.13[c]	3.9/3.8[c]	Patients with polyps ≥ 6 mm detected by primary CTC were offered same-day OC
Johnson et al. (2008)	Single cohort, TS	≥ 50	2531	—	—	3.9/4.3[b]	
Graser et al. (2009)	Single cohort, TS	50–81	307	7.5/8.1[b]	0.3/0.3[b]	9.4/9.8[b]	Parallel comparison of CTC, OC, FS, FIT, and gFOBT
Stoop et al. (2012)	RCT (COCOS trial)	50–75	CTC: 982 OC: 1276	5.4/6.3[b,e]	0.5/0.5[b]	6.1/8.7[b]	Patients with ≥ 1 lesions ≥ 10 mm detected by CTC were referred for OC
Sali et al. (2016)	RCT (SAVE trial)	54–65	CTC: 1286 OC: 153	2.6/2.0[b,e]	0.5/0[b]	5.2/7.2[b]	CTC arm divided into reduced cathartic preparation and full cathartic preparation. In the CTC groups, participants with a colonic mass or ≥ 1 polyps > 6 mm were referred for OC
Regge et al. (2017)	RCT (Proteus trial)	58–60	2595	3.8[b,e]	0.4[b]	5.1[b]	CTC with non-cathartic preparation The aim of this trial was to compare participation rates and detection rates between FS and CTC in a screening setting

COCOS, Colonoscopy or Colonography for Screening; CT, computed tomography; CTC, CT colonography; gFOBT, guaiac faecal occult blood test; FIT, faecal immunochemical test; FS, flexible sigmoidoscopy; OC, optical colonoscopy; RCT, randomized controlled trial; TS, tandem study or studies.

[a] Advanced neoplasia may include adenomas ≤ 10 mm with prominent villous components or high-grade dysplasia.

[b] Per participant or patient.

[c] Per polyp.

[d] Mean age (standard deviation).

[e] Advanced adenomas ≥ 10 mm.

the participation rate, defined as the number of invitees undergoing the examination relative to the total number of invitees, and the detection rate, defined as the number of participants with advanced neoplasia relative to the total number of invitees. The CDR per 100 participants was equivalent in the CT colonography and colonoscopy arms (both 0.5%; $P = 0.91$), and the CDR per 100 invitees was 0.1 in the CT colonography arm and 0.2 in the colonoscopy arm ($P = 0.50$). The overall advanced ADR per 100 participants was higher in the colonoscopy arm (8.2%) than in the CT colonography arm (5.6%) ($P = 0.02$), and the advanced ADR per 100 participants for adenomas 10 mm or larger was also higher in the colonoscopy arm (6.3%) than in the CT colonography arm (5.4%), although the difference was not statistically significant (Stoop et al., 2012). [Because enrolment was considerably lower than initial targets, the Working Group expressed concerns that the study had insufficient statistical power.]

Two RCTs in Italy compared the detection rate and the participation rate between CT colonography and other CRC screening methods. The SAVE trial randomized adults to CT colonography, FIT, and colonoscopy to compare the participation rate, detection rate, and screening costs (Sali et al., 2013, 2016). A cohort of approximately 16 000 adults aged 54–65 years with no history of CRC screening was randomized into three groups. Group 1 ($n = 1286$ of 4825 eligible invitees) was invited to undergo CT colonography, and the CT arm was divided into reduced cathartic preparation and full cathartic preparation groups. Group 2 ($n = 4677$ of 9288 eligible invitees) was invited to undergo three rounds of biennial FIT. Group 3 ($n = 153$ of 1036 eligible invitees) was invited to undergo colonoscopy. Adults in the CT colonography arm with one or more polyps 6 mm or larger or with a colonic mass were invited to undergo colonoscopy, and adults with no lesions or with polyps smaller than 6 mm were classified as having negative results and were invited to undergo FOBT after 5 years. The advanced ADR was 4.7% in the CT colonography arm versus 7.2% in the colonoscopy arm, and the detection rate for all advanced neoplasia was 5.2% in the CT colonography arm versus 7.2% in the colonoscopy arm. [The investigators considered the smaller size of the colonoscopy arm ($n = 153$) as a limitation of the study and emphasized that the principal interest in comparing the CT colonography arm ($n = 1286$) and the colonoscopy arm related to participation rate and not detection rate.] CT colonography detected more CRC compared with FIT (0.5% vs 0.1%) and more advanced adenomas (4.7% vs 1.6%) per participant (Sali et al., 2016). [The Working Group noted the difference in the size of the arms as a limitation.]

The second RCT in Italy, the Proteus trial, included two RCTs comparing the acceptability and detection rate between CT colonography and sigmoidoscopy within a population-based screening programme: a pragmatic RCT comparing participation rates (Proteus 1) and an efficacy RCT comparing advanced ADR and CDR (Proteus 2) (Regge et al., 2014, 2017). The target population comprised adults aged 58 years residing in the Piedmont region and adults aged 60 years residing in Verona. Adults who agreed to participate were randomized to either sigmoidoscopy or CT colonography with non-cathartic preparation. Participants in the CT colonography arm with no lesions or with lesions smaller than 6 mm were interpreted as having negative results; participants with lesions 6 mm or larger were invited to undergo colonoscopy. In the sigmoidoscopy arm, polyps smaller than 10 mm detected during sigmoidoscopy were removed and sent for histological evaluation, and participants with polyps 10 mm or larger or with "high-risk polyps" (at least one advanced adenoma < 10 mm, or more than two small tubular adenomas with low-grade dysplasia) were referred for colonoscopy. In Proteus 2, comparable CDRs and ADRs were

reported for CT colonography and sigmoidoscopy. The CDR was 0.4% for CT colonography and 0.3% for sigmoidoscopy, and the advanced ADR for lesions 10 mm or larger was 3.8% for CT colonography and 3.5% for sigmoidoscopy. The detection rate for proximal advanced neoplasia for CT colonography (2.7%) was double that for sigmoidoscopy (1.3%); the detection rate for distal advanced neoplasia was 2.9% for CT colonography and 4.1% for sigmoidoscopy. [The investigators speculated that quality issues, such as the non-cathartic preparation, suboptimal distension, and a new computer-aided detection reading algorithm, may have contributed to the lower than expected detection rates in the distal colon (Regge et al., 2017).]

(c) Modelling studies

Simulation modelling of different screening strategies provides an opportunity to estimate their comparative effectiveness and to estimate conventional end-points such as CRC incidence, mortality, and LYG associated with screening.

Lucidarme et al. (2012) used a simulation model to assess the outcomes and cost–effectiveness of colonoscopy, CT colonography, and gFOBT (without rehydration) based on varying rates of attendance over a 10-year period. The screening intervals for colonoscopy, CT colonography, and gFOBT were 10 years, 5 years, and 2 years, respectively, with colonoscopy surveillance intervals of 3–5 years, depending on the nature of positive findings at screening. An unconventional, but practical, end-point was used: the rate of remaining CRC, defined either as screened and undetected disease or as unscreened and undetected disease (in keeping with simulated attendance rates), to estimate the cost per CRC avoided over 10 years. For example, with no screening, the remaining CRC rate per 10 000 people was estimated to be 123 cancers per 10 000 adults older than 50 years, equivalent to the expected cumulative incidence over the 10-year period. With 100% participation in screening, which represents one screening colonoscopy or two screening CT colonographies over the 10-year period, the model estimated that the remaining CRC rate per 10 000 adults was 17 in the colonoscopy arm and 2 in the CT colonography arm (Lucidarme et al., 2012). [The Working Group noted that in the CT colonography arm there were two opportunities to diagnose a CRC, compared with one opportunity in the colonoscopy arm, consistent with a 5-year screening interval for CT colonography compared with a 10-year screening interval for colonoscopy.] Overall, for any participation rate in the simulation, CT colonography screening was the most effective but not always the most cost-effective strategy; gFOBT was the least effective but most cost-effective strategy, and colonoscopy had an intermediate effectiveness and was the least cost-effective strategy (Lucidarme et al., 2012).

The Cancer Intervention and Surveillance Modeling Network (CISNET) recently estimated the long-term effectiveness of CT colonography for the USPSTF's update of its 2008 CRC screening recommendations (Bibbins-Domingo et al., 2016); modelling conducted for the 2008 update did not include CT colonography (Zauber et al., 2008). The modelling was conducted with three separate microsimulation models (SimCRC, MISCAN, and CRC-SPIN) and was used to simulate the effects of different ages at the start of screening and the end of screening, and of different screening intervals, on life years lost and LYG as a measure of benefit, and the number of lifetime colonoscopies as a measure of the burden of screening for an individual aged 40 years at average risk beginning screening at various ages in the simulations (Knudsen et al., 2016). Screening strategies included annual HSgFOBT and FIT, mt-sDNA, sigmoidoscopy every 10 years with annual FOBT or sigmoidoscopy every 5 years without FOBT, CT colonography, and colonoscopy. In all three microsimulations, CT colonography test characteristics were derived from the ACRIN 6664 trial (Johnson et al., 2008). For

comparisons within CT colonography strategies and between simulations of all CRC screening tests, the incremental number of colonoscopies (ΔCOL), the incremental LYG (ΔLYG), and the efficiency ratio (i.e. ΔCOL/ΔLYG) relative to the next-less-effective efficient strategy were calculated for the efficient and near-efficient strategies. The study simulated 15 unique CT colonography screening strategies representing different ages at the start of screening (45, 50, or 55 years), ages at the end of screening (75, 80, or 85 years), and screening intervals (5 years or 10 years). In the analyses, across all three models, the estimated median reduction in the lifetime risk of dying from CRC associated with screening with CT colonography every 5 years between age 50 years and age 75 years was 72–85%. In comparison, the median reduction in the lifetime risk of dying from CRC associated with screening was 72–81% with annual FIT, 77–85% with annual FIT plus sigmoidoscopy every 10 years, and 79–90% with colonoscopy every 10 years (Knudsen et al., 2016).

Barzi et al. (2017) used a Markov model to simulate CRC screening with 13 strategies (gFOBT, FIT, mt-sDNA, sigmoidoscopy, colonoscopy, and CT colonography), including CT colonography every 10 years, on a cohort of 100 000 adults aged 50–75 years in the USA followed up for 35 years or until death. The outcome measures included discounted LYG and prevented cases of CRC. In the base case model, there was no difference between CT colonography and colonoscopy in terms of discounted LYG (15.225 vs 15.227 LYG). CT colonography detected more cancers (3594 vs 3462) but prevented fewer cancers (1068 vs 930) and fewer CRC deaths (922 vs 863). The corresponding reduction in the risk of CRC was 23% with colonoscopy and 20% with CT colonography; the corresponding reduction in the risk of CRC death was 34% for colonoscopy and 30% for colonoscopy. CT colonography was the second most efficient strategy among the 13 strategies compared in the simulation (Barzi et al., 2017).

3.5.3 Adverse effects

The potential adverse effects of CT colonography include perforation, non-serious adverse events associated with colon preparation (such as abdominal pain), and examination-related pain, vasovagal syncope, and presyncope. Other potential harms are an increased risk of radiation-induced cancer from a single examination or multiple examinations, and extracolonic findings.

Perforation during CT colonography screening is very rare and is typically associated with insufflation. A common finding in most reports of perforation during CT colonography is the presence of symptoms such as inflammatory bowel disease, ulcerative colitis, and cancer. Lin et al. (2016a) identified 15 studies that addressed serious adverse events associated with CT colonography in screening and mixed populations (screening and diagnostic examination). The risk of perforation during CT colonography was less than 0.02% overall (2 per 10 000 CT colonography procedures); in 11 prospective studies restricted to screening populations (n = 10 272), no perforation events were reported (Lin et al., 2016a). In another systematic review and meta-analysis of 11 studies including more than 100 000 patients (including 7 among the 15 studies from Lin et al., 2016a), 28 colon perforations were reported, for an estimated perforation rate of 0.04% overall and 0.02% in asymptomatic patients (Bellini et al., 2014).

Although only low-dose, non-enhanced multidetector CT protocols are recommended for screening asymptomatic adults at average risk, there is still concern about the estimated risk of radiation-induced cancer from a single examination and multiple examinations, and the cumulative dose that may be accrued from examinations for other conditions (Brenner & Hall, 2007). The systematic review by Lin et al. (2016a) of CT colonography screening studies revealed few studies that reported average exposures and

dose levels, but the evidence reflected a decrease in exposures over time with newer multidetector scanners and greater attention to dose-reducing protocols. For example, in the ACRIN 6664 study, which enrolled participants in 2005–2006, the estimated mean effective dose per CT colonography screening study was 8 mSv for women and 7 mSv for men, whereas more recent data from a 2011 survey of practices in the USA revealed that the mean effective radiation dose for CT colonography screening had declined to 4.4 mSv (Boellaard et al., 2012). This effective dose level is greater than that of a chest X-ray (0.4 mSv) and a mammogram (0.4 mSv) but less than that of most diagnostic CT procedures (American College of Radiology, 2017) and is estimated to be equivalent to about 16 months of natural background radiation.

Berrington de González et al. (2011) estimated the radiation-related risk of cancer using risk projection models based on the report of the Biological Effects of Ionizing Radiation (BEIR) VII committee (Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, 2006) and screening protocols from the ACRIN 6664 trial (Berrington de González et al., 2011). A single CT colonography examination at age 50 years would result in a slightly higher risk (0.06%) than a single screening examination at age 70 years (0.03%). A series of CT colonography examinations every 5 years from age 50–80 years, which include additional radiation exposure from follow-up CT examinations for incidental, extracolonic findings, were estimated to result in a 0.15% risk of radiation-induced cancer (Berrington de González et al., 2011). The estimated benefit of screening in avoiding a CRC death was estimated to be considerably higher than the estimated risk of radiation-induced death from CRC screening, with a ratio ranging from 35:1 to 47:1 (Berrington de González et al., 2011).

Extracolonic findings represent potential harms, but in some instances the detection of an extracolonic finding may be beneficial. Extracolonic findings were reported in 27–69% of CT colonography examinations (Lin et al., 2016a) and included small masses, suspected cancers, aneurysms, and adenopathy. Detection of unsuspected, clinically significant findings, such as extracolonic cancers, which are uncommon, and abdominal aortic aneurysms, may represent a benefit to the patient. However, some extracolonic findings may be insignificant, requiring no further evaluation, whereas others are judged to be potentially serious enough to warrant additional imaging, which may prove to be unproductive and result in an increased radiation dose and in diagnostic and therapeutic procedures that may also result in serious complications. On the C-RADS scale ranging from E0 to E4 (where E0 is a compromised examination and E1 or E2 represents no or insignificant extracolonic findings), E3 is judged as likely unimportant but may warrant additional workup, and E4 is a potentially important finding that requires follow-up (Zalis et al., 2005).

Lin et al. (2016a) summarized the challenges of obtaining clear estimates of the burden of extracolonic findings from studies that often include heterogeneous patient samples (asymptomatic vs mixed populations), variations in reporting extracolonic findings (all vs suspected malignancies only), variable age ranges in the study group (the risk of extracolonic findings increases with age), variations in reporting medical follow-up including treatment, and variations in duration and completeness of follow-up. In a review of 21 studies ranging in size from 75 patients to 10 286 patients, Lin et al. (2016a) reported that the frequency of E3 and E4 findings ranged from 5% to 37%, and the frequency of E4 findings ranged from 1.7% to 12%. In studies that reported medical follow-up, 1.4–11% of patients were referred for further evaluation, but only 3% or less underwent treatment. In a report from a large single practice (Pooler et al., 2016), 88.3% of the patients with extracolonic findings had

category E1 and E2 extracolonic findings (not clinically relevant), 9.1% had E3 findings (likely unimportant), and 2.5% had E4 findings (potentially important). The potential benefit of extracolonic findings was higher in the E4 group, with 68% of patients receiving a diagnosis of clinically significant disease (malignancies, abdominal aortic aneurysms, etc.), whereas patients with an E3 finding were very unlikely to have clinically significant extracolonic disease (8.3%).

3.5.4 Benefit–harm ratio and cost–effectiveness

The benefits of CT colonography include high sensitivity for advanced adenomas and cancer, and the possibility that some extracolonic findings represent important occult disease. Harms associated with CT colonography include perforation (for which the risk is lower than that with colonoscopy), radiation-induced cancer, the need to undergo a second colon preparation if the findings are positive and same-day colonoscopy is not feasible, and the downstream effects of the detection of extracolonic findings that warrant further investigation and are determined to be benign. The existing evidence indicates that CT colonography has a favourable benefit–harm ratio.

The cost–effectiveness of CT colonography can be estimated relative to no screening or relative to other screening tests (de Haan et al., 2015). The costs of CT colonography include costs associated with the initial examination, costs associated with follow-up colonoscopy, and costs associated with the evaluation and treatment of extracolonic findings. The review of the studies of cost–effectiveness of CT colonography relative to no screening found that in all studies CT colonography screening, at different intervals, was cost-effective relative to no screening (Hassan & Pickhardt, 2013). Knudsen et al. (2010) also estimated that CT colonography screening every 5 years was cost-beneficial (i.e. less costly) relative to no screening in the Medicare population in the USA, and Heresbach et al. (2010) showed that CT colonography screening easily meets conventional criteria for cost–effectiveness compared with no screening.

Comparative cost–effectiveness, when CT colonography is compared with other screening tests, is sensitive to model parameters, i.e. the cost of the tests, additional programme costs, testing intervals, test accuracy, downstream costs, and assumptions about the natural history of the disease. Although model assumptions, including test performance, intervals, and participation rates, vary considerably in existing models, most comparisons have been with colonoscopy and have shown that colonoscopy every 10 years is more cost-effective than CT colonography is (Knudsen et al., 2010; Lee et al., 2010). However, cost–effectiveness is significantly influenced by the cost and the estimated accuracy of the tests being compared and, in particular, the participation rate. CT colonography has been shown to be more cost-effective than colonoscopy when the participation rate of CT colonography exceeds that of colonoscopy (Pickhardt et al., 2007b; Knudsen et al., 2010; Hassan & Pickhardt, 2013). For example, assuming 100% participation in screening in the Medicare population in the USA, Knudsen et al. (2010) showed that the LYG from 5-yearly CT colonography was similar to the LYG from 10-yearly colonoscopy but that the programme costs of CT colonography were higher. However, if the relative participation in CT colonography screening was 25% higher than participation in other tests, then CT colonography could be cost-effective if reimbursed at US$ 488 per examination (Knudsen et al. 2010).

In a recent simulation of CRC screening in the Netherlands, van der Meulen et al. (2018) compared the cost–effectiveness of CT colonography versus colonoscopy in a microsimulation model (MISCAN) using data from the COCOS trial. In the comparison of 10-yearly screening with colonoscopy and CT colonography in 1000

adults aged 50–70 years with 100% participation, screening with colonoscopy resulted in fewer CRC deaths and more QALYs gained (106 vs 81) compared with CT colonography. The costs of the colonoscopy programme were higher than those of the CT colonography programme, but treatment costs were lower, which resulted in lower total programme costs for colonoscopy. In contrast, when observed CT colonography participation rates from the COCOS trial were used, which were higher than colonoscopy participation rates, CT colonography screening had higher costs but was associated with a higher reduction in CRC deaths and more QALYs gained (29 vs 22). Based on observed participation rates, the simulation showed that colonoscopy screening with more than two lifetime screens would be less cost-effective than CT colonography screening.

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3.6 Participation in screening for colorectal cancer

The conceptual frameworks that have been proposed to analyse factors that influence access to, delivery of, and quality of screening (Green & Kreuter, 2005; Anhang Price et al., 2010; Sabatino et al., 2012) acknowledge that screening is a process of care that occurs in a multilevel environment, including at the policy, organization, provider, and patient levels (Table 3.6.1). The delivery by providers and the use of screening by individuals are influenced by several factors that interact synergistically at these different levels of the health-care system.

3.6.1 Determinants of participation in colorectal cancer screening

(a) At the policy level

The type of insurance coverage and the cost of the test have been consistently shown to influence screening rates and subjects' preferences for specific tests (Gimeno Garcia et al., 2014; May et al., 2017; White et al., 2017). Insurance status is the most important determinant of use of screening services in the USA, where screening is primarily opportunistic (Gellad & Provenzale, 2010). Also, co-payment [financial participation by the screenee] for a CRC screening test was found to be associated with lower screening rates among subjects with lower income (Fedewa et al., 2015). An analysis of temporal trends in CRC mortality before and after introduction of screening in the USA supports the hypothesis that screening rates are lower in populations with lower (uninsured) socioeconomic status (SES) than in populations with higher SES, and that this difference contributed to the observed widening of the disparity in population mortality (Breen et al., 2017).

Compared with areas where only opportunistic screening is available, higher screening rates have been reported and disparities by SES tended to be smaller in areas where organized programmes had been introduced (Eisinger et al., 2008; Carrozzi et al., 2015a). However, studies conducted within organized FOBT-based programmes (de Klerk et al., 2018) showed substantial differences in participation between the least deprived and the most deprived subjects, suggesting that lower SES may still be a barrier to screening participation even in organized settings. In settings where most CRC screening relies on office-based interventions delivered by primary care physicians, subjects without access to primary care are excluded from participation (Levin et al., 2011; White et al., 2017).

(b) At the organizational level

(i) Invitation

Organizational measures that enable subjects to adopt the recommended behaviours play a crucial role. Studies in opportunistic settings showed that delivering informational material was associated with an increase in screening rates only if providers offered support for scheduling screening appointments and subjects were not requested to make arrangements on their own (Costanza et al., 2007; Sequist et al., 2009). There is strong evidence that reminders (i.e. active invitations sent by mail to subjects who are due, or overdue, for CRC screening) are effective in increasing participation in screening (Sabatino et al., 2012; Camilloni et al., 2013). Other factors related to service organization that are consistently inversely related to participation in screening are the amount of time required to perform screening and the distance of the subject's residence from the test provider (Jepson et al., 2000; Federici et al., 2006a; Koo et al., 2012). Population-based programmes provide the organizational framework for reducing inequities in screening access by using call-and-recall systems, which ensure that each eligible subject has the opportunity to participate.

Table 3.6.1 Determinants of participation in colorectal cancer screening by level of care

Level of care	Facilitators for participation	Barriers to participation
Policy	Implementation of organized population-based programmes providing screening and assessment free of charge	Co-payment Lack of insurance coverage when not free of charge Cost of the test
Organization of screening	Reminders sent to invitees Reminders sent to providers *Endoscopy screening:* Enhanced office and patient management (invitation letters plus monitoring of response plus motivational interview)[b] *gFOBT/FIT screening:* Mailing of test kits	Distance of the subject's residence from the provider Time required to perform screening Need for the patient to make own arrangements to schedule the test Male sex (FIT) Female sex (endoscopy) Test characteristics (participation in a single round: colonoscopy < sigmoidoscopy < FIT)[c]
Provider[a]	*Enabling factors:* GP training focused on communication skills	*Predisposing factors:* Negative attitudes towards screening and prevention Lack of knowledge about screening effectiveness and procedures *Enabling factors:* Lack of time for preventive interventions
Patient[a]	*Predisposing factors:* Perceived susceptibility to CRC Informational brochure/enhanced procedural informational brochure Advance notification letter *Reinforcing factors:* Invitation letter signed by GP Family history of CRC or direct experience of CRC affecting relatives or friends *Enabling factors:* Adoption of preventive practice/healthy lifestyle *Endoscopy screening:* Face-to-face counselling[b] Narrative invitation letter (using stories about similar people to counter perceived barriers and cultivate self-efficacy)[b] *gFOBT/FIT screening:* Telephone and text message reminders[b] Telephone contact with a navigator[b] Telephone assistance[b]	*Predisposing factors:* Negative attitudes towards screening and prevention Fatalistic attitude towards cancer Anxiety associated with repeated testing Cultural and religious values Lack of knowledge about screening effectiveness and procedures SES/education level, mediated through differences in knowledge, beliefs (fatalism), and expectations (perceived relative weights of short-term inconveniences and long-term benefits) Ethnicity, mediated through education level, access to care, and knowledge *Enabling factors:* Life difficulties

CRC, colorectal cancer; FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; GP, general practitioner; SES, socioeconomic status.

[a] Determinants are classified according to the framework of the Precede–Proceed model (Green & Kreuter, 2005).

[b] Assessment conducted in opportunistic settings.

[c] Acceptability of the screening strategies is context-specific, and it may vary across jurisdictions. Assessment of participation should be one of the aims of pilot screening studies.

(ii) Screening modality

Multiple tests are currently used for CRC screening, and they have different effectiveness, acceptability, safety, and cost profiles. Dislike of the recommended test appears to be a specific barrier to participation in CRC screening (Lo et al., 2013).

Participation rates in programmes with stool-based tests for blood are higher in women than in men (Klabunde et al., 2015; Ponti et al., 2017), whereas participation rates in endoscopy-based programmes are higher in men than in women (Segnan et al., 2005; Ponti et al., 2017).

(c) At the provider level

The involvement of general practitioners (GPs) was shown to be effective in increasing participation in both organized programmes (Grazzini et al., 2000; Raine et al., 2016) and opportunistic settings (Seifert et al., 2008; Koo et al., 2012). Participation in screening was shown to be closely linked to the GP's level of motivation for screening (Federici et al., 2006a) and to the level of support provided by other trusted primary care physicians (Malila et al., 2008), in particular for less-educated people or older people, who are less likely to use written informational material (Senore et al., 2010). However, some studies reported that these populations are less likely to receive advice about CRC screening from a GP or other primary care physician (Sabatino et al., 2008; Ferroni et al., 2012), which would suggest that inadequate GP counselling may contribute to the observed SES-related gradient in participation.

The lack of knowledge of primary care physicians about the effectiveness of recommended screening modalities and about test characteristics and screening protocols appears to be an important barrier to screening participation in several countries (Koo et al., 2012; Honein-AbouHaidar et al., 2016; Muliira et al., 2016). Enhancing health-care providers' knowledge about CRC screening should increase participation in CRC screening. Other provider-associated barriers are failure to recall patients or to identify high-priority patients for screening, and lack of time dedicated to preventive care (Stone et al., 2002).

The characteristics of the provider may also play a role in participation rates. Women may perceive endoscopy examinations to be less embarrassing if they are conducted by a female endoscopist (Menees et al., 2005). The lack of a sex difference in participation rates when sigmoidoscopy screening was delivered by a female nurse (Robb et al., 2010) supports this hypothesis.

(d) At the patient level

Lack of awareness of CRC and of the purposes of CRC screening, and negative perceptions or attitudes (e.g. worry about pain, discomfort, embarrassment associated with the test, fear about test results, shyness about being screened, the perception that screening is not necessary, or fatalistic views of cancer) emerge as barriers to screening participation, in both qualitative and quantitative studies, and were consistently associated with a lower participation rate (Galal et al., 2016; Honein-AbouHaidar et al., 2016; Wools et al., 2016). Anxiety associated with regular repetition of screening tests was a strong negative predictor of participation in CRC screening, even among those who believed the screening to be effective (Senore et al., 2010).

Culture- and religion-specific barriers to screening participation may pose additional hurdles, independent of financial considerations, that limit participation in CRC screening. Subjects who hold traditional views of care tend to have lower screening participation, probably as a result of misconceptions about CRC and about screening, a distrust of conventional medicine, or a lack of familiarity with screening tests. Religious objections and cultural background, which may affect an individual's perception of the acceptability of the test, have been reported as

barriers to participation in endoscopy screening (Galal et al., 2016; Honein-AbouHaidar et al., 2016; Taha et al., 2016).

Perceived susceptibility to CRC is a facilitator for participation in screening, although several studies have shown that perception of a high CRC risk may be associated with an increase in participation in endoscopy but not in FOBT (Wools et al., 2016). Health motivation, measured by either the adoption of health-promoting behaviours (e.g. undergoing mammography screening, having a cholesterol check, or visiting a GP or dentist) or the avoidance of unhealthy habits (e.g. smoking or alcohol consumption), has been identified as a factor that is associated with a higher likelihood of participating in CRC screening, although lower participation has been reported among individuals who reported a very healthy lifestyle (Sicsic & Franc, 2014).

The persistent differences in participation in CRC screening by SES, or education level, also in the context of established population-based programmes (de Klerk et al., 2018), may be partially explained by differences in knowledge, beliefs, and expectations (Honein-AbouHaidar et al., 2016; Smith et al., 2016): groups with lower SES may consider screening to be more frightening and less beneficial compared with groups with higher SES, even if screening is publicized in an identical way and is provided free of charge, at a convenient location and time, to all SES groups. Better self-rated health and lower cancer fatalism, which are directly associated with higher participation in FOBT screening, mediate the impact of SES on participation (Miles et al., 2011). Qualitative research findings indicate that cognitive factors, including fatalistic beliefs about CRC (Lo et al., 2013; Honein-AbouHaidar et al., 2016) and the individual's perception of the relative weights of short-term inconveniences and long-term benefits (Whitaker et al., 2011), are associated with SES and mediate the negative impact of social deprivation on participation. Social cognition variables (i.e. knowledge, risk awareness, and attitudes) were shown to be strongly associated with intention but only weakly associated with action; action is better predicted by factors related to life difficulties (Power et al., 2008), which are likely to be associated with higher deprivation levels (Smith et al., 2016).

SES may also mediate the impact of ethnicity on participation: ethnic differences in screening participation tend to decrease (Liss & Baker, 2014), or even to disappear (Doubeni et al., 2010), after adjustment for level of knowledge, SES indicators, or access to care. Also, a screening survey in Italy showed a strong correlation between the participation rate of immigrants and that of Italians by screening programme, suggesting that some structural determinants of accessibility are common to different ethnicities (Turrin et al., 2015).

Studies in different countries reported a positive association between having a family history of CRC or having had direct experience of CRC affecting relatives or friends and the likelihood of responding to an invitation to CRC screening (Koo et al., 2012; Galal et al., 2016; Honein-AbouHaidar et al., 2016), although no such effect was observed in other studies.

Support from a partner plays a strong role: married adults are more likely than non-married adults to participate in CRC screening (Artama et al., 2016; Galal et al., 2016; Wools et al., 2016; Honein-AbouHaidar et al., 2016).

(e) Follow-up of subjects with abnormal findings

The potential reduction of mortality through screening can be achieved only if subjects with abnormal findings receive timely and appropriate follow-up, following evidence-based guidelines. According to reports from surveys monitoring the receipt of appropriate follow-up care by patients with abnormal results, a substantial proportion (8–34%) of subjects with positive

test results are not undergoing the recommended assessment (Yabroff et al., 2003; Ponti et al., 2017).

The following interventions have been found to be successful in increasing the proportion of screen-positive individuals who receive timely follow-up: reducing financial barriers to further investigations and providing reminders by mail or telephone; providing written informational material, telephone counselling, or face-to-face counselling; and addressing fears related to abnormal findings (Bastani et al., 2004; Zorzi et al., 2014).

3.6.2 Interventions to increase participation in endoscopy screening

Randomized trials of interventions to increase participation in endoscopy screening (colonoscopy or sigmoidoscopy) are presented in Table 3.6.2. Of the 11 trials found in the literature, seven were of colonoscopy, three were of sigmoidoscopy, and one was of either sigmoidoscopy or colonoscopy. Five of the trials were conducted in the USA and six in Europe. All of the trials in the USA (Denberg et al., 2006; Turner et al., 2008; Ling et al., 2009; Jandorf et al., 2013; Jensen et al., 2014) and two of the trials in Europe (Gray & Pennington, 2000; Boguradzka et al., 2014) assessed participation in the context of opportunistic screening. Of the other four trials in Europe, one assessed participation within a sigmoidoscopy screening trial (Wardle et al., 2003), two assessed participation in subjects identified from population registries (Senore et al., 1996; Blom et al., 2002), and one assessed participation in an organized population-based screening programme (Senore et al., 2015a).

Four trials evaluated patient navigation, management, coaching, or counselling versus a control arm of usual care or an informational brochure or leaflet (Turner et al., 2008; Ling et al., 2009; Jandorf et al., 2013; Boguradzka et al., 2014). Of these trials, two found significantly higher participation in the intervention arm than in the control arm (OR, 1.63; 95% CI, 1.11–2.41 and OR, 5.33; 95% CI, 3.55–8.00), one found an effect of borderline significance (OR, 2.14; 95% CI, 0.99–4.63), and one reported a non-significant effect. An additional trial evaluated different methods of having a patient interact with a nurse coordinator and found no significant difference (Blom et al., 2002).

Four trials evaluated the impact of invitation letters on participation rates (Senore et al., 1996; Ling et al., 2009; Jensen et al., 2014; Senore et al., 2015a). A 2 × 2 factorial study showed that participation was higher with a narrative invitation than with a non-narrative invitation (OR, 4.81; $P < 0.05$), but no significant difference was found for a tailored invitation versus a standard (stock) invitation (Jensen et al., 2014). Another study of a tailored invitation letter versus a non-tailored invitation letter also found no significant difference (Ling et al., 2009). A study of an advance notification letter versus usual care found significant differences (RR, 1.17; 95% CI, 1.10–1.25 and RR, 1.19; 95% CI, 1.12–1.27) (Senore et al., 2015a). A study of personal letters signed by a GP versus a study coordinator found no significant difference (Senore et al., 1996).

Two trials that examined providing an informational brochure versus usual care both found a significant difference, although it was of modest magnitude (Wardle et al., 2003; Denberg et al., 2006). One trial examined the addition of a discussion with the GP to providing an informational leaflet and found no significant difference (Gray & Pennington, 2000).

3.6.3 Interventions to increase participation in screening with stool-based tests for blood

More than 25 RCTs have assessed interventions to increase participation in gFOBT and/or FIT screening in asymptomatic individuals at average risk of CRC in high-income

Table 3.6.2 Randomized trials of interventions to increase participation in endoscopy screening (colonoscopy or sigmoidoscopy)

Reference	Country	Screening modality	Intervention arm	Control arm	Outcome
Senore et al. (1996)	Italy	Sigmoidoscopy	Personal letter signed by GP (arm A)	Personal letter signed by study coordinator	29.3% vs 26.8%*
			Arm A plus letter signed by well-known scientist (arm B)	Personal letter signed by study coordinator	24.9% vs 26.8%*
Gray & Pennington, (2000)	United Kingdom	Sigmoidoscopy	Informational leaflet and discussion with GP	Informational leaflet only	No significant difference
Blom et al. (2002)	Sweden	Sigmoidoscopy	Nurse telephoned patient	Patient instructed to telephone nurse	Uppsala: 50% vs 45%* Malmö/Lund: 31% vs 30%*
Wardle et al. (2003)	United Kingdom	Sigmoidoscopy	Psychoeducational booklet	Usual care	53.5% vs 49.9%**
Denberg et al. (2006)	USA	Colonoscopy	Mailed informational brochure	Usual care	OR = 1.20 (95% CI, 1.09–1.33)
Turner et al. (2008)	USA	Colonoscopy	Peer coaching	Mailed brochure	OR = 2.14 (95% CI, 0.99–4.63)
Ling et al. (2009)	USA	Colonoscopy or sigmoidoscopy	Tailored invitation letter	Non-tailored invitation letter	OR = 1.08 (95% CI, 0.72–1.62)
			Enhanced patient management	Non-enhanced patient management	OR = 1.63 (95% CI, 1.11–2.41)
Jandorf et al. (2013)	USA	Colonoscopy	Peer navigation; health professional navigation	Usual care	No significant differences
Boguradzka et al. (2014)	Poland	Colonoscopy	Counselling	Informational leaflet	OR = 5.33 (95% CI, 3.55–8.00)
Jensen et al. (2014)	USA	Colonoscopy	Narrative invitation	Non-narrative invitation	OR = 4.81**
			Tailored invitation	Stock invitation	OR = 1.19*
Senore et al. (2015a)	Italy	Sigmoidoscopy	Advance notification letter (arm B)	Usual care	RR = 1.17 (95% CI, 1.10–1.25)
			Arm B plus offer of contacting GP (arm C)	Usual care	RR = 1.19 (95% CI, 1.12–1.27)

CI, confidence interval; GP, general practitioner; OR, odds ratio; RR, relative risk.
*$P > 0.05$.
**$P < 0.05$.

countries (Australia, Israel, and countries in North America and western Europe). In view of the very large number of RCTs, the main focus of this section is on recent systematic reviews.

The most recent systematic review (Rat et al., 2017a) included RCTs published up to September 2015 (Table 3.6.3). The 24 RCTs that met the inclusion criteria were categorized according to whether the intervention focused on information provided to those invited to screening, physician practice, or type of test (i.e. gFOBT vs FIT). The interventions that increased participation in gFOBT and/or FIT screening were: advance notification letter (OR, 1.20–1.51); postal mailing of kits (OR, 1.31–2.89); written, telephone, and text message reminders (OR, 1.94–7.70); and telephone contact with an advisor (OR, 1.36–7.72). The interventions focused on physician practice that were effective were an invitation letter signed by a GP (OR, 1.26), GP training focused on communication skills (OR, 1.22), and reminder letters sent to GPs (OR, 14.8). For RCTs that compared gFOBT with FIT, the results were mixed.

In the USA, the Community Preventive Services Task Force published an update of its systematic review on the effectiveness of interventions to increase participation in cancer screening (Sabatino et al., 2012), based on published literature up to October 2008. Interventions were categorized as increasing community demand for screening, reducing barriers to access, and increasing screening service delivery by health-care providers. One-on-one education, client reminders, and reducing structural barriers were effective in increasing use of CRC screening.

The results of another systematic review (Senore et al., 2015b) indicated that multifactor interventions that target factors outside the control of individual clinicians are most effective in increasing participation in gFOBT and/or FIT. In organized CRC screening programmes (implying that there are no financial barriers to the potential participant), letters of invitation, especially if signed by the person's GP, and reminder letters sent to non-participants were found to be effective in increasing participation. Physician reminders were also found to increase participation in screening.

A three-group cluster RCT (Rat et al., 2017b), completed after the most recent meta-analysis and conducted within the organized CRC screening programme in France, reported that providing GPs with a list of their patients who were not up to date with screening was associated with a small increase in the participation rate in FIT screening. At 1 year, the participation rate in screening was 24.8% (95% CI, 23.4–26.2%) in the group who received specific reminders, 21.7% (95% CI, 20.5–22.8%) in the group who received generic reminders, and 20.6% (95% CI, 19.3–21.8%) in the usual care group.

3.6.4 Comparison of participation in two screening methods

(a) Comparing stool-based tests for blood

A meta-analysis of seven informative comparative trials (Vart et al., 2012) reported a higher participation among people invited to FIT than among those invited to gFOBT (RR, 1.21; 95% CI, 1.09–1.33). Also, the adoption of FIT in some population-based programmes in the United Kingdom resulted in a reduction in the participation gap by age, sex, and deprivation level observed in the gFOBT-based programmes (Digby et al., 2013; Moss et al., 2017).

(b) Comparing endoscopic methods

In a trial in Italy (Segnan et al., 2007), participation was significantly lower among subjects invited to colonoscopy than among those invited to sigmoidoscopy screening (27% vs 32%; OR, 0.74; 95% CI, 0.68–0.80).

Two studies also assessed the impact of offering a choice between different tests on participation. In the study in Italy (Segnan et al., 2005), participation was lower among subjects who were

Table 3.6.3 Randomized trials of interventions to increase participation in screening for colorectal cancer with stool-based tests for blood

Reference	Country	Type of intervention	Participation rate (%)	OR (95% CI)
Advance notification letter				
van Roon et al. (2011)	The Netherlands	NA	57.8 vs 51.5	1.20 (1.07–1.34)
Cole et al. (2007)	Australia	NA	25.2 vs 18.2	1.51 (1.13–2.02)
Mant et al. (1992)	United Kingdom	NA	31.7 vs 25.5	1.35 (0.99–1.87)
Postal mailing of kits				
Mant et al. (1992)	United Kingdom	NA	25.5 vs 20.6	1.31 (0.98–1.85)
Ore et al. (2001)	Israel	NA	19.9 vs 15.9	1.31 (1.04–1.67)
Giorgi Rossi et al. (2011)[a]	Italy	NA	14.6 vs 10.7	1.42 (1.18–1.71)
Giorgi Rossi et al. (2011)[b]	Italy	NA	63.0 vs 56.8	1.30 (1.12–1.5)
Green et al. (2013)	USA	NA	50.8 vs 26.3	2.89 (2.42–3.45)
Tinmouth et al. (2015)	Canada	NA	20.1 vs 9.6	2.35 (1.93–2.90)
Presentation and content of written information				
Myers et al. (2014)	USA	Message focusing on loss vs gain	36 vs 40	0.87 (0.73–1.03)
Multicentre Australian Colorectal-neoplasia Screening (MACS) Group (2006)	Australia	Shared decision-making	27.4 vs 18.6	1.65 (1.04–2.64)
Cole et al. (2007)	Australia	Advocacy messages or messages focusing on risk	40.3 vs 36	1.20 (0.95–1.53)
Hewitson et al. (2011)	United Kingdom	Enhanced procedural informational leaflet	58.2 vs 52.2	1.26 (1.01–1.58)
Neter et al. (2014)	Israel	Implementation intentions	71.4 vs 67.9	1.18 (1.12–1.24)
Reminders				
Lee et al. (2009)	USA	Educational patient reminder by mail	64.6 vs 48.4	1.94 (1.45–2.60)
Green et al. (2013)	USA	Mailed reminder letters	57.5 vs 50.8	1.31 (1.11–1.55)
Baker et al. (2014)	USA	Telephone and text message reminders	73.8 vs 26.7	7.70 (4.98–12.03)
Telephone contacts with a navigator, medical assistant, or nurse				
Myers et al. (2014)	USA	Telephone call with instructions	48 vs 37	1.57 (1.27–1.92)
Green et al. (2013)	USA	Telephone assistance	64.7 vs 57.5	1.36 (1.14–1.61)
Baker et al. (2014)	USA	Telephone contact with a personal navigator for non-compliant patients	82.2 vs 37.3	7.72 (4.91–12.3)
Myers et al. (2014)	USA	Telephone contact with a navigator	21.5 vs 15.3	1.51 (1.03–2.24)
Video and computers				
Gimeno-García et al. (2009)	Spain	Video-based educational intervention	69.9 vs 54.4	1.91 (0.95–3.89)
Miller et al. (2005)	USA	Counselling provided by automated informatics software	62 vs 63	0.96 (0.51–1.79)

Table 3.6.3 (continued)

Reference	Country	Type of intervention	Participation rate (%)	OR (95% CI)
Intervention requiring GP involvement				
Hewitson et al. (2011)	United Kingdom	Invitation letter signed by GP	58.1 vs 52.3	1.26 (1.01–1.58)
Aubin-Auger et al. (2014)	France	GP training focused on communication skills	36.7 vs 24.5	1.22 (1.07–1.41)
Vinker et al. (2002)	Israel	Reminder letters sent to GPs	16.5 vs 1.2	14.8 (8.1–29.6)

CI, confidence interval; GP, general practitioner; NA, not applicable; OR, odds ratio.

[a] Non-responders to a first invitation.

[b] Responders in the previous round.

offered a choice between FIT and sigmoidoscopy (27.1%) than among those who were invited to undergo screening with either biennial FIT (28.1–30.1%) or sigmoidoscopy (28.1%), although the difference was not statistically significant. A trial in Australia (Multicentre Australian Colorectal-neoplasia Screening (MACS) Group, 2006) found that the participation rate of people who were offered a choice between FIT, FIT plus sigmoidoscopy, CT colonography, and colonoscopy was not higher than that of those invited to screening with FIT (27% vs 23%; $P = 0.3$). [The Working Group noted that the sample size was rather small, and thus the results were statistically uncertain.]

In a population-based programme in Italy (Senore et al., 2013), the sequential offer of sigmoidoscopy followed by invitation to FIT for those who refused sigmoidoscopy was shown to be an effective approach, resulting in a participation rate of 19% among those who refused sigmoidoscopy. Similar findings have been reported in a pilot screening study in the Netherlands (Hol et al., 2012).

(c) Comparing endoscopy-based and stool-based strategies

The characteristics of studies that compared participation rates in screening with endoscopy-based and stool-based strategies, offered either alone or in combination, are presented in Table 3.6.4.

(i) Sigmoidoscopy and stool-based tests for blood

Three trials compared the participation in relation to invitation to gFOBT plus sigmoidoscopy screening versus gFOBT screening alone in three different countries. In a study in the United Kingdom (Berry et al., 1997), participation in screening with gFOBT was similar to that in gFOBT plus sigmoidoscopy (50% vs 48%), but only 20% of subjects invited to screening with gFOBT plus sigmoidoscopy actually underwent sigmoidoscopy. In a similar study in Denmark (Rasmussen et al., 1999), the participation rate was 40% among subjects invited to screening with gFOBT plus sigmoidoscopy, compared with 52% among those invited to screening with gFOBT alone. Similar results were reported in a study in Sweden (Brevinge et al., 1997) that compared subjects invited to screening with gFOBT and those invited to screening with gFOBT plus sigmoidoscopy (61% vs 39%; $P < 0.001$), but the difference was reduced when comparing subjects invited to screening with gFOBT and those invited to screening with sigmoidoscopy alone (55% vs 49%; $P < 0.01$).

In a trial in Australia, screening with FIT plus sigmoidoscopy was associated with a decrease in participation compared with screening with FIT alone (14% vs 27%; $P < 0.001$) (Multicentre Australian Colorectal-neoplasia Screening (MACS) Group, 2006). In a trial in Italy that randomized the practices of GPs to screening with either gFOBT or sigmoidoscopy, the observed participation rates were 17% with gFOBT and 7% with sigmoidoscopy ($P < 0.001$) (Federici et al., 2006b). In two studies in Italy (Segnan et al., 2005, 2007), the participation among subjects invited to screening with FIT was similar to that among those invited to screening with sigmoidoscopy, with participation rates of 28% and 32%, respectively, in both groups. In a study in the Netherlands (Hol et al., 2010), participation was higher among subjects invited to screening with FIT than among those invited to screening with sigmoidoscopy (61% vs 32%; $P < 0.001$).

(ii) Colonoscopy and stool-based tests for blood

In the COLONPREV study in Spain, participation was lower in the colonoscopy arm than in the FIT arm (34% vs 25%; $P < 0.001$), and if the invited participants were given the opportunity to choose the method, more participants were interested in screening with FIT than in undergoing a colonoscopy (Quintero et al., 2012).

Table 3.6.4 Characteristics of studies comparing participation rates in screening for colorectal cancer with a stool-based test for blood versus an endoscopic method, or in combination

Reference	Types of tests	Eligible patients	Age range (years)
Berry et al. (1997)	gFOBT vs gFOBT+FS	6371	50–74
Brevinge et al. (1997)	gFOBT vs gFOBT+FS gFOBT vs FS	3183	55–56
Rasmussen et al. (1999)	gFOBT vs gFOBT+FS	10 978	50–75
Segnan et al. (2005)	gFOBT vs FS	22 676	55–64
Federici et al. (2006b)	gFOBT vs FS	2987	50–74
Multicentre Australian Colorectal-neoplasia Screening (MACS) Group (2006)	FIT vs FS+FIT vs colonoscopy	672	50–54
Segnan et al. (2007)	FIT vs FS or colonoscopy	18 114	55–64
Hol et al. (2010)	gFOBT or FIT vs FS	14 341	50–74
Lisi et al. (2010)	gFOBT vs colonoscopy	8378	55–64
Quintero et al. (2012)	FIT vs colonoscopy	57 302	50–69

FIT, faecal immunochemical test; FS, flexible sigmoidoscopy; gFOBT, guaiac faecal occult blood test.
Adapted from Hassan et al. (2012). Meta-analysis: adherence to colorectal cancer screening and the detection rate for advanced neoplasia, according to the type of screening test. *Alimentary Pharmacology & Therapeutics*, 36(10): 929–940, with permission from John Wiley & Sons. (Hassan et al., 2012).

Similar results were reported in a trial in Italy (Segnan et al., 2007), which found lower participation rates with colonoscopy than with FIT screening (27% vs 32%; $P < 0.001$).

In another trial conducted in Italy that randomized the practices of GPs to screening with either gFOBT or colonoscopy, the observed participation rates were 27% with gFOBT and 10% with colonoscopy ($P < 0.001$) (Lisi et al., 2010). Similar findings were reported from a study in Australia (Multicentre Australian Colorectal-neoplasia Screening (MACS) Group, 2006), which found participation rates of 27% with FIT and 18% with colonoscopy ($P < 0.02$). [The Working Group noted that the sample size of the Australian RCT was rather small, and thus the results were statistically uncertain.]

(iii) Meta-analysis

A recent meta-analysis, which included 9 of the 10 studies considered here, concluded that endoscopy tests were associated with lower participation compared with stool-based tests for blood (RR, 0.67; 95% CI, 0.56–0.80), although the statistical heterogeneity across the studies was high (Hassan et al., 2012).

[The Working Group noted that all studies comparing endoscopy versus stool-based tests for blood reported data on participation for a single invitation round. Hence, this approach tends to overestimate the difference in participation between stool-based tests for blood and endoscopy strategies, because a single endoscopy is efficient to achieve the expected protective effect, whereas repeated testing is required in stool-based tests for blood. For stool-based tests, the proportion of regular attendees tends to decrease over time.]

(e) Comparing CT colonography and other screening methods (endoscopy-based or stool-based strategies)

Four studies were identified that compared participation in CT colonography with that in colonoscopy, sigmoidoscopy, or FIT. In the COCOS trial in the Netherlands, Stoop et al. (2012) compared participation in screening with colonoscopy and CT colonography among adults aged 50–74 years. The proportion of invitees that

participated was significantly higher for CT colonography (34%) than for colonoscopy (22%). In the SAVE trial, Sali et al. (2016) investigated the participation rates for FIT, colonoscopy, and CT colonography with reduced or full bowel preparation. A reduced preparation for CT colonography increased the participation rate for CT colonography (28% vs 25%; $P = 0.047$); the participation rate was highest for FIT (50%) and lowest for colonoscopy (14%). In the Proteus trial, Regge et al. (2017) reported that the participation rates of individuals aged 58–60 years who were invited to screening with either CT colonography or sigmoidoscopy were similar (30% vs 27%). Moawad et al. (2010) sought to determine patient preferences between colonoscopy and CT colonography in an open access system. A total of 250 consecutive asymptomatic adults at average risk undergoing CRC screening completed a survey that assessed their reasons for choosing CT colonography rather than colonoscopy. Convenience was the most commonly cited reason for choosing CT colonography over other tests. Of the 250 patients, 91 reported that they would not have undergone screening if an option for CT colonography had not been available, and 95% of adults who had undergone both procedures ($n = 57$) reported that they preferred CT colonography. Overall, it is generally observed that participation in CT colonography is higher than that in colonoscopy, lower than that in FIT, and similar to that in sigmoidoscopy.

3.6.5 Informed decision-making

Cancer screening should be promoted and offered only if the benefits clearly outweigh the harms. However, because the risk of CRC and death from CRC is relatively low (often in the range of 2–10%), the balance between potential benefits and harms may be different for different individuals. Therefore, it is prudent to involve the target population in the decision-making process about participation in the screening programme. The decision about participation needs to take into account personal values and preferences. Enthusiastic persuasion and "nudging" (the purposeful alteration of choices presented to people, to influence their decisions) for participation in screening programmes are discouraged (Editorial, 2009; Woloshin et al., 2012).

Shared decision-making, a concept that has evolved in recent years, should be used to facilitate an informed choice about whether to participate in cancer screening programmes. For shared decision-making, transparent, comprehensive, and informative facts should be provided about the potential benefits and harms of screening, and the expected burden of the screening test and follow-up procedures should be clearly explained. Informational material for decision-making in cancer screening programmes is often derived with the help of stakeholders and organizations and individuals who are not involved in the screening programme (Editorial, 2009).

Key features of informed decision-making in cancer screening include (i) the use of innovative visual decision aids to facilitate the transfer of information to all target individuals, irrespective of education, SES, and previous knowledge, (ii) the use of absolute risks of disease and absolute effects and harms of the screening tests and of the follow-up treatment, and (iii) frequent updating of decision aids with new knowledge and evidence (Agoritsas et al., 2015).

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3.7 Emerging techniques

Several tests for CRC screening are at different stages of development, including new stool-based tests, tests based on visual inspection, and blood-based tests (Table 3.7.1).

3.7.1 Stool-based tests

CRC develops from normal mucosa through a series of cumulative mutations (Vogelstein & Kinzler, 1993). Cellular debris from growing neoplastic lesions is released into the stool effluent, and through that mechanism provides an opportunity to screen for CRC. Currently, one such test is commercially available; it is based in part on detection of DNA with mutations in stool.

(a) Multitarget stool DNA test

(i) Technique

Several stool-based DNA tests have been developed during the past decade. Early efforts focused on panels of genes that are commonly mutated during the progression of cancer (e.g. *KRAS*, *APC*, and *BAT-26*). However, results in screening populations showed poor sensitivity, missing approximately half of the invasive cancers detected at colonoscopy (Imperiale et al., 2004). Increased recognition of the importance of gene methylation as an early marker of cancer prompted the addition of methylated gene markers to the panel. Also, to improve sensitivity, haemoglobin immunoassay was added to the test, leading to a new designation as the multitarget stool DNA (mt-sDNA) test (see Table 3.7.1). Currently, the mt-sDNA test detects *KRAS* point mutations and aberrantly methylated *NDRG4* and *BMP3*, as well as haemoglobin. *B-actin* is used to measure DNA quality. Stabilizing buffers have been added to prevent DNA degradation after sample deposit, and improved analytical techniques (e.g. quantitative allele-specific real-time target and signal amplification assay) have been developed (Bailey et al., 2016; Sweetser & Ahlquist, 2016).

No adjustment in diet or medication is needed by the participant to perform the test, but testing should be avoided in cases of diarrhoea or of bleeding due to haemorrhoids or menses. Whole stool is collected in a container that is placed in the toilet bowl, and the participant separately probes the stool for FIT. The participant then adds a preservative to the container and sends out both the container and the probe to the laboratory. The laboratory must receive the sample within 72 hours of collection to be able to process the test.

Processing of the samples occurs at the manufacturer's laboratory. The results for each marker are incorporated into a logistic regression equation to determine whether the test result is positive or negative (Lidgard et al., 2013); a quantitative value of 183 or more indicates a positive test result (Sweetser & Ahlquist, 2016).

Quality control measures are taken during laboratory processing. Specifically, control samples for the DNA assay and the haemoglobin immunoassay components of the test are run alongside the patient samples to ensure adequate processing.

(ii) Screening performance

Test performance of the newest iteration of the mt-sDNA test was examined in a large screening population (n = 9989) in the USA (Imperiale et al., 2014; Table 3.7.2). In this study, all individuals underwent screening with colonoscopy, FIT, and the mt-sDNA test. In that population, 65 individuals had CRC and 757 had at least one advanced colorectal adenoma. The sensitivity of the mt-sDNA test was 92.3% for cancer and 42.4% for advanced neoplasia, significantly higher than that of FIT (73.8% for cancer and 23% for advanced neoplasia). The mt-sDNA test was also significantly more sensitive than FIT in detecting large (≥ 10 mm) serrated lesions (42.4% vs 5.1%); however, the specificity for the

Table 3.7.1 Comparison of the most mature emerging technologies for colorectal cancer screening with respect to key features and patient considerations

Technology	Key advantages	Major disadvantages	Time needed for data acquisition	Time needed for reading	Patient considerations	Suggested follow-up frequency when test result is negative
mt-sDNA	Non-invasive No preparation At-home testing	Expensive Modest sensitivity for cancer precursors	Minutes, by patient, around the time of a bowel movement	Minutes; automated	Requires patient to handle/sample own stool	3 yr
Capsule colonoscopy	Total colon examination No intubation of colon or rectum	Cannot control pace of capsule transit, with potential for non-informative/ incomplete examinations Modest sensitivity for cancer precursors	≥ 6 hours	30 minutes or more	Extensive preparation with boosting to propel capsule Long acquisition times	5 yr
Plasma DNA (*mSEPT9*)	Non-invasive No preparation	Expensive Insensitive for early cancer and cancer precursors	Minutes, for a single blood draw	Hours to complete laboratory assays	A single blood draw	Annual

mSEPT9, methylated *Septin 9*; mt-sDNA, multitarget stool DNA; yr, year or years.

Table 3.7.2 Performance of emerging technologies for detection of colorectal cancer and advanced neoplasia

Technology	No. of prospective studies in screening populations	Cancer		Preneoplastic lesions ≥ 10 mm		References
		Per-lesion sensitivity (%)	Per-patient sensitivity (%)	Per-patient sensitivity (%)	Per-patient specificity (%)	
mt-sDNA	1	NA	92.3	42[a]	87[a]	Imperiale et al. (2014) Redwood et al. (2016)
Capsule colonoscopy	2	75	100	85–92[b]	95–97[b]	Rex et al. (2015) Spada et al. (2016)
Plasma DNA (*mSEPT9*)	2[c]	NA	50–68	11–22[d]	80–91[d]	Church et al. (2014) Potter et al. (2014)

mSEPT9, methylated *Septin 9*; mt-sDNA, multitarget stool DNA; NA, not applicable.

[a] Advanced adenomas + sessile serrated lesions.

[b] Polyps.

[c] The second study is a reanalysis of the test using frozen plasma from the original participants with a revised assay.

[d] Advanced adenomas.

non-advanced lesions was 86.6% for the mt-sDNA test compared with 94.9% for FIT. In the mt-sDNA test, the performance of the haemoglobin immunoassay component alone was similar to that of FIT.

[Although this large tandem-design cross-sectional study provided insights into the performance of the mt-sDNA test compared with that of FIT, the Working Group noted that the study did not directly provide information about the comparative effectiveness of the two technologies. The performance of FIT was influenced by the established thresholds for haemoglobin levels, which define a positive test result and determine the sensitivity and the specificity (see Section 3.2.1). To the extent that FIT with a lower haemoglobin threshold is used, the results with FIT can approximate those achieved with the mt-sDNA test in this study, with the potential exception of the detection of serrated lesions and polyps, for which FIT has poor sensitivity (Brenner et al., 2014). Also, the study did not provide a comparison in which the two technologies were applied over time.]

There is evidence that the levels of methylated stool markers increase with age. A single study in 500 individuals who had normal colonoscopy findings and who had a freezer-archived stool sample examined factors associated with the levels of methylated stool markers (Ahlquist et al., 2012). All four genes examined (*BMP3*, *NDRG4*, *vimentin*, and *TFPI2*) were significantly more methylated with increasing age across the age range studied (44–85 years). No associations were found with the other host factors examined in this analysis (e.g. sex, race, body mass index, alcohol consumption, and smoking status). Therefore, theoretically, the specificity might decrease with age. In the large-scale study in the USA (Imperiale et al., 2014), the specificity of the mt-sDNA test was higher in those younger than 65 years (94%) than in those 65 years and older (87%). [The Working Group noted that these studies were performed in the USA. How this test would function in populations outside the USA is not well studied, and there are some data suggesting that DNA marker panels would need to be adjusted in other populations (Park et al., 2017).]

(iii) Preventive effects

There are no RCTs or observational studies of the mt-sDNA test with outcomes of CRC incidence or CRC mortality. Like for CT colonography, most studies of mt-sDNA effectiveness have been tandem studies of a single screening event in a cohort, comparing the outcome (detection rates of CRC and/or advanced neoplasia) with that of established techniques such as FIT or colonoscopy as the reference standard.

Imperiale et al. (2014) compared the detection rates of the mt-sDNA test with those of FIT and colonoscopy. The study population was asymptomatic adults aged 50–84 years at average risk (who were scheduled for screening colonoscopy); recruitment was weighted towards adults aged 65 years and older, to ensure a higher prevalence of cancer. Among the 12 776 participants who were enrolled in the study, 9989 had results that could be fully evaluated; on colonoscopy, 65 (0.7%) were found to have colorectal adenocarcinomas (of which 60 were screening-relevant cancers) and 757 (7.6%) had advanced precancerous lesions, i.e. advanced adenomas (adenomatous polyps ≥ 10 mm or with > 25% villous component or with high-grade dysplasia) or sessile serrated lesions 10 mm or larger. By comparison, the mt-sDNA test detected 0.6% with CRC (vs 0.48% with FIT), 0.56% with screening-relevant cancers (vs 0.44% with FIT), and 3.2% with advanced precancerous lesions (vs 2.2% with FIT) (Imperiale et al., 2014). [Although the mt-sDNA test showed higher detection rates than the FIT used in this study, use of a different FIT may have resulted in different findings.]

A second screening study comparing the mt-sDNA test with colonoscopy was undertaken in asymptomatic Alaska Native adults aged

40–85 years who were scheduled for screening or surveillance colonoscopy (Redwood et al., 2016). Alaska Native people face several challenges related to CRC screening: (i) they are at high risk of CRC, with earlier onset; (ii) most live in remote areas, where access to endoscopy is limited and regular screening with any test is challenging; and (iii) there is a high prevalence of endemic gastrointestinal bleeding from *Helicobacter pylori* gastritis, and hence the specificity of FOBT is poorer (76%) in this population (Redwood et al., 2014). Because of these considerations, there was interest in comparing detection rates of FIT with those of the mt-sDNA test in this population. The primary outcome measure was the detection of CRC, advanced adenomas (adenomatous polyps ≥ 10 mm or with > 25% villous component or with high-grade dysplasia), or sessile serrated lesions 10 mm or larger found on screening or surveillance colonoscopy, described as screening-relevant neoplasia. Advanced adenomas were independently reviewed before unblinding. Among 868 enrolled participants, 661 completed the study, of whom 435 were in the screening group and 226 were in the surveillance group. In the screening group, 50% of the screening-relevant neoplasia were detected by mt-sDNA compared with 31% by FIT (P = 0.01), and 45% of the advanced adenomas were detected by mt-sDNA compared with 28% by FIT ($P < 0.05$). Detection rates for sessile serrated lesions (n = 25) were not reported separately for the two study groups, but for lesions larger than 10 mm, 67% were detected by mt-sDNA compared with 11% by FIT (P = 0.07), and for lesions 10 mm or smaller, 38% were detected by mt-sDNA compared with 6% by FIT (P = 0.07). [The Working Group noted that these findings are consistent with those from the study by Imperiale et al. (2014), but that this is a small study in a unique, high-risk population and therefore is not easily generalizable to individuals at average risk of CRC.]

Modelling studies have begun to include the mt-sDNA test in simulations for comparison with other screening tests. Knudsen et al. (2016) examined 17 unique strategies for mt-sDNA screening in their microsimulation model for the USPSTF (for detailed information on the models, see also Section 3.2.6 and Section 3.3.6). The strategies varied the starting and ending ages for screening and used screening intervals of 1 year, 3 years, and 5 years for the test. Annual screening with mt-sDNA at age 50–75 years was efficient (i.e. a strategy that provided the largest incremental increase in LYG per additional screening) or near-efficient (within 98% of the efficient frontier) in all three models; however, mt-sDNA every 3 years, which is recommended by the manufacturer, and every 5 years was not as efficient as the other stool-based tests performed annually. Annual mt-sDNA testing was not a recommended strategy, because its efficiency ratio was lower than the efficiency of the benchmark (i.e. colonoscopy every 10 years at age 50–75 years). However, in terms of deaths averted per 1000 individuals screened, outcomes were similar: 22–24 deaths averted for colonoscopy every 10 years, 22–24 for mt-sDNA testing every year, 19–22 for mt-sDNA testing every 3 years, and 20–23 for FIT every year (Bibbins-Domingo et al., 2016).

Barzi et al. (2017) included mt-sDNA testing at screening intervals of 1 year and 2 years in their comparison of 10-year outcomes for 13 CRC screening strategies. Screening with mt-sDNA every year compared with every 2 years resulted in a negligible difference in the number of diagnosed CRCs (3870 vs 3860), but with both annual and biennial screening, the CRC detection rate exceeded that with one-time colonoscopy (3462). However, the model predicted a smaller reduction in the risk of CRC for annual and biennial screening with mt-sDNA compared with colonoscopy (14% vs 23%), and a smaller reduction in the risk of death from CRC (21% for annual screening with mt-sDNA and 18% for biennial

screening with mt-sDNA vs 34% for colonoscopy) (Barzi et al., 2017).

(iv) Adverse effects

There are no documented adverse effects from the process of undergoing mt-sDNA screening. As with other stool-based screening tests for CRC, adverse effects are associated with follow-up colonoscopy for positive test results, and with false-positive results (see Section 3.2.4). A positive mt-sDNA test result followed by a negative colonoscopy result may be attributable to failure to detect a visible lesion, to very early neoplastic changes that are not yet visible, to the detection by the molecular panel of aerodigestive or supracolonic neoplasms, or to test specificity.

In two screening studies with mt-sDNA (Imperiale et al., 2014; Redwood et al., 2016), the percentage of advanced neoplasia or CRC not detected in follow-up colonoscopies after a positive mt-sDNA result was about 10% (range, 7–13%) and did not fluctuate with age. These patients may undergo more aggressive short-term surveillance because of concerns about a greater range of possible explanations for false-positive findings compared with other stool-based tests.

Cotter et al. (2017) measured outcomes (mortality, incidence, and other symptoms) after a false-positive test result among patients with false-positive and true-negative test results with mt-sDNA. Among 1050 eligible patients (patients with a positive mt-sDNA test result and those with a negative colonoscopy result) with a median follow-up of 4 years, the cumulative incidence of aerodigestive malignancies (8 cases, including 1 CRC, 3 pancreatic cancers, 3 lung cancers, and 1 bile duct cancer) did not exceed the expected incidence, and false-positive status was not associated with excess mortality or "alarm symptoms". Evidence related to patient anxiety in response to false-positive findings has not been reported.

(v) Cost–effectiveness

In a comparative microsimulation modelling study, Lansdorp-Vogelaar et al. (2010) used the MISCAN and SimCRC models to evaluate the comparative cost–effectiveness of the mt-sDNA test, FIT, sigmoidoscopy, sigmoidoscopy plus FIT, and colonoscopy. The base case evaluated CRC screening intervals of 3 years and 5 years, performance characteristics of the first- and second-generation mt-sDNA tests for detection of adenoma and cancer, and a reimbursement rate of US$ 350. With 100% participation in CRC screening, the models obtained similar reductions in the risk of CRC incidence with 3-yearly and 5-yearly screening with mt-sDNA (30–49%) compared with annual FIT screening (32–40%), but the estimated reduction in the risk of CRC incidence was considerably larger (53–72%) with colonoscopy every 10 years. Compared with other screening tests, mt-sDNA at intervals of 3 years and 5 years was the most costly and least effective screening test, but the costs were still within the conventional criteria for cost–effectiveness (< US$ 15 000 per LYG). The authors concluded that mt-sDNA would be an efficient strategy with the modelled reimbursement rate and screening every 3 years if the participation rate was 50% greater than that of the other screening tests, or if reimbursement costs were less than US$ 60.

Ladabaum & Mannalithara (2016) used a Markov model to evaluate the comparative cost–effectiveness of CRC screening with mt-sDNA every 3 years, FIT every year, and colonoscopy every 10 years in adults at average risk. Despite the improved performance of mt-sDNA over FOBTs, and better sensitivity compared with FIT (see Section 3.7.1(a)(ii)), annual FIT and colonoscopy every 10 years were more effective and less expensive than mt-sDNA every 3 years, assuming 100% participation and a cost–effectiveness threshold of less than US$ 100 000 per QALY gained. Sensitivity analyses produced findings similar to those of the previous study; in

an organized screening programme, mt-sDNA every 3 years would need to achieve greater participation rates of regular screeners (68% vs 50%) and of intermittent screeners (32% vs 27%) compared with FIT, or would need to be reimbursed at 60% less than the base case rate, to be preferred to FIT at the highest threshold (< US$ 100 000 per QALY gained) of cost–effectiveness. With opportunistic screening, based on participation rates of 15% for regular screeners and 30% for intermittent screeners, mt-sDNA would need to achieve nearly twice the participation rate to be under the cost–effectiveness threshold of US$ 100 000 per QALY gained.

(b) Other stool-based tests

Although identification of haemoglobin as a protein marker in stool is a well-recognized screening approach, other stool protein markers have also been evaluated. Generally, evaluation of these other markers has occurred in small observational studies in which detection rates of CRC and advanced neoplasia are estimated. Pyruvate kinase type M2 is a protein that regulates tumour growth and is not specific to CRC. In one meta-analysis that identified 10 individual studies assessing the use of stool pyruvate kinase type M2 in the detection of CRC, the sensitivity of the marker was 79% and the specificity was 81% (Li et al., 2012). Calprotectin is a calcium-binding protein that is found predominantly in neutrophils. In one large prospective evaluation study in a screening population (n = 2321), the sensitivity of this marker for CRC was 63% and the specificity was 76% (Hoff et al., 2004).

Beyond these single protein markers, there is also interest in developing broader panels of proteins present in stool that might be used for screening (Ang et al., 2011; Bosch et al., 2017). However, this work remains preliminary. In addition, there is also interest in examining the faecal microbiome as a screening tool, but this development is largely still at the discovery phase (Yu et al., 2017).

3.7.2 Capsule colonoscopy

Building on capsule technology to evaluate the small bowel, a capsule to evaluate the large bowel was first released and evaluated in 2006 (Eliakim et al., 2006). This technology enables a total colon examination to be performed with no bowel intubation or sedation (Table 3.7.1).

(a) Technique

The technology currently used is a second-generation system with improved performance with respect to imaging of the large bowel. Equipment to perform capsule colonoscopy, which is currently commercially available from a single vendor, requires three components: a capsule, a data recorder, and a workstation to read the acquired images. The ingestible capsule has dimensions of approximately 11 mm × 32 mm. The device has a camera at each end and a battery that enables the capture of images for approximately 10 hours. On the basis of the initial experience, refinements were made to improve the performance of the capsule. The current, second-generation capsule has a viewing angle for each camera of 172°, which enables a near-360° view of the colon. The capsule can capture up to 35 images per second. Another improvement in the technology was the development of an adaptive frame rate; this was made possible in part by real-time communication between the capsule and the data recorder worn by the patient. Finally, data from the recorder are downloaded to a workstation, to assist the clinician with image review (Spada et al., 2015, 2016).

Preparation for capsule colonoscopy is necessary for several important reasons. As is the case for conventional colonoscopy, the quality of the examination can be compromised by residual stool coating the colonic mucosa. In fact, suboptimal preparation is a greater threat to the test performance for capsule colonoscopy than for traditional colonoscopy, because with capsule colonoscopy there is no opportunity to wash

the bowel or remove residual effluent through suction. In addition, there is a requirement to "push" the capsule to and through the colon to complete the examination during the 10-hour battery life of the device (Spada et al., 2015). Generally, colon preparation is accomplished with a full dose (4 L) of polyethylene glycol, of which half is taken the day before the procedure and half on the day of the procedure. Boosting of the movement of the capsule is most commonly accomplished with sodium phosphate (NaP). Preparation also includes dietary adjustment (e.g. a clear liquid diet) the day before the procedure, and occasionally the use of suppositories to assist with capsule excretion. Even with these aggressive preparation and boosting regimens, the quality of the examination can be an issue. In a recent meta-analysis of studies of colon capsule colonoscopy, adequate cleansing levels were achieved in 81% of cases and capsule excretion within the usual battery life (10 hours) was achieved in 90% of cases (Spada et al., 2016).

After the capsule is excreted, the images that were obtained need to be interpreted. Given that the capsule generates thousands of images, reading them can be cumbersome. The reading time can exceed 50 minutes in more than 25% of cases (Farnbacher et al., 2014). There have been efforts to develop computer-assisted reading algorithms, building on similar technology used for the capsule to evaluate the small bowel. The proprietary software can develop previews of significant findings that are tailored by the reader. For example, images of interest can be set to various percentages to enable the reader to have a quick overview of the study. This software was formally assessed in one recent study (Farnbacher et al., 2014). By using such settings, the reader could cut the reading time by 90% while still identifying 98% of patients with at least one significant polypoid finding. The use of such software might facilitate same-day examination of individuals, enabling them to be moved quickly from capsule to colonoscopy because they have at least one lesion that requires polypectomy.

[The Working Group concluded that compared with other structural screening options (e.g. colonoscopy and CT colonography), capsule colonoscopy is more demanding for the patient and the examiner, requiring more intensive procedural preparation, longer patient examination, and extended clinician interpretation times. Prolonged examination and interpretation limit the opportunity for same-day colonoscopy, which avoids two separate colon preparations.]

Some individuals may not be suitable for screening with capsule colonoscopy. For example, individuals with a swallowing disorder are probably not well suited for this test. To reach the colon, the device must traverse the entire proximal gastrointestinal tract, including the small bowel. For individuals with extensive prior surgery and/or known adhesive disease, there is a risk of the capsule becoming stuck in the small bowel. Finally, certain individuals are at higher risk of complications with NaP (e.g. people with hypertension who are taking angiotensin-converting-enzyme inhibitors), and therefore screening by capsule colonoscopy entails more risk for those individuals.

The European Society of Gastrointestinal Endoscopy guideline addressed the use of the colon capsule (Spada et al., 2012). Key recommendations included the use of split-dose polyethylene glycol for the preparation and the use of sodium phosphate boosters where possible. Also, the guideline recommended standardized reporting practices, including for the quality of the preparation, the completeness of the examination, and the description (i.e. size, morphology, location) of identified polyps. The guideline recommended follow-up colonoscopy for those with a polyp 6 mm or larger or three or more polyps of any size, and a follow-up interval of 5 years in a CRC screening setting after a negative examination result.

(b) Screening performance

A large tandem study assessed the performance of capsule colonoscopy in a screening population (Rex et al., 2015). In the final cohort (n = 695), capsule colonoscopy identified individuals with one or more polyps 6 mm or larger with a sensitivity of 81% (95% CI, 77–84%) and a specificity of 93% (95% CI, 91–95%). Four cancers were identified by colonoscopy, and three were detected during the blinded capsule interpretation (per-lesion sensitivity, 75%); the other cancer (a 10 mm sessile lesion) was visible during unblinded review. [In the individual with that cancer, other lesions were identified that would have prompted total colonoscopy.]

A second tandem study in the Czech Republic (Suchanek et al., 2015) assessed the performance of capsule colonoscopy in 236 consecutively enrolled adults older than 50 years. The sensitivity of capsule colonoscopy was 77% for polyps 6 mm or larger, 88% for polyps 10 mm or larger, and 100% for adenomas 10 mm or larger; the specificity was 97% for polyps 6 mm or larger and 99% for polyps 10 mm or larger. Two cancers were diagnosed with both methods. The overall sensitivity and specificity for lesions 10 mm or larger were similar in the two studies (Spada et al., 2016).

Capsule colonoscopy, also referred to as capsule endoscopy, is approved in the USA for examining the proximal colon in patients with incomplete colonoscopies, or for patients who are not candidates for colonoscopy or sedation, but it is not approved for CRC screening in adults at average risk, probably because of the limited data available on performance in a screening population (Rex et al., 2017).

(c) Preventive effects

There are no RCTs or observational studies of capsule colonoscopy with outcomes of CRC incidence or CRC mortality. Like with other emerging technologies, single-test tandem studies comparing the detection rates of cancer and of precursor lesions with capsule colonoscopy and with conventional colonoscopy as the reference standard have been conducted [most of these investigations have been in small, heterogeneous study populations]. In one study evaluating the detection rates with capsule colonoscopy in 689 subjects (Rex et al., 2015), the detection rate for adenomas 6 mm or larger was [14%], and the detection rate for adenomas 10 mm or larger was [5.8%]. The cancer detection rate was [0.4%] (3 of the 4 cancers identified by colonoscopy), and after unblinding the cancer was visible in multiple photos taken by the capsule.

(d) Adverse effects

Few serious adverse events associated with capsule colonoscopy have been documented (Spada et al., 2012, 2016). In a tandem study in a screening population, Rex et al. (2015) reported no serious capsule-related events. Among 884 patients enrolled in the study, 142 non-serious events were reported in 101 patients, of which 128 were related to bowel preparation. Three non-serious events associated with the capsule were related to the procedure; these included gagging, vomiting, and abdominal cramping (Rex et al., 2015). Capsule retention, defined as a capsule that remains in the digestive tract for longer than 2 weeks, occurred in fewer than 2% of patients (Rondonotti, 2017).

(e) Benefit–harm ratio and cost–effectiveness

No data are available on the benefit–harm ratio of capsule colonoscopy. Hassan et al. (2008) used a simulation model to compare capsule colonoscopy with conventional colonoscopy and observed that capsule colonoscopy was less cost-effective than conventional colonoscopy if the participation rates were equal. If the participation rate for capsule colonoscopy was 30% higher than that for conventional colonoscopy, then capsule colonoscopy was more cost-effective than conventional colonoscopy.

3.7.3 Blood-based tests

(a) Single-gene plasma DNA test (mSEPT9 DNA test)

Blood-based DNA tests are another example of a new class of CRC screening tests. Blood testing as a screening test for CRC has been referred to as the "holy grail of cancer detection research" (Ransohoff, 2003), because the barrier to participation is reduced to a single blood draw, which may well be combined with other annual tests (e.g. a cholesterol test) (Table 3.7.1). Although the relative simplicity of this technique is an advantage of this approach, commitment to follow-up testing with colonoscopy (after a positive screening result) remains an important consideration.

(i) Technique

DNA of tumour origin is present in minute quantities in the plasma of patients with cancer (Pawa et al., 2011). To date, it has been more promising to search for tumour-associated methylation changes. Through a well-described process (Payne, 2010), investigators evaluated a host of potentially relevant DNA methylation markers. From that group, the methylated *Septin 9* gene (*mSEPT9*) was selected for further development and evaluation, on the basis of favourable test characteristics in case–control studies for this marker compared with other potential candidate markers (Lofton-Day et al., 2008). Septins as a family of genes have critical functions in multiple cellular processes, including apoptosis (Hall & Russell, 2004).

From the perspective of the patient, the *mSEPT9* DNA test requires no preparation, including no changes in diet and no use of medication. The individual undergoes a single phlebotomy, and the sample is sent to the laboratory for processing. The details of the processing vary by the version of the test used (Epi proColon, 2017), but processing requires two steps. In step one, DNA is extracted from the plasma and is subsequently incubated in bisulfite solution, to alter unmethylated cytosine residues in the DNA. In step two, the bisulfite-converted DNA is assayed using real-time duplex polymerase chain reaction, and the presence of *mSEPT9* is specifically identified through the use of a fluorescence detection probe. The processing time is estimated to be 8 hours (Lamb & Dhillon, 2017).

The laboratory-based *mSEPT9* DNA test has well-described external and internal controls. External controls include known positive and negative samples that are run alongside the patient sample. As an internal control, β-actin DNA is used as a marker of DNA quality.

Variations of the test are approved for use in different countries. In the USA, the United States Food and Drug Administration approved the test for use in people who are unwilling to undergo any other screening test; in Europe and China, a slightly different version of the test for the same marker is approved. Although both are second-generation tests, the version used in the USA requires only one of three replicates to be reported as positive, whereas the version used in Europe requires two of three replicates to be reported as positive (Lamb & Dhillon, 2017).

(ii) Screening performance

The performance of the *mSEPT9* DNA test as a screening tool was assessed directly in a large-scale (n = 7941) prospective study (Church et al., 2014). Blood samples were drawn from asymptomatic adults aged 50 years or older at least 1 day before colon preparation was initiated. Colonoscopy was subsequently completed. Results for 53 individuals with cancer and 1457 without neoplasia were available. When the *mSEPT9* DNA test was analysed on the basis of two replicate samples, the sensitivity of the test for cancer was 48.2% and the specificity was 91.5%. The sensitivity for the detection of more advanced lesions was higher (e.g. sensitivity of 77.4% for stage IV cancer vs 35% for stage I cancer). In post hoc analyses, the test characteristics were

recalculated using a third replicate sample. The sensitivity increased to 63.9% and, as expected, the specificity decreased to 88.4% (Church et al., 2014). A follow-up analysis of this cohort was also performed using the optimized (i.e. second-generation) test. The sensitivity for detection of CRC increased to 68%, and the specificity decreased to 79% (Potter et al., 2014).

A meta-analysis identified 14 studies that evaluated the performance of the *mSEPT9* DNA test (Zhang et al., 2017). The study design and the application of the test varied across the studies, resulting in significant heterogeneity. For detection of CRC, the pooled sensitivity was 67% (95% CI, 61–73%) and the pooled specificity was 89% (95% CI, 86–92%). In another meta-analysis of 25 studies (Song et al., 2017), 2613 CRC cases and 6030 controls were included, and the sensitivity ranged from 48.2% to 95.6% and the specificity ranged from 79.1% to 99.1%.

As discussed above (see Section 3.7.1(a)(ii)), there is some evidence that methylation of genes increases with age, which has the potential to decrease test specificity in older individuals. Also, analysis by race suggested some increased false-positivity in African American people compared with White people (Potter et al., 2014). In fact, the meta-analysis by Zhang et al. (2017) also demonstrated variation in performance across ethnicity.

(iii) Preventive effects

There are no RCTs or observational studies of plasma DNA tests with outcomes of CRC incidence or CRC mortality. As with other emerging technologies, single-test tandem studies comparing the detection rates of cancer and of precursor lesions are the principal methodological strategy for evaluating the efficacy of the test. Only one evaluation of the *mSEPT9* DNA test has been carried out in an asymptomatic screening population, and it is described above (Church et al., 2014).

Ladabaum et al. (2013) estimated the comparative effectiveness of the *mSEPT9* DNA test, FOBT, FIT, sigmoidoscopy, and colonoscopy using a validated decision analytical model. The performance parameters used for the *mSEPT9* DNA test were those observed by Church et al. (2014) with two and three replicates with biennial screening. All screening strategies assumed 100% participation. In the base case, screening with the *mSEPT9* DNA test decreased CRC incidence by 35–41% and CRC mortality by 53–61%.

In terms of the comparative effectiveness of the *mSEPT9* DNA test, all of the established screening strategies considered in the analysis were more effective than the *mSEPT9* DNA test.

(iv) Adverse effects

There are no reports of adverse effects of CRC screening with the *mSEPT9* DNA test. Potential adverse effects are those related to the process of phlebotomy (blood draw). With the current low specificity, a significant fraction of asymptomatic adults undergoing screening and receiving positive test results would be referred for colonoscopy, and the risks associated with bowel preparation and colonoscopy would apply.

(v) Benefit–harm ratio and cost–effectiveness

No data were available on the benefit–harm ratio associated with CRC screening with the *mSEPT9* DNA test, and only one study on cost–effectiveness was available to the Working Group. Ladabaum et al. (2013) compared the cost–effectiveness of the *mSEPT9* DNA test with that of established screening strategies. In an analysis based on the estimates of specificity and sensitivity from Church et al. (2014), CRC screening with the *mSEPT9* DNA test was cost-effective compared with no screening, but not cost-effective compared with established screening tests, because it was less effective and more costly. Because screening participation is variable and is influenced by test preference, comparisons between strategies may yield different results.

For example, FIT was the preferred strategy with 100% participation, but when the participation rate was reduced to less than 70%, it was no longer more effective than the two-reagent *mSEPT9* DNA test, and when the participation rate was reduced to less than 85%, it was no longer more effective than the three-reagent *mSEPT9* DNA test. [The Working Group noted that where increasing participation in a CRC screening programme depends on the availability of preference-sensitive options, tests that are less effective in head-to-head comparisons than tests that have more favourable characteristics may become more attractive.]

(b) Multiple-gene plasma DNA test

A 29-gene marker panel is currently commercially available and has been marketed in some countries as an option for CRC screening. The gene panel is based on the hypothesis that myelomonocytic cells are recruited to neoplasia and that genes in those cells could be used as biomarkers for detection (Nichita et al., 2014). The test has been assessed within a case–control study that recruited patients in the Republic of Korea and Switzerland. The initial study to develop the panel included 144 individuals, with 46 patients with at least one large polyp, 48 patients with CRC, and 50 controls. The 48 CRCs were equally split (n = 12) across the four stages. Through a process of repeated statistical analysis, a final list of 29 genes was developed to compose the DNA panel. To evaluate the clinical relevance of the 29-gene panel, penalized logistic regression was applied to the data set and the models were validated by non-overlapped bootstrap methods. In the validation model, the sensitivity of the test for the detection of CRC was 75% (Ciarloni et al., 2015).

In a second publication (Ciarloni et al., 2016), the 29-gene test was again examined in a selected population. Although the second study was larger than the initial study (n = 594), only the population in Switzerland was included. Again, a case–control design was used, with 149 controls, 103 patients with at least one large adenoma, and 97 patients with CRC, with a preponderance of late-stage cancers (44 in stages I and II and 53 in stages III and IV). When both sets of tests were considered, the sensitivity for the detection of CRC was 75%, with a higher sensitivity in those with late-stage cancer (90% for stages III and IV vs 56% for stages I and II). The specificity, determined by a negative colonoscopy result, was reported as 92%.

[The Working Group noted that the validation strategies used suggested extreme overfitting of the model and that the test had not been evaluated for test characteristics in a large prospective asymptomatic screening population using colonoscopy as a reference standard. The spectrum of cases was weighted to later-stage disease, and there was evidence that the test characteristics were better in those with more advanced disease.]

3.7.4 Tests based on other markers

(a) Protein markers in serum

There are a host of potential pathways to abnormal protein production during carcinogenesis that could be detected in serum. The protein could be the direct product of an abnormally modified gene. Alternatively, protein products released from inflamed or bleeding tissue associated with cancer might also be detected. Finally, approaches to identify antibodies made in response to neoplastic tissue have also been studied. Tumour-derived markers such as carcinoembryonic antigen and carbohydrate antigens (e.g. CA 19-9) have been extensively studied in serum (Hundt et al., 2007). [The studies on test performance are generally small and have a case–control design.] The results varied according to a variety of factors, including the spectrum of patients with cancer studied (early- vs late-stage disease) and the thresholds used to define a positive test result. Generally, results with such markers have been disappointing, with

sensitivities of about 50% and skewed towards those with more advanced disease. Given the relative lack of sensitivity for individual serum markers, efforts have been made to more broadly study the proteome. Several groups have used mass spectrometric analysis to examine protein patterns in individuals with cancer and those without. Although the studies that have compared the test characteristics of protein patterns with those of tumour markers alone show more promising results (Pawa et al., 2011), those studies are small and cross-sectional in nature.

(b) RNA markers in stool or serum

During the past decade there has been increasing interest in the role of the transcriptome in colorectal carcinogenesis. The initial work focused more directly on protein-coding RNA. Free messenger RNA (mRNA) is not stable in blood. However, mRNA isolated from circulating leukocytes can be analysed. Analyses have been performed of mRNA coding for a host of potentially relevant biological markers (e.g. carcinoembryonic antigen, cytokeratins, and mucins) (Hundt et al., 2007). [In these small studies comparing selected cancer cases with controls, the test characteristics were not appropriate for screening.]

There is growing interest in non-coding RNA as a biomarker for cancer, including CRC (Esteller, 2011; Kita et al., 2017). Perhaps the best-studied species are the microRNAs (miRNAs). These are short (18–22 bp) segments of non-coding RNA. Compared with mRNA, these short segments are more stable and less prone to degradation even at extremes of temperature or pH, and therefore they are better suited as biomarkers (Yiu & Yiu, 2016). miRNAs serve as modulators of the translation of mRNA and can thus influence the growth and development of tumours through a variety of mechanisms. Importantly, they are detectable in both serum and stool. In one representative study examining miRNA in stool, investigators compared miRNA expression in 29 individuals undergoing colonoscopy (10 with CRC). Levels of miR-21 and miR-106a in stool were significantly increased in individuals with CRC compared with those without CRC (Link et al., 2010). [The Working Group noted that although this area of research is developing quickly, the studies are preliminary, focusing on panels of markers in CRC cases and controls. Large-scale studies in screening populations are not available at this time.]

(c) Volatile organic compounds in breath-based tests

There has been some interest in examining volatile organic compounds exhaled through breath as a potential biomarker. Tumour growth has been associated with cell membrane peroxidation and the subsequent emission of volatile organic compounds (Peng et al., 2010). Volatile organic compounds can be identified in several different ways (de Boer et al., 2014). Individual volatile gases can be separated out from a breath sample using gas chromatography–mass spectrometry (GC-MS). Alternatively, a sensor array, which has been called an "electronic nose", can more broadly evaluate smell prints, driven by the underlying profile of volatile organic compounds.

Studies evaluating the role of volatile organic compounds as a biomarker for CRC are relatively limited (Markar et al., 2015). A proof-of-principle study used trained canine olfaction to distinguish between individuals with cancer and those without. A Labrador retriever, with 33 breath samples, appropriately detected CRC confirmed with colonoscopy, with a sensitivity of 91% and a specificity of 99% (Sonoda et al., 2011). From a clinical standpoint, it would be difficult to implement canine detection into standard laboratory practice, but the study has prompted further work using more traditional approaches to detect volatile organic compounds. For example, separate investigators (Altomare et al., 2013; Amal et al., 2016) have used GC–MS in CRC cases and controls to identify potentially discriminating

volatile organic compounds. Using this type of approach in small numbers of individuals results in sensitivities of approximately 85% and specificities in the range 83–94%. [The Working Group noted that the studies are small and preliminary and require validation. Large-scale prospective evaluations of volatile organic compounds in screening populations have not been performed.]

(d) Urinary markers

Urinary markers are under development but are not reviewed here.

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3.8 Populations at high risk of colorectal cancer

Populations at high risk for the development of CRC include the following categories of individuals: those with (i) a specific genetic predisposition; (ii) a family history of colorectal neoplasia; (iii) a personal history of colorectal neoplasia (cancer or premalignant lesions); and (iv) pre-existing medical conditions including inflammatory bowel disease, acromegaly, previous ureterosigmoidostomy, and cystic fibrosis (Table 3.8.1). Because individuals at high risk require more intensive testing, the term "surveillance" is generally used, and the term "screening" is reserved for asymptomatic populations at average risk.

3.8.1 Genetic predisposition

This category includes all individuals with specific genetic characteristics that confer a higher-than-average risk of developing CRC and other cancer types (Table 3.8.2). These genetic abnormalities induce syndromes that can be divided into three broad categories: (i) non-polyposis syndromes, (ii) adenomatous polyposis syndromes, and (iii) non-adenomatous polyposis syndromes. It should be noted that although current strategies for identifying individuals at high risk of CRC consist of syndrome-specific genetic testing, stimulated by the recognition of the phenotype associated with that syndrome and followed by surveillance of affected individuals, there is increasing interest in multigene panel testing for individuals with CRC when a hereditary component is suspected. This is now possible with the advent of massively parallel or next-generation sequencing, and it has been suggested that using a panel of high-penetrance genes associated with CRC in patients referred to cancer genetics services could be an efficient and cost-effective means of identifying genetic predisposition to CRC (Gallego et al., 2015).

(a) Non-polyposis syndromes

(i) Lynch syndrome

Definitions

Lynch syndrome is caused by germline mutations in mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*), which result in a deficiency in MMR functions and confer an increased risk of developing hypermutated tumours that display high microsatellite instability (MSI-H tumours) (Stoffel & Yurgelun, 2016).

Lynch syndrome is the underlying cause of about 3% of all CRCs and is also associated with ovarian cancer, endometrial cancer, stomach cancer, and other cancer types (Hampel et al., 2008). Lynch syndrome was initially called hereditary non-polyposis CRC (HNPCC), to distinguish it from CRC genetic syndromes with a polyposis phenotype, but this term was later dropped in recognition of the wide range of cancer types to which Lynch syndrome predisposes (Umar et al., 2004). CRCs that arise in patients with Lynch syndrome also suffer loss of one or two of the MMR proteins that are coded for by the MMR genes (Umar et al., 2004). The estimated population prevalence of mutations in MMR genes is about 1 in 3000 (Dunlop et al., 2000). Recent evidence from a large prospective Lynch syndrome database estimated the lifetime risk of any cancer by age 70 years to be about 80%; the cumulative excess risk at age 60 years varies from 46% for *MLH1* mutations to 0% for *PMS2* mutations (Møller et al., 2017). [These estimates may be attenuated as a result of surveillance.]

CRCs with MMR deficiency account for about 15% of all CRCs, but not all of these are Lynch syndrome cancers; most (12% of all CRCs) are sporadic cancers that arise through the serrated pathway (and are more likely to be located in the proximal colon), in which the *MHL1* gene is silenced not by a mutation but by hypermethylation of the promoter region of the gene (Stoffel

Table 3.8.1 High-risk groups for the development of colorectal cancer

High-risk group	Lifetime risk of colorectal cancer
Hereditary colorectal cancer	> 50%
Familial colorectal cancer	20–90%
Individuals with a personal history of colorectal cancer or colorectal adenoma	15–20%
Individuals with other diseases (e.g. ulcerative colitis)	10–20%

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Table 3.8.2 Genetically determined conditions associated with increased risk of colorectal cancer

Category	Condition	Mutations
Non-polyposis syndromes	Lynch syndrome	Mutations in MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*)
	Familial colorectal cancer	Mutations in *FAN1*, *RPS19*, *RPS20*, and *NTHL1*, but unifying genetic cause not identified
Adenomatous polyposis syndromes	Familial adenomatous polyposis	Mutation in *APC*
	MUTYH-associated polyposis	Mutation in *MUTYH*
	Polymerase proofreading-associated polyposis	Mutations in *POLE* and *POLD1*
	Constitutional mismatch repair deficiency	Biallelic germline mutations in MMR genes
Non-adenomatous polyposis syndromes	Peutz–Jeghers syndrome	Mutation in *STK11*
	Cowden syndrome	Mutation in *PTEN*
	Juvenile polyposis syndrome	Mutations in *BMPR1A* and *SMAD4*
	Serrated polyposis syndrome	Mutations in *GREM1* and *MUTYH*, but unifying genetic cause not identified
Genetic variants	Increased risk of colorectal cancer	Multiple single-nucleotide polymorphisms

& Yurgelun, 2016). Therefore, isolated MSI-H tumours that show *MLH1* loss of function are unlikely to be caused by Lynch syndrome. Nevertheless, the presence of a MSI-H tumour heightens the probability of Lynch syndrome, and therefore has important implications for screening and surveillance. In addition, there is evidence that MSI-H tumours do not benefit from adjuvant 5-fluorouracil chemotherapy (Carethers et al., 2004), although, stage for stage, they have a better prognosis compared with non-MSI-H tumours (Gryfe et al., 2000); more recently, evidence has emerged that metastatic MSI-H tumours respond well to immune checkpoint inhibitors (Le et al., 2015).

The Amsterdam family history criteria are a set of diagnostic criteria developed to help identify families with an autosomal dominant pattern of inherited risk of CRC; the criteria are the following: three or more family members with CRC or another Lynch syndrome cancer, in two or more consecutive generations with one case diagnosed at age < 50 years, and one of the affected relatives being a first-degree relative of the other two, with familial adenomatous polyposis excluded (Vasen et al., 1991). However, fewer than 50% of people with identified mutations in MMR genes come from families that fulfil these criteria (Stoffel & Yurgelun, 2016). In addition, about 50% of families that do fulfil the criteria do not have mutations in MMR genes. Such families

are described using the term "familial CRC" (see below).

Effectiveness of surveillance

If a carrier of a MMR mutation has been identified, or if a family fulfils the Amsterdam criteria, even in the absence of an identifiable mutation, then endoscopic surveillance is universally recommended. In a case–control study of Lynch syndrome family members, regular colonoscopy at intervals of 3 years was shown to reduce the risk of CRC by 50%, to prevent death from CRC, and to produce a relative reduction in all-cause mortality of 65% (Järvinen et al., 2000). [The Working Group noted that these results were derived from fairly small numbers (133 in the study group and 119 in the control group).]

A longitudinal cohort study conducted in the Netherlands reported a 70% reduction in the standardized mortality ratio for CRC after the introduction of colonoscopy every 1–2 years starting at age 20–25 years for Lynch syndrome family members with at least one family member identified with a germline mutation in one of the MMR genes (de Jong et al., 2006).

Surveillance strategies

There is debate about the optimal surveillance interval. Three prospective studies (Engel et al., 2010; Vasen et al., 2010; Stuckless et al., 2012) and one retrospective study (Mecklin et al., 2007) have examined the performance of colonoscopy surveillance in Lynch syndrome family members (Table 3.8.3). Most cancers diagnosed between surveillance episodes were diagnosed at an early stage (stage I or II), and most were located in the proximal colon, emphasizing the need for careful proximal colonoscopy. On the basis of these studies, recent European guidelines suggest that the surveillance interval should be 1–2 years (Vasen et al., 2013).

A cost–effectiveness analysis concluded that, on average, regular endoscopic examination confers an increase in life expectancy of 7 years for Lynch syndrome family members, and total colonoscopy is the preferred surveillance modality, given the high risk of adenomas and cancer and the high incidence of lesions in the proximal colon (Vasen et al., 1998). The evidence relating to the age at which surveillance should start indicates that age 25 years is appropriate, because it is from this age that the risk increases substantially, both in those defined by family history (Lynch et al., 1993) and in those with proven mutations (Vasen et al., 1996).

(ii) Familial colorectal cancer

Definition

The term "familial colorectal cancer", previously known as familial colorectal cancer type X (FCCTX), is used to describe the 40–50% of families with CRC that fulfil the Amsterdam criteria but are not found to have germline mutations in the MMR genes (Stoffel & Yurgelun, 2016). There is some debate about whether patients with MSI-H tumours with no mutations in MMR genes should be included in this group. Either way, current evidence suggests that this is a genetically heterogeneous group, and although several candidate genes have been identified, no unifying genetic pattern has emerged yet (Muzny et al., 2012).

Surveillance strategies

CRC risk is slightly lower in patients with familial CRC than in those with Lynch syndrome (see Section 3.8.1(a)). However, it is generally agreed that even when genetic screening has excluded genetically defined Lynch syndrome, the surveillance strategy in families that fulfil the Amsterdam criteria should be the same as that for patients with Lynch syndrome (Cairns et al., 2010).

Table 3.8.3 Outcomes from surveillance of patients with Lynch syndrome

Reference	Number of participants	Mean duration of follow-up (years)	Surveillance interval recommended (years)	Number (%) of interval cancers	Location in proximal colon (%)	Local stage (stage I or II) (%)	Deaths from colorectal cancer
Mecklin et al. (2007)	420	6.7	2	26 (62%)	57	80	5
Engel et al. (2010)	1126	3.7	1	25 (2.2%)	NR	95	NR
Vasen et al. (2010)	745	7.2	1–2	33 (4.4%)	62	83	0
Stuckless et al. (2012)	109	~10	1–2	21 (19.2%)	62	78	1

NR, not reported.
Adapted from Vasen et al. (2013).

(b) Adenomatous polyposis syndromes

(i) Familial adenomatous polyposis

Definition

Familial adenomatous polyposis (FAP) is caused by germline mutations in the adenomatous polyposis coli (*APC*) gene, a tumour suppressor gene that has a role in Wnt signalling and is mutated in most cases of sporadic CRC that do not display MSI (Muzny et al., 2012). FAP is easily recognized in most patients because of its phenotypic characteristics, consisting of hundreds to thousands of adenomatous polyps throughout the large bowel. The population prevalence is about 1 in 14 000, and FAP accounts for fewer than 1% of all CRCs (Bülow et al., 1995) [this percentage is now about 0.07%, as a result of effective recognition and surgical prophylaxis].

Although FAP displays an autosomal dominant pattern of inheritance, about 25% of cases are not associated with a family history and are caused by new mutations. It is in this de novo subgroup that most of the cancers now arise, because there is no opportunity to identify gene mutation carriers from a family history (Cairns et al., 2010). There is significant phenotypic heterogeneity in FAP mutations, and some mutations are associated with an attenuated form of FAP (attenuated FAP) that leads to fewer polyps and a later age of onset of both polyps and cancer (Sieber et al., 2006). In most cases of FAP, polyposis will develop in the second or third decade of life, and the risk of developing CRC is 90% by age 70 years (Vasen et al., 2008).

FAP is also associated with adenocarcinoma of the duodenum and the ampulla of Vater (lifetime risk, ~7%), diffuse fundic gland polyposis of the stomach, gastric adenomas, and papillary thyroid cancer (Stoffel & Yurgelun, 2016).

Effectiveness of surveillance

During the period from the 1970s to the 1990s, polyposis registries were set up in several countries (including Denmark, Finland, Sweden, and the USA) to improve the management of this condition. In studies based on these registries, the incidence of CRC in symptomatic patients with FAP was much higher than that in asymptomatic individuals with FAP who were under surveillance (47–70% vs 3–10%) (Alm, 1975; Bussey, 1975; Järvinen et al., 1984; Bülow, 1986; Vasen et al., 1990). In addition, the registration of FAP cases followed by regular surveillance consistently reduced CRC-specific mortality (Bertario et al., 1994; Bülow et al., 1995; Belchetz et al., 1996; Heiskanen et al., 2000).

Surveillance strategies

For classic FAP, it is usual to offer sigmoidoscopy surveillance, because the rectum appears to be affected in all cases. In the case of attenuated FAP, in which the polyp load is smaller and polyps are more likely to be located in the proximal colon, colonoscopy is recommended (Vasen et al., 2008).

In terms of the interval between examinations, because studies on the natural history of FAP indicate that, on average, 10–15 years elapse between the diagnosis of the first adenoma and the development of invasive malignancy, endoscopy (colonoscopy or sigmoidoscopy as recommended) every 2 years is recommended (Bussey, 1975; Vasen et al., 2008).

The age at which endoscopic screening should start is dependent on the risk of developing invasive malignancy. Early studies carried out in the 1970s and 1980s found that the risk of developing CRC before age 20 years is very low, and data from the European FAP registries indicate that no cases have been recorded before age 10 years (Vasen et al., 2008). Therefore, for classic FAP, sigmoidoscopy surveillance is recommended from about age 11 years (Vasen et al., 2008). In attenuated FAP, because the onset of CRC is much later, with no case having been reported before age 24 years (Burt et al., 2004; Nielsen et al., 2007), it is recommended that colonoscopy at intervals of 2 years should start at about age 20 years. The duration of surveillance after the appearance of the first adenomas should be decided jointly by the patient and the surgeon; there may be good reasons for deferring colectomy, but because the risk of CRC increases rapidly after age 25 years (Cairns et al., 2010), it should be carried out before then, unless the polyp load is very small and there is no high-grade dysplasia.

In the unusual situation where no mutation can be identified in an individual with a FAP phenotype, for their first-degree relatives, in whom the risk of having FAP is 50%, annual endoscopic surveillance from the early teenage years until age 30 years, and thereafter every 3–5 years until age 60 years, is recommended by consensus (Cairns et al., 2010).

If colectomy and ileorectal anastomosis have been carried out, lifelong annual endoscopic surveillance is recommended, because the risk of cancer in the remaining large bowel is about 25% (Nugent & Phillips, 1992).

(ii) Rare adenomatous polyposis syndromes

MUTYH-associated polyposis is an autosomal recessive condition caused by biallelic mutations in *MUTYH*, a base excision repair gene (Stoffel & Yurgelun, 2016). The phenotype is highly variable, ranging from multiple polyps, both adenomatous and hyperplastic, to CRC in the absence of coexisting polyps. *MUTYH*-associated polyposis is a rare cause of CRC, but two mutations (*Y165C* and *G382D*) have been identified that have a carrier rate of about 1% in populations of European origin (Balaguer et al., 2007).

Polymerase proofreading-associated polyposis (Palles et al., 2013) and constitutional mismatch repair deficiency (Bakry et al., 2014) are caused by germline mutations that increase the risk of CRC; because they are so rare, they are not considered in further detail here.

Strategies for surveillance

There is no evidence specifically relating to surveillance strategies for these very rare conditions, but a similar approach to that taken with FAP is recommended.

(c) Non-adenomatous polyposis syndromes

(i) Hamartomatous polyposis syndromes

Peutz–Jeghers syndrome (PJS) results from germline mutations in the *STK11* gene, although in about 50% of cases that meet the clinical criteria, genetic testing is negative (Hemminki et al., 1998). Affected individuals develop

multiple hamartomas throughout the gastrointestinal tract and mucocutaneous pigmentation, and have an increased risk of cancer of the colorectum, stomach, and other extraintestinal sites. The lifetime risk of these cancers has been estimated to be between 45% and 90%. The population prevalence is probably about 1 in 50 000, and these cancers account for fewer than 0.01% of all CRCs (Cairns et al., 2010). The cumulative risk by age 70 years is on the order of 40% (Hearle et al., 2006). When a *STK11* gene mutation has been identified, complete colonoscopy is recommended at intervals of 2 years from age 25 years (Cairns et al., 2010). Because PJS is rare, the effectiveness of this approach has not been clearly established.

Cowden syndrome, also called *PTEN* hamartoma tumour syndrome (PHTS), is defined by germline mutations in the *PTEN* tumour suppressor gene, which is involved in the Akt/PKB signalling pathway, and is associated with an increased risk of a variety of cancer types. The phenotype is highly variable, and in the gastrointestinal tract consists of hamartomas, adenomas, serrated polyps, lipomas, and ganglioneuromas (Heald et al., 2010). When a *PTEN* gene mutation has been identified, the risk of CRC does appear to be increased, but the increase in risk has not been precisely defined, and definitive guidance for surveillance is not available (Cairns et al., 2010).

Juvenile polyposis syndrome (JPS) is another hamartomatous polyposis syndrome and is associated with mutations in the *BMPR1A* and *SMAD4* genes (Roth et al., 1999; Woodford-Richens et al., 2000). The risk of developing CRC is significant, amounting to 40% (Brosens et al., 2007). The prevalence of JPS is estimated to be 1 in 120 000, and it accounts for fewer than 0.01% of CRCs (Cairns et al., 2010). When a *BMPR1A* or *SMAD4* gene mutation has been identified, colonoscopy is recommended at intervals of 2 years from age 15 years (Cairns et al., 2010). Because JPS is rare, the effectiveness of this approach has not been clearly established.

(ii) Serrated polyposis syndrome

Serrated polyposis syndrome (SPS) is defined as more than 5 serrated colonic polyps proximal to the sigmoid, with at least 2 polyps larger than 10 mm, any serrated polyps in the proximal colon when there is a first-degree relative with SPS, or more than 20 serrated polyps (WHO Classification of Tumours Editorial Board, 2019; Rex et al., 2012). Although germline mutations in the *GREM1* and *MUTYH* genes have been associated with SPS (Jaeger et al., 2012), this is not universal. Individuals with SPS have an increased risk of CRC with MMR deficiency (IJspeert et al., 2017).

When the World Health Organization (WHO) criteria for SPS have been met, or when a *GREM1* or *MUTYH* mutation has been identified, colonoscopy at intervals of 1–2 years is recommended (East et al., 2017) [this is a weak recommendation, based on low-quality evidence]. Recent work indicates that several clinical risk factors could be used to stratify patients with SPS for different surveillance intervals (IJspeert et al., 2017).

3.8.2 Family history of colorectal neoplasia

(a) Definitions

It is well established that individuals with a family history of CRC have a higher risk of developing CRC. A close familial relationship, an early age at diagnosis, and the number of affected relatives are each indicators of elevated risk (Cairns et al., 2010). There is a large body of evidence from observational studies, most of which have been summarized in meta-analyses, which consistently found an approximately 2-fold increased risk of CRC in people with a first-degree relative with CRC compared with people with no such family history (Johns & Houlston, 2001; Baglietto et al., 2006; Butterworth et al., 2006; Johnson et al., 2013; Table 3.8.4).

Table 3.8.4 Meta-analyses of studies on the incidence of colorectal cancer in individuals with a family history of colorectal neoplasia

Reference	Number of studies Study design	Years of publication	Study design analysed	Family history	Number of studies in analysis	Summary estimate (95% CI)
Johns & Houlston (2001)	26 Cohort Case–control	1958–1999	Mixed	≥ 1 FDR	26	2.25 (2.00–2.53)
				≥ 2 FDR	6	4.25 (3.01–6.08)
				FDR at age < 45 yr	5	3.87 (2.40–6.22)
				FDR at age 45–59 yr	5	2.25 (1.85–2.72)
				FDR at age > 59 yr	3	1.82 (1.47–2.25)
Baglietto et al. (2006)	20 Cohort Case–control	1982–2003	Mixed	≥ 1 FDR	20	2.26 (1.86–2.73)
Butterworth et al. (2006)	47 Cohort Nested case–control Case–control Cross-sectional	1979–2004	Mixed	≥ 1 FDR	47	2.24 (2.06–2.43)
				≥ 2 FDR	10	3.97 (2.60–6.06)
				FDR at age < 50 yr	4	3.55 (1.84–6.83)
				FDR at age ≥ 50 yr	4	2.18 (1.56–3.04)
				≥ 1 SDR	5	1.73 (1.02–2.94)
			Cohort	≥ 1 FDR	13	2.29 (1.93–2.71)
			Case–control	≥ 1 FDR	34	2.21 (2.02–2.42)
Johnson et al. (2013)	16 Cohort Case–control Nested case–control Cross-sectional	1989–2009	Mixed	≥ 1 FDR	16	1.80 (1.61–2.02)

CI, confidence interval; FDR, first-degree relative or relatives; SDR, second-degree relative or relatives; yr, year or years.

The risk of CRC can be increased 2–4-fold if two or more first-degree relatives are affected with CRC (Fuchs et al., 1994; Taylor et al., 2010; Schoen et al., 2015; Weigl et al., 2016). The strength of the association decreases with increasing age. In people with a first-degree family history of CRC, the risk of CRC was found to be highest before or at age 40 years and to decrease with age afterwards (Samadder et al., 2015).

If a first-degree relative was diagnosed with CRC before age 50 years, then the risk of CRC was found to be more than 3-fold that of people with no family history of CRC (Butterworth et al., 2006; Taylor et al., 2010), more than 2-fold if the diagnosis was before age 60 years (Johns & Houlston, 2001; Samadder et al., 2014, 2015), and mostly less than 2-fold if the diagnosis was after age 60 years (Taylor et al., 2010; Samadder et al., 2014, 2015).

The risk of CRC in people with a family history of adenomatous polyps has not been as well investigated, and only a few well-designed studies exist (Lowery et al., 2016). Winawer et al. (1996) reported an almost 2-fold increased risk if adenomas were detected in a first-degree relative, and an even higher risk if the adenoma was detected before age 60 years; these findings were later confirmed by other studies (Ahsan et al., 1998; Cottet et al., 2007). A recent study in Hong Kong Special Administrative Region, China, investigated the risk of advanced adenomas in people with a family history of adenomatous polyps and found a much higher risk if the affected first-degree relative had an advanced adenoma compared with any adenoma (Ng et al., 2016). People with one affected second-degree relative were found to have a 20–50% higher risk of CRC, and the risk was somewhat higher with a greater number of affected second-degree relatives or if second-degree relatives were younger than 50 years or younger than 60 years at diagnosis (Taylor et al., 2010; Samadder et al., 2014, 2015; Weigl et al., 2016).

The association of a family history of adenomatous polyps with an increased risk of colorectal neoplasia is presumably due to a combination of heritable factors and shared environmental factors. It is recognized that up to 30% of CRCs are attributable to hereditary factors, but only 5% are attributable to the highly penetrant mutations that account for the syndromes described above (Broderick et al., 2017). It follows that the remainder (25%) are probably caused, at least in part, by the accumulation of low-penetrance genetic variants. Genome-wide association studies (GWAS) have so far identified up to 37 single-nucleotide polymorphisms (SNPs) with a positive association with CRC, although recent meta-analyses did not confirm the association with CRC for 22 of the SNPs (Montazeri et al., 2016). The presence or absence of these SNPs can be used to construct a polygenic risk score, and it has been shown that people with a polygenic risk score in the top 1% have an almost 3-fold increased risk of CRC compared with the population median (Frampton et al., 2016). However, it should be emphasized that the effect of family history cannot be explained entirely by genetic variation, because it has been shown that family history by itself is a risk factor that operates independently from the SNPs that are currently known to be associated with CRC (Weigl et al., 2018).

(b) Surveillance strategies

People with a family history of CRC are generally advised to start CRC screening earlier than the population at average risk. Colonoscopy is the preferred and recommended examination for screening and surveillance in this high-risk group, because a large proportion of cancers are also located in the proximal colon (Slattery & Kerber, 1994; Cairns et al., 2010; Rex et al., 2017).

Expert organizations tend to recommend earlier screening with colonoscopy in first-degree relatives of patients with CRC (Table 3.8.5). For example, screening colonoscopy should begin at

Table 3.8.5 Screening recommendations for individuals with a family history of colorectal neoplasia

Recommending association Reference	Family history	Recommended starting age of surveillance	Recommended surveillance interval
United States Multi-Society Task Force on Colorectal Cancer Rex et al. (2017)	CRC or advanced adenoma in 2 FDR diagnosed at any age CRC or advanced adenoma in 1 FDR diagnosed at age < 60 yr	Colonoscopy beginning 10 yr before the age at diagnosis of the youngest affected FDR or at age 40 yr, whichever is earlier	Colonoscopy every 5 yr
	CRC or advanced adenoma in 1 FDR diagnosed at age ≥ 60 yr	Begin screening at age 40 yr; tests are as per the average-risk screening recommendations Annual FIT if colonoscopy is refused	Intervals are as per the average-risk screening recommendations
German Guideline Program in Oncology GGPO (2019)	CRC in FDR	Colonoscopy beginning 10 yr before the age at diagnosis of the youngest affected FDR or at age 40–45 yr, at the latest	Colonoscopy after no more than 10 yr
	Adenoma in FDR detected at age < 50 yr	Colonoscopy 10 yr before the age at which the adenoma was detected in the affected FDR	Colonoscopy after no more than 10 yr
British Society of Gastroenterology and Association of Coloproctology for Great Britain and Ireland Cairns et al. (2010)	CRC in 3 FDR, none aged < 50 yr CRC in 2 FDR, mean age < 60 yr	Colonoscopy at age 50 yr	Colonoscopy every 5 years to age 75 yr
	CRC in 2 FDR diagnosed at age ≥ 60 yr CRC in 1 FDR diagnosed at age < 50 yr	Once-only colonoscopy at age 55 yr	If normal, no follow-up
Asia Pacific Working Group on Colorectal Cancer Sung et al. (2015)	Not specified	Early screening is warranted for FDR of patients with CRC	No recommendation yet
Pan American Health Organization PAHO (2016)	Not specified	Screening should begin before age 50 yr	No recommendation yet
Cancer Council Australia Cancer Council Australia Colorectal Cancer Guidelines Working Party (2017)	CRC in 1 FDR diagnosed at age < 55 yr CRC in 2 FDR diagnosed at any age CRC in 1 FDR and ≥ 2 SDR diagnosed at any age	FIT every 2 yr from age 40 yr to age 49 yr Colonoscopy every 5 yr from age 50 yr to age 74 yr	
	CRC in ≥ 3 FDR or SDR, with ≥ 1 diagnosed at age < 55 yr CRC in ≥ 3 FDR diagnosed at any age	FIT every 2 yr from age 35 yr to age 44 yr Colonoscopy every 5 yr from age 45 yr to age 74 yr	

CRC, colorectal cancer; FDR, first-degree relative or relatives; FIT, faecal immunochemical test; SDR, second-degree relative or relatives; yr, year or years.

age 40 years in the USA and at age 40–45 years in Germany, or at least 10 years before the age at which CRC was diagnosed in the youngest affected first-degree relative (Brenner et al., 2008; GGPO, 2019; Rex et al., 2017). Expert organizations in the United Kingdom recommend screening colonoscopy for people with a family history of CRC starting at age 50–55 years (Cairns et al., 2010). A recent exception to the strong emphasis on colonoscopy is the recommendation of Cancer Council Australia, which recommends screening with FIT biennially in the first 10 years from age 35 years or 40 years, depending on the family history risk category, followed by colonoscopy every 5 years (Cancer Council Australia Colorectal Cancer Guidelines Working Party, 2017). In other countries and regions, development of guidelines is currently under way (PAHO, 2016; Sung et al., 2015).

The most up-to-date guidelines from the United States Multi-Society Task Force on Colorectal Cancer no longer differentiate between a history of CRC and a history of advanced adenomas in first-degree relatives with respect to the timing of the first screening colonoscopy (Rex et al., 2017). Also, the Task Force recommends a shorter surveillance interval of 5 years for those with two first-degree relatives or one first-degree relative younger than 60 years diagnosed with either CRC or advanced adenoma (Rex et al., 2017).

The United Kingdom guidelines recommend colonoscopy intervals every 5 years if CRC was detected in three first-degree relatives (none younger than 50 years) or in two first-degree relatives at a mean age at diagnosis of younger than 60 years (Cairns et al., 2010). European and German guidelines do not support special surveillance intervals for risk groups defined by family history (Dove-Edwin et al., 2005; Malila et al., 2012; GGPO, 2019).

The surveillance interval of 5 years for individuals with affected first-degree relatives was first mentioned in the guidelines for screening and surveillance from the USA in 2003 (Winawer et al., 2003), but evidence for the effectiveness of specific surveillance intervals is lacking. A recent RCT compared the detection rates of advanced adenomas in people with first-degree relatives diagnosed with CRC before age 50 years or with two first-degree relatives diagnosed with CRC at any age, and found no statistically significant difference at colonoscopy after 3 years (3.5%) and after 6 years (6.9%) (Hennink et al., 2015).

Most guidelines incorporate the age of the affected first- or second-degree relatives (< 60 years or ≥ 60 years), to account for the higher risk of CRC if the affected relative was diagnosed at a comparably younger age, which is supported by many studies (e.g. Winawer et al., 1996; Cottet et al., 2007). Still, the population frequency of having first-degree relatives diagnosed with CRC after age 60 years is 3.4%, so it is much more likely than having first-degree relatives diagnosed before age 60 years (0.8%) or before age 50 years (0.3%) (Taylor et al., 2010).

(c) Effectiveness of surveillance

The recommendation for individuals with a family history of CRC and with a negative colonoscopy to undergo another colonoscopy after 5 years instead of after 10 years, as is recommended for people at average risk, is based largely on the assumption that polyps grow more rapidly or transform more rapidly into cancer in this risk group, derived from clinical experience in the absence of empirical evidence. Only recently have a few observational studies actually analysed the effectiveness of colonoscopy in relation to family history of CRC (Brenner et al., 2011; Nishihara et al., 2013; Samadder et al., 2017). All three studies used CRC incidence as the outcome (Table 3.8.6).

In the study by Brenner et al. (2011), a very similar and strong reduction in the risk of CRC was observed if a colonoscopy was performed in the previous 1–10 years, regardless of whether first-degree relatives were affected. Nishihara

Table 3.8.6 Studies of the effectiveness of colonoscopy in individuals with a family history of colorectal cancer on colorectal cancer incidence

Reference Country	Study design Sample size	Study period Age group	Family history category Colonoscopy group	Relative risk (95% CI)	Adjustments
Brenner et al. (2011) Germany	Population-based case–control study 1688 cases 1932 controls	2003–2007 ≥ 50 yr	FDR with CRC: No colonoscopy Any colonoscopy 1–10 yr previously No FDR with CRC: No colonoscopy Any colonoscopy 1–10 yr previously	Odds ratio: 1 0.20 (0.13–0.32) 1 0.23 (0.19–0.28)	Age, sex, age, education level, general health screening, smoking status, BMI, use of NSAIDs, and use of HRT
Nishihara et al. (2013) USA	Prospective cohort study 88 902 participants	1988–2008 30–55 yr at baseline	FDR with CRC: No colonoscopy Any colonoscopy ≤ 5 yr previously Any colonoscopy > 5 yr previously No FDR with CRC: No colonoscopy Any colonoscopy ≤ 5 yr previously Any colonoscopy > 5 yr previously	Hazard ratio: 1 0.44 (0.30–0.66) 0.91 (0.55–1.52) 1 0.42 (0.35–0.51) 0.43 (0.32–0.58)	Age, sex, BMI, smoking status, aspirin use, physical activity level, red meat intake, total energy intake, alcohol consumption, folate intake, calcium intake, use of multivitamins, use of NSAIDs, and use of cholesterol-lowering drugs
Samadder et al. (2017) USA	Prospective cohort study 131 349 individuals with negative first colonoscopy at average risk, 7515 with first negative colonoscopy and FDR with CRC	2001–2011 50–80 yr at baseline	FDR with CRC: Negative colonoscopy 0–2 yr previously Negative colonoscopy 2.1–5 yr previously Negative colonoscopy 5.1–7 yr previously Negative colonoscopy 7.1–10 yr previously No FDR with CRC: Negative colonoscopy 0–2 yr previously Negative colonoscopy 2.1–5 yr previously Negative colonoscopy 5.1–7 yr previously Negative colonoscopy 7.1–10 yr previously	SIR: 0.15 (0.00–0.43) 0.47 (0.14–0.79) 0.77 (0.20–1.34) 0.65 (0.08–1.22) 0.15 (0.08–0.23) 0.26 (0.19–0.32) 0.33 (0.22–0.43) 0.60 (0.44–0.76)	Age and sex

BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; FDR, first-degree relative; HRT, hormone replacement therapy; NSAIDs; non-steroidal anti-inflammatory drugs; SIR, standardized incidence ratio; yr, year or years.

et al. (2013) analysed the reduction in CRC risk by time since colonoscopy and found no reduction in risk in people with a first-degree family history of CRC whose most recent colonoscopy was performed more than 5 years earlier, whereas a significant reduction in risk was observed in people with no first-degree family history of CRC. [The Working Group noted that these results should be interpreted with caution with respect to considerations of surveillance intervals, because the studies did not differentiate between positive and negative index colonoscopies and because the absolute risk of CRC in people with a first-degree family history of CRC is generally higher than that in people with no such family history.]

Samadder et al. (2017) investigated the differences in CRC risk by time since a first negative colonoscopy in relation to a first-degree family history of CRC. In that study, which linked the Utah Population Database with cancer registry data and health-care data, the risk of CRC after a negative colonoscopy was generally reduced in individuals with no first-degree family history of CRC (measured up to 10 years after the negative colonoscopy). In individuals with a first-degree family history of CRC, the risk was similarly reduced up to 5 years after a negative colonoscopy; there was also a suggestion of a reduced risk 5–10 years after a negative colonoscopy in this group, but the standardized incidence ratios were not statistically significant for this interval. [The Working Group considered that the authors' interpretation that the results support a surveillance interval of 5 years in people with a first-degree family should be interpreted with caution, because of the limited power of the analyses in this risk group.]

3.8.3 Personal history of colorectal neoplasia

(a) Definitions

For a detailed description of the histopathology of colorectal neoplasia, see Section 1.2. Advanced adenomas are characterized by size (≥ 10 mm) and/or high-grade dysplasia and/or villous histology, and are considered high-risk adenomas, although the most common and strongest risk factor among the advanced characteristics is the size of the tumour. Any of these characteristics distinguishes them from non-advanced adenomas.

Sessile serrated lesions and polyps are common, are located mainly in the proximal colon, and are difficult to detect because of their sessile or flat morphology. Sessile serrated lesions smaller than 10 mm with no cytological dysplasia are classified among the low-risk lesions (Lieberman et al., 2012). Sessile serrated lesions 10 mm or larger and sessile serrated lesions with cytological dysplasia are considered to be high-risk lesions, with significant malignant potential (Erichsen et al., 2016). Traditional serrated adenomas are much less common, have a sessile or pedunculated shape, and are located mainly in the distal colon. Because of their malignant potential, they are considered high-risk adenomas (Erichsen et al., 2016).

Patients with a previous history of CRC have an increased risk of developing a subsequent cancer in the remaining colorectum (Bouvier et al., 2008), and in patients with a previous diagnosis of advanced adenoma, the risk of CRC is also increased (Atkin & Saunders, 2002).

(b) Increase in risk of cancer

Studies on the subsequent risk of colorectal neoplasia and CRC mortality in patients with low-risk adenomas and with high-risk adenomas at baseline examination are presented in Table 3.8.7 and Table 3.8.8, respectively.

In an earlier meta-analysis of observational studies, the risk of advanced adenomas

Table 3.8.7 Studies on subsequent risk of colorectal neoplasia and colorectal cancer mortality in patients with low-risk adenomas at baseline examination (selected recent studies)

Reference Country	Study design Study period Sample size	Follow-up	Outcome	Diagnosis at baseline	Relative risk (95% CI)	Adjustments Comments
Lieberman et al. (2007) USA	Prospective cohort study 1994–1997 1171 with neoplasia, 501 neoplasia-free controls	5.5 yr	Advanced neoplasia	No adenoma 1–2 tubular adenomas < 10 mm	1.00 1.92 (0.83–4.42)	Age and family history of CRC
Martínez et al. (2009) USA	Pooled prospective cohort studies 9167 with adenomas	3.9 yr (median)	Advanced neoplasia	2 adenomas vs 1 adenoma Adenoma size: 5–9 mm vs < 5 mm	1.39 (1.17–1.66) 1.17 (0.95–1.42)	Age, sex, race, family history of CRC, previous polyp, smoking status, BMI, baseline number of adenomas, adenoma size, location, histology, high-grade dysplasia, and study
Miller et al. (2010) USA	Retrospective cohort study 391 with and without adenomas	5–10 yr	Advanced neoplasia	No adenoma Adenoma < 5 mm Adenoma 5–9 mm Tubular adenoma 1 adenoma 2 adenomas	1.0 1.5 (0.6–3.9) 1.1 (0.4–3.3) 0.9 (0.4–2.3) 0.9 (0.3–3.2) 1.5 (0.5–4.5)	Unadjusted
Brenner et al. (2012) Germany	Case–control study 2582 cases, 1798 controls	10 yr	CRC	No previous endoscopy LRA < 3 yr ago LRA 3–5 yr ago LRA 6–10 yr ago	1.0 0.2 (0.1–0.2) 0.4 (0.2–0.6) 0.8 (0.4–1.5)	Age, sex, residence, education level, general health screening, family history of CRC, smoking status, use of NSAIDs, and use of HRT
Cottet et al. (2012) France	Prospective cohort study 5779 with adenomas	7.7 yr	CRC	LRA	SIR: 0.68 (0.44–0.99)	Age and sex
Løberg et al. (2014) Norway	Retrospective cohort study 1993–2011 40 826 with adenomas	7.7 yr (median)	CRC mortality	Low-risk adenoma	SMR: 0.75 (0.63–0.88)	Age Low risk: 1 adenoma, no villous growth pattern, no high-grade dysplasia
Atkin et al. (2017) United Kingdom	Retrospective cohort study 1990–2010 11 944 with intermediate-risk adenomas	7.9 yr (median)	CRC	Lower-risk group	0.51 (0.29–0.84)	Age and sex Lower risk, any of these: 1–2 adenomas 10–19 mm, 3–4 adenomas < 10 mm

BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; HRT, hormone replacement therapy; LRA, low-risk adenoma; NSAIDs; non-steroidal anti-inflammatory drugs; SIR, standardized incidence ratio; SMR, standardized mortality ratio; yr, year or years.

Table 3.8.8 Studies on subsequent risk of colorectal neoplasia and colorectal cancer mortality in patients with high-risk adenomas at baseline examination (selected studies)

Reference Country	Study design Study period Sample size	Follow-up	Outcome	Diagnosis at baseline	Relative risk (95% CI)	Adjustments Comments
Lieberman et al. (2007) USA	Prospective cohort study 1994–1997 1171 with neoplasia, 501 neoplasia-free controls	5.5 yr	Advanced neoplasia	No adenoma > 3 tubular adenomas < 10 mm 1 tubular adenoma ≥ 10 mm Villous adenoma HGD adenoma	1.00 5.01 (2.10–11.96) 6.40 (2.74–14.94) 6.05 (2.48–14.71) 6.87 (2.61–18.07)	Age and family history of CRC
Martínez et al. (2009) USA	Pooled prospective cohort studies 9167 with adenomas	3.9 yr (median)	Advanced neoplasia	3 adenomas vs 1 adenoma 4 adenomas vs 1 adenoma ≥ 5 adenomas vs 1 adenoma Proximal adenoma vs distal adenoma vs adenoma < 5 mm 10–19 mm ≥ 20 mm Tubulovillous/villous vs tubular High-grade dysplasia, yes vs no	1.85 (1.46–2.34) 2.41 (1.71–3.40) 3.87 (2.76–5.42) 1.68 (1.43–1.98) 2.27 (1.84–2.78) 2.99 (2.24–4.00) 1.28 (1.07–1.52) 1.05 (0.81–1.35)	Age, sex, race, family history of CRC, previous polyp, smoking status, BMI, baseline number of adenomas, adenoma size, location, histology, high-grade dysplasia, and study
Miller et al (2010) USA	Retrospective cohort study 1997–2006 391 with and without adenomas	5–10 yr	Advanced neoplasia	No neoplasia Adenoma ≥ 10 mm ≥ 3 adenomas Villous/tubulovillous adenoma	1.0 2.2 (0.7–6.6) 1.9 (0.8–4.6) 4.2 (1.5–11.5)	Unadjusted
Brenner et al. (2012) Germany	Case–control study 2003–2010 2582 cases, 1798 controls	10 yr	CRC	No previous endoscopy HRA < 3 yr ago HRA 3–5 yr ago HRA 6–10 yr ago	1.0 0.4 (0.3–0.7) 0.5 (0.3–0.8) 1.1 (0.5–2.6)	Age, sex, residence, education level, general health screening, family history of CRC, smoking status, use of NSAIDs, and use of HRT
Cottet et al. (2012) France	Prospective cohort study 1990–1999 5779 with adenomas	7.7 yr	CRC	High-risk adenoma	SIR: 2.23 (1.67–2.92)	Age and sex
Løberg et al. (2014) Norway	Retrospective cohort study 1993–2011 40 826 with adenomas	7.7 yr (median)	CRC mortality	High-risk adenoma	SMR: 1.16 (1.02–1.31)	Age Higher risk, any of these: ≥ 2 adenomas, adenoma with villous histology, high-grade dysplasia

Table 3.8.8 (continued)

Reference Country	Study design Study period Sample size	Follow-up	Outcome	Diagnosis at baseline	Relative risk (95% CI)	Adjustments Comments
Holme et al. (2015) Norway	Trial follow-up study 1999–2001 91 175 screening trial participants	10.9 yr (median)	CRC	Polyp-free Serrated polyp ≥ 10 mm Adenoma ≥ 10 mm Villous histology High-grade dysplasia ≥ 3 adenomas	1.0 3.3 (1.3–8.6) 2.8 (1.5–5.2) 1.1 (0.5–2.5) 2.7 (1.3–5.8) 2.3 (1.2–4.5)	Age and sex
Atkin et al. (2017) United Kingdom	Retrospective cohort study 1990–2010 11 944 with intermediate-risk adenomas	7.9 yr (median)	CRC	Higher-risk group	SIR: 1.30 (1.06–1.57)	Age and sex Higher risk, any of these: suboptimal examination quality, proximal polyps, high-grade dysplasia, adenoma ≥ 20 mm

BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; HGD, high-grade dysplasia; HRA, high-risk adenoma; HRT, hormone replacement therapy; NSAIDs; non-steroidal anti-inflammatory drugs; SIR, standardized incidence ratio; SMR, standardized mortality ratio; yr, year or years.

after 5 years in adults with one or two low-risk adenomas was similar to that in the population at average risk (Saini et al., 2006). More recent studies with up to 10 years of follow-up have confirmed no increased risk of CRC over the longer interval (Lieberman et al., 2007; Miller et al., 2010; Brenner et al., 2012; Cottet et al., 2012).

In the National Cancer Institute Pooling Project in the USA, the risk of advanced neoplasia was increased more than 2-fold in people with a history of adenomas of 10–19 mm compared with adenomas smaller than 5 mm, after 3–5 years of follow-up, and was increased 3-fold in people with a history of adenomas 20 mm or larger (Martínez et al., 2009). In the same study, the risk of advanced neoplasia was increased by about 30% if the adenoma showed villous or tubulovillous histology. However, in that study there was no association of high-grade dysplasia with subsequent occurrence of advanced neoplasia, although such associations were observed in other studies (Winawer et al., 2006; Atkin et al., 2017).

In another study, compared with the reference group with no neoplasia at baseline examination, the risk of advanced neoplasia increased strongly (RR, 6.05–6.87) in patients with adenomas 10 mm or larger, with villous histology and with high-grade dysplasia, after 5.5 years of follow-up (Lieberman et al., 2007). [The Working Group noted the large confidence intervals in these associations.]

(c) Surveillance strategies

The surveillance strategy for individuals with a personal history of colorectal neoplasia depends on the findings at baseline examination (Table 3.8.9). The section below summarizes the currently available surveillance strategies in such populations.

RCTs (European Polyp Surveillance I–III) are currently under way to assess the intervals for follow-up of patients with low-risk adenomas (5 years vs 10 years) and compared with those with high-risk adenomas (3 years vs 5 years) (Jover et al., 2016).

(i) One or two tubular adenomas smaller than 10 mm at baseline examination

As a result of improvements in colonoscopy, the detection rates of polyps, particularly those of small polyps, have increased (Brenner et al., 2015). Findings of one or two tubular adenomas with no villous components or high-grade dysplasia are considered to be low-risk adenomas.

Recent expert guidelines from countries with long-standing screening practices, such as the USA and countries in Europe, generally recommend having surveillance colonoscopy 5–10 years after the removal of low-risk adenomas (Lieberman et al., 2012; Hassan et al., 2013), or following recommendations for the next screening as if there had been no relevant findings at colonoscopy (Atkin et al., 2012). The United Kingdom guidelines recommend surveillance after 5 years, or no surveillance (Cairns et al., 2010) (see Table 3.8.9).

A recent meta-analysis and two individual studies that have not yet been considered in the existing guidelines observed a lower risk of CRC incidence and mortality after the removal of low-risk adenomas compared with that in the general population at average risk. These results, in addition to the results of earlier studies, challenge current recommendations and suggest that an extended interval of surveillance or no surveillance may apply after the removal of low-risk adenomas (Atkin et al., 2017; Dubé et al., 2017; Løberg et al., 2017). [The Working Group noted that in the studies of Atkin et al. (2017) and Løberg et al. (2017) the definitions of low-risk adenomas were more inclusive than only one or two adenomas smaller than 10 mm.]

Table 3.8.9 Expert guidelines for colonoscopy surveillance after adenoma removal

Findings at baseline examination	Guideline recommendations for time until surveillance colonoscopy				
	United States Multi-Society Task Force on Colorectal Cancer (Lieberman et al., 2012)	European Union (Atkin et al., 2012)	European Society of Gastrointestinal Endoscopy (Hassan et al., 2013)	British Society of Gastroenterology (Cairns et al., 2010; East et al., 2017)	Cancer Council Australia (Barclay et al., 2013)
1–2 tubular adenomas < 10 mm	5–10 yr	Routine screening	Screening after 10 yr	5 yr or screening	5 yr
3–4 tubular adenomas < 10 mm	3 yr	3 yr	3 yr	3 yr	3 yr
5–10 tubular adenomas < 10 mm	3 yr	1 yr	3 yr	1 yr	1 yr
≥ 1 advanced adenomas	3 yr	3 yr	3 yr	–	–
1–2 adenomas ≥ 10 mm	3 yr	3 yr	3 yr	3 yr	3 yr
≥ 3 adenomas ≥ 10 mm	3 yr	3 yr	3 yr	1 yr	< 5 adenomas ≥ 10 mm: 3 yr 5–9 adenomas ≥ 10 mm: 1 yr > 9 adenomas ≥ 10 mm: < 1 yr
≥ 1 adenoma ≥ 20 mm	–	1 yr	–	–	–
Sessile serrated lesion ≥ 10 mm or with dysplasia	3 yr	–	3 yr	3 yr	3 yr
Sessile serrated lesion < 10 mm and no dysplasia	5 yr	–	5 yr	Routine screening	5 yr
Traditional serrated adenoma	3 yr	–	3 yr	3 yr	–

yr, year or years.

(ii) Three or more adenomas at baseline examination

Patients with three or more adenomas at baseline examination have an increased risk of colorectal neoplasia soon after the baseline examination. It is assumed that with the prevalence of multiple adenomas, single adenomas may be missed; this may explain, at least in part, the higher adenoma detection rates at follow-up examinations (Lieberman et al., 2012). In an analysis of the National Cancer Institute Pooling Project, the risk of advanced adenomas during a follow-up of 3–5 years increased in a linear manner with each additional adenoma detected at baseline (Martínez et al., 2009).

According to guidelines from the USA and the European Society of Gastroenterology, patients with 3–10 adenomas smaller than 10 mm are considered to have a high risk of colorectal neoplasia and are advised to have surveillance colonoscopy 3 years after the baseline examination. According to guidelines from Australia, the European Union, and the United Kingdom, patients with three or four small adenomas are considered to be an intermediate-risk group, and surveillance after 3 years is recommended, whereas patients with five or more small adenomas are classified as a high-risk group, and a surveillance interval of 1 year is recommended (Cairns et al., 2010; Atkin et al., 2012; Barclay et al., 2013). For the small group of patients with more than 10 adenomas at baseline examination, the recommendation is to have genetic counselling or surveillance colonoscopy within less than 3 years (Lieberman et al., 2012; Hassan et al., 2013).

(iii) One or more advanced adenomas at baseline examination

Patients with one or more advanced adenomas belong to the high-risk group. Guidelines from Europe and the USA recommend that such patients undergo surveillance colonoscopy after 3 years (Atkin et al., 2012; Lieberman et al., 2012; Hassan et al., 2013); the European Union guidelines also suggest surveillance after 1 year if an adenoma is 20 mm or larger (Atkin et al., 2012). The United Kingdom guidelines recommend a surveillance interval of 3 years if one or two adenomas are 10 mm or larger (intermediate risk) and a surveillance interval of 1 year if at least three adenomas are 10 mm or larger (high risk) (Cairns et al., 2010). The guidelines from Australia recommend a surveillance interval of 3 years after the detection of one to four adenomas 10 mm or larger, and a surveillance interval of 1 year after the detection of five to nine adenomas 10 mm or larger (Barclay et al., 2013).

(iv) Serrated lesions and polyps at baseline examination

The quality of evidence with respect to surveillance after the removal of serrated lesions and polyps is still low and limited (Hiraoka et al., 2010; Schreiner et al., 2010; Lieberman et al., 2012; Holme et al., 2015; Szylberg et al., 2015; East et al., 2017; Dekker & IJspeert, 2018). Expert guidelines from Europe and the USA recommend surveillance colonoscopy after 3 years for patients with high-risk serrated polyps and lesions, and after 5 years for those with low-risk serrated polyps and lesions (Lieberman et al., 2012; Hassan et al., 2013). The United Kingdom guidelines also recommend a surveillance interval of 3 years for patients with high-risk serrated adenomas, but no special surveillance is recommended for those with low-risk serrated polyps and lesions (Cairns et al., 2010).

3.8.4 Medical conditions

Several medical conditions have been associated with the risk of developing CRC: inflammatory bowel disease, acromegaly, ureterosigmoidostomy, and cystic fibrosis.

Patients with inflammatory bowel disease, both ulcerative colitis and Crohn disease, have

an increased risk of CRC. Patients with a long history of extensive colitis (> 10 years with > 50% involvement of the colon) have 7 times the risk of patients with inflammatory bowel disease of lesser severity (Beaugerie et al., 2013). In addition, patients with ulcerative colitis with primary sclerosing cholangitis have a 4-fold increased risk of CRC compared with those without ulcerative colitis, and have an increased risk from the time of diagnosis (Soetikno et al., 2002).

Acromegaly is caused by increased levels of circulating growth hormone and its tissue mediator, insulin-like growth factor 1 (IGF-1). Although acromegaly is rare, this condition has been recognized as a risk factor for CRC and adenomas; prospective studies have found an odds ratio of 1.9 for adenoma and of 6.0 for CRC (Jenkins, 2006).

Adenomas and adenocarcinomas can form at the anastomosis site after ureterosigmoidostomy, although it is unclear whether they arise from the colonic or ureteric epithelium. It has been estimated that this occurs in 2.6% of patients, with a median latency of 26 years (Kälble et al., 2011).

Cystic fibrosis is also known to be associated with an increased risk of CRC, and the risk of CRC is higher in individuals who have had an organ transplant (Gini et al., 2018).

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