

European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition

Introduction



Co-Funded by
the Health Programme
of the European Union

Authors

I. Lansdorp-Vogelaar¹, L. von Karsa²

Institutions

¹ Erasmus MC, University Medical Centre, Rotterdam, the Netherlands

² Quality Assurance Group, Early Detection and Prevention Section, International Agency for Research on Cancer, Lyon, France

Keywords

- mass screening
- colorectal neoplasms
- population-based programme
- effectiveness
- cost-effectiveness
- quality assurance recommendations
- evidence-based guidelines

Multidisciplinary, evidence-based guidelines for quality assurance in colorectal cancer screening and diagnosis have been developed by experts in a project coordinated by the International Agency for Research on Cancer. The full guideline document covers the entire process of population-based screening. It consists of 10 chapters and over 250 recommendations, graded according to the strength of the recommendation and the supporting evidence. The 450-page guidelines and the extensive evidence base have been published by the European Commission. The first chapter deals with the evidence for the effectiveness of CRC screening; key operational parameters such

as age-range, interval between two negative screening examinations, and some combinations of tests; and cost-effectiveness. The content of the chapter is presented here to promote international discussion and collaboration by making the principles and standards recommended in the new EU Guidelines known to a wider professional and scientific community. Following these recommendations has the potential to enhance the control of colorectal cancer through improvement in the quality and effectiveness of the screening process, including multi-disciplinary diagnosis and management of the disease.

Background

According to the most recent estimates by the International Agency for Research on Cancer [33] colorectal cancer (CRC) is the most common cancer in Europe with 432 000 new cases in men and women reported annually. It is the second most common cause of cancer deaths in Europe with 212 000 deaths reported in 2008. Worldwide CRC ranks third in incidence and fourth in mortality with an estimated 1.2 million cases and 0.6 million deaths annually. The European Union (EU) recommends population-based screening for breast, cervical and colorectal cancer using evidence-based tests with quality assurance of the entire screening process including diagnosis and management of patients with screen-detected lesions [21]. The EU policy takes into account the principles of cancer screening developed by the World Health Organization [137] and the extensive experience in the EU in piloting and implementing population-based cancer screening programmes [131]. Screening is an important tool in cancer control in countries with a significant burden of CRC, provided the screening services are high quality [132]. The presently reported multidisciplinary, evidence-based guidelines for quality

assurance in colorectal cancer screening and diagnosis have been developed by experts and published by the EU [109].

Methods

The methods used are described in detail elsewhere in this supplement [74]. Briefly a multidisciplinary group of authors and editors experienced in programme implementation and quality assurance in colorectal cancer screening and in guideline development collaborated with a literature group consisting of epidemiologists with special expertise in the field of CRC and in performing systematic literature reviews. The literature group systematically retrieved, evaluated and synthesized relevant publications according to defined clinical questions (modified Patient-Intervention-Comparison-Outcome-Study method). Bibliographic searches for most clinical questions were limited to the years 2000 to 2008 and were performed on Medline, and in many cases also on Embase and The Cochrane Library. Additional searches were conducted without date restrictions or starting before 2000 if the authors or editors who were experts in the field knew

Bibliography

DOI <http://dx.doi.org/10.1055/s-0032-1308898>

Endoscopy 2012; 44: SE15–SE30

© Georg Thieme Verlag KG
Stuttgart · New York
ISSN 0013-726X

Corresponding author

I. Lansdorp-Vogelaar

Department of Public Health
Erasmus MC
University Medical Centre
Room AE-32
P.O. Box 2040
3000 CA Rotterdam
The Netherlands
i.vogelaar@erasmusmc.nl
qas@iarc.fr

that there were relevant articles published before 2000. Articles of adequate quality recommended by authors because of their clinical relevance were also included.

Only scientific publications in English, Italian, French and Spanish were included. Priority was given to recently published, systematic reviews or clinical guidelines. If systematic reviews of high methodological quality were retrieved, the search for primary studies was limited to those published after the last search date of the most recently published systematic review, i.e. if the systematic review had searched primary studies until February 2006, primary studies published after February 2006 were sought. If no systematic reviews were found, a search for primary studies published since 2000 was performed.

In selected cases references not identified by the above process were included in the evidence base, i.e. when authors of the chapters found relevant articles published after 2008 during the period when chapter manuscripts were drafted and revised prior to publication. The criteria for relevance were: articles concerning new and emerging technologies where the research grows rapidly, high-quality and updated systematic reviews, and large trials giving high contribution to the robustness of the results or allowing upgrading of the level of evidence.

The methodological quality of the retrieved publications was assessed using the criteria obtained from published and validated check lists. Evidence tables were prepared for the selected studies. The evidence tables, clinical questions and bibliographic literature searches are documented elsewhere [73].

In the full guidelines document [109] over 250 recommendations were formulated according to the level of the evidence and the strength of the recommendation using the following grading scales.

Level of evidence:

- I** multiple randomised controlled trials (RCTs) of reasonable sample size, or systematic reviews (SRs) of RCTs
- II** one RCT of reasonable sample size, or 3 or less RCTs with small sample size
- III** prospective or retrospective cohort studies or SRs of cohort studies; diagnostic cross sectional accuracy studies
- IV** retrospective case-control studies or SRs of case-control studies, time-series analyses
- V** case series; before/after studies without control group, cross sectional surveys
- VI** expert opinion

Strength of recommendation:

- A** intervention strongly recommended for all patients or targeted individuals
- B** intervention recommended
- C** intervention to be considered but with uncertainty about its impact
- D** intervention not recommended
- E** intervention strongly not recommended

Some statements of advisory character considered to be good practice but not sufficiently important to warrant formal grading were included in the text.

Results



Several guiding principles and 17 graded recommendations are provided in Chapter 1.

Guiding principles

1. The aim of screening as a tool for cancer control is to lower the burden of cancer in the population by discovering latent disease in its early stages and treating it more effectively than if diagnosed later when symptoms have appeared.
2. As such, screening is a commendable method to reduce the burden of disease. However, population screening targets a predominantly healthy population, and should therefore only be conducted after a careful consideration of both harms and benefits.
3. In 1968 the World Health Organisation (WHO) defined the first set of principles for population screening [137]. These principles are still valid today. Together with the substantial experience in implementation of population-based screening programmes in the EU, they have been taken into account in the Council Recommendation on Cancer Screening of 2 December 2003 [21].
4. The Council Recommendation spells out fundamental principles of best practice in early detection of cancer and invites EU Member States to take common action to implement cancer screening programmes with an organised, population-based approach and with appropriate quality assurance at all levels, taking into account European quality assurance guidelines for cancer screening, where they exist.
5. The Council Recommendation calls for introduction of new cancer screening tests in routine healthcare only after they have been evaluated for efficacy in randomised controlled trials (RCTs) and after other relevant aspects such as cost-effectiveness in the different healthcare systems have been taken into account. Only the FOBT for men and women aged 50–74 years has been recommended for CRC screening by the EU to date.
6. Any screening policy for colorectal cancer should also take into account the available evidence and the numerous other principles and standards of best practice laid down in the Council Recommendation.
7. The overwhelming majority of colorectal cancer screening examinations performed in the EU use the primary screening test recommended by the Council of the European Union; the Faecal Occult Blood Test (FOBT). The purpose of the European Guidelines for Quality Assurance in Colorectal Cancer Screening is not to provide recommendations on which other modalities might now be suitable for CRC screening in the EU. Instead, the new European Guidelines provide guiding principles and evidence-based recommendations on the quality assurance which should be followed when implementing CRC screening using the various modalities currently adopted in publically mandated programmes in the EU Member States.

Recommendations and conclusions¹

Guaic FOBT

- 1.1 There is good evidence that invitation to screening with FOBT using the guaiac test reduces mortality from colorectal cancer (CRC) by approximately 15% in average-risk populations of appropriate age (**I**).^{Sect 1.2.1.1}
- 1.2 RCTs have only investigated annual and biennial screening with guaiac FOBT (gFOBT) (**II**). To ensure effectiveness of gFOBT screening, the screening interval in a national screening programme should not exceed two years (**II–B**).^{Sect 1.2.1.2}
- 1.3 Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years (**IV**). The age range for a national screening programme should at least include 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. From there the age range could be expanded to include younger and older individuals, taking into account the balance between risk and benefit and the available resources (**VI–B**).^{Sect 1.2.1.3}

Immunochemical FOBT

- 1.4 There is reasonable evidence from an RCT (**II**) that iFOBT screening reduces rectal cancer mortality, and from case control studies (**IV**) that it reduces overall CRC mortality.^{Sect 1.2.2.1} Additional evidence indicates that iFOBT is superior to gFOBT with respect to detection rate and positive predictive value for adenomas and cancer (see also Ch. 4 [41], Rec. 4.2) (**III**).^{Sect 1.2.2.1; 4.2.5; 4.3; 4.4.2}
- 1.5 Given the lack of additional evidence, the interval for iFOBT screening can best be set at that of gFOBT, and should not exceed three years (**VI–C**).^{Sect 1.2.2.2}
- 1.6 In the absence of additional evidence, the age range for a screening programme with iFOBT can be based on the limited evidence for the optimal age range in gFOBT trials (see Rec. 1.3) (**VI–C**).^{Sect 1.2.2.3; 1.2.1.3}

Sigmoidoscopy

- 1.7 There is reasonable evidence from one large RCT that flexible sigmoidoscopy (FS) screening reduces CRC incidence and mortality if performed in an organised screening programme with careful monitoring of the quality and systematic evaluation of the outcomes, adverse effects and costs (**II**).^{Sect 1.3.1.1}
- 1.8 The available evidence suggests that the optimal interval for FS screening should not be less than 10 years and may even be extended to 20 years (see Rec. 1.11) (**IV–C**).^{Sect 1.3.1.2; 1.3.2.2}
- 1.9 There is limited evidence suggesting that the best age range for FS screening should be between 55 and 64 years (**III–C**). After age 74, average-risk FS screening should be discontinued, given the increasing co-morbidity in this age range (**V–D**).^{Sect 1.3.1.3}

¹ **Sect** (superscript) after each recommendation in the list refers the reader to the section/s of the Guidelines dealing with the respective recommendation.*

Rec (superscript) throughout the chapter refers to the number of the recommendation dealt with in the preceding text.*

* The first digit of the section numbers and recommendation numbers refers to the respective chapter in the guidelines. For Chapters 2 to 10 see: [70, 76, 41, 126, 121, 93, 120, 7, 9] respectively.

Colonoscopy

- 1.10 Limited evidence exists on the efficacy of colonoscopy screening in reducing CRC incidence and mortality (**III**). However, recent studies suggest that colonoscopy screening might not be as effective in the right colon as in other segments of the colorectum (**IV**).^{Sect 1.3.2.1}
- 1.11 Limited available evidence suggests that the optimal interval for colonoscopy screening should not be less than 10 years and may even extend up to 20 years (**III–C**).^{Sect 1.3.2.2}
- 1.12 Indirect evidence suggests that the prevalence of neoplastic lesions in the population below 50 years of age is too low to justify colonoscopic screening, while in the elderly population (75 years and above) lack of benefit could be a major issue. The optimal age for a single colonoscopy appears to be around 55 years (**IV–C**). Average risk colonoscopy screening should not be performed before age 50 and should be discontinued after age 74 (**V–D**).^{Sect 1.3.2.3}

Combination of FOBT and sigmoidoscopy

- 1.13 The impact on CRC incidence and mortality of combining sigmoidoscopy screening with annual or biennial FOBT has not yet been evaluated in trials. There is currently no evidence for extra benefit from adding a once-only FOBT to sigmoidoscopy screening (**II**).^{Sect 1.4}

New screening technologies under evaluation

- 1.14 There currently is no evidence on the effect of new screening tests under evaluation on CRC incidence and mortality (**VI**). New screening technologies such as CT colonography, stool DNA testing and capsule endoscopy should therefore not be used for screening the average-risk population (**VI–D**).^{Sect 1.5}

Cost-effectiveness

- 1.15 Costs per life-year gained for both FOBT and endoscopy screening strategies are well below the commonly-used threshold of US\$ 50 000 per life-year gained (**III**).^{Sect 1.1.2.4; 1.2.2.4; 1.3.1.4; 1.3.2.4}
- 1.16 There is some evidence that iFOBT is a cost-effective alternative to gFOBT (**IV**).^{Sect 1.2.2.4}
- 1.17 Available studies differ with respect to what screening strategies are most cost-effective. No recommendation of one screening strategy over the others can be made based on the available evidence of cost-effectiveness (**III–D**).^{Sect 1.2.1.4}

1.1 Population perspective



1.1.1 Colorectal cancer in Europe

Colorectal cancer (CRC) is an important health problem in Europe. Each year approximately 432 000 people are newly diagnosed with CRC [33]. About half of these patients die of the disease making CRC the second leading cause of cancer deaths in Europe.

CRC mortality varies among the 27 EU Member States, with Hungary having the highest mortality rates and Cyprus having the lowest (● **Table 1.1**). At least part of the differences in CRC mortality can be explained by differences in lifestyle, screening practices and treatment between countries [132].

1.1.2 Population screening for colorectal cancer

CRC is particularly suitable for screening. The disease is believed to develop in a vast majority of cases from non-malignant precursor lesions called adenomas, according to the adenoma-carcinoma sequence (● Fig. 1.1) [75, 79]. Adenomas can occur anywhere in the colorectum after a series of mutations that cause neoplasia of the epithelium. Adenomas are most often polypoid, but can also be sessile or flat [48]. An adenoma grows in size and can develop high-grade neoplasia. At a certain point in time, the adenoma can invade the submucosa and become malignant. Initially, this malignant cancer is not diagnosed and does not give symptoms yet (preclinical). It can progress from localised (stage I) to metastasised (stage IV) cancer, until it causes symptoms and is diagnosed. In developed countries, approximately 40–50% of the population develop one or more adenomas in a lifetime [48], but the majority of these adenomas will never develop into CRC. Only 5–6% of the population actually develop CRC [54]. The average duration of the development of an adenoma to CRC is unobserved, but is estimated to take at least 10 years [138]. This long latent phase provides an excellent window of opportunity for early detection of the disease.

When detected in the adenoma-phase, removal of the adenoma can prevent the incidence of CRC [139]. But even when detected as an early-stage cancer, prognosis is considerably better than for late-stage cancer [18] as can be seen in ● Fig. 1.2. Several screening tests for CRC are available, including guaiac and immunochemical faecal occult blood tests (FOBT), sigmoidoscopy, colonoscopy, CT colonography (CTC), stool DNA testing and capsule endoscopy.

1.1.3 Principles of population screening

The aim of population screening is to discover latent disease in the population in order to detect a disease in its early stages and enable it to be treated adequately before it poses a threat to the individual and/or the community [137]. As such, screening is a commendable method to reduce the burden of disease. However, population screening targets an (apparently) healthy population, and should therefore only be conducted after a careful consideration of both harms and benefits.

In 1968, the World Health Organisation (WHO) defined the first set of principles for population screening [137]. These were:

1. The condition sought should be an important health problem for the individual and community.
2. There should be an accepted treatment or useful intervention for patients with the disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognisable latent or early symptomatic stage.
5. There should be a suitable screening test or examination.
6. The test should be acceptable for the population.
7. The natural history of the disease should be adequately understood.
8. There should be an agreed policy for referring for further examination and whom to treat as patients.
9. The cost should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case finding should be a continuing process and not a once only project.

These principles were later extended and further elaborated for the implementation of the national screening programmes in the Netherlands [42]:

Table 1.1 Age-standardised (Europe) incidence and mortality rates for colorectal cancer by country and gender, rate per 100 000 in 2008 (data source: [32]).

Country/Region	Females		Males	
	Incidence	Mortality	Incidence	Mortality
Austria	33.4	14.0	55.5	24.4
Belgium	42.3	15.5	66.3	22.7
Bulgaria	34.4	14.6	53.2	26.5
Cyprus	23.4	9.3	34.3	12.4
Czech Republic	44.3	19.1	91.2	40.3
Denmark	52.6	22.7	68.4	29.8
Estonia	32.8	16.7	47.7	29.0
Finland	29.1	11.0	41.4	16.8
France	36.4	14.0	54.8	23.0
Germany	41.5	15.4	68.5	25.0
Greece	17.1	10.1	24.7	14.6
Hungary	43.8	25.2	93.8	53.3
Ireland	42.9	15.4	66.9	27.9
Italy	43.7	14.3	68.3	23.6
Latvia	28.8	18.3	45.5	29.2
Lithuania	29.3	16.7	49.9	29.1
Luxembourg	38.1	13.2	63.8	22.1
Malta	29.9	18.0	47.9	25.8
Netherlands	25.7	15.7	49.3	29.8
Poland	34.4	16.6	61.6	30.6
Portugal	27.9	14.7	41.2	25.2
Romania	43.9	20.2	88.6	46.9
Slovakia	37.4	18.9	74.6	37.4
Slovenia	34.1	15.0	60.4	28.6
Spain	38.4	15.4	47.8	20.6
Sweden	46.2	18.5	65.1	26.0
United Kingdom	35.4	14.4	54.9	21.9

1. Treatment started at an early stage should be of more benefit than treatment started later.
2. The time between test and result and between result and treatment must be as short as possible.
3. The recruitment procedure should not limit people in their freedom to participate or not in the screening programme.
4. Potential participants should receive adequate information about pros and cons of participation.
5. Benefits and risks should also be well known to healthcare providers.
6. Public education should promote a broad accessibility of the programme. It should however not include a moral pressure effect.
7. There should be quality assurance (QA) and quality control (QC) procedures for the whole screening programme.
8. Screening programmes are concerted actions meeting organisational and managerial requirements.

The above principles have been taken into account in the current EU policy on cancer screening which is laid down in the Council Recommendation on Cancer Screening of 2 December 2003 [21]. They show that evaluation of efficacy is a necessary condition for adopting population screening but not sufficient by itself. Many other aspects such as side effects, costs and infrastructure should also be considered. Population screening is a process that starts with educating the population about the (screening of the) disease and ends with the follow-up and treatment of patients with abnormal test results (see Sect. 1.1.4). Quality assurance and control forms a crucial aspect of this process (see Chapter 2 [70]). This introductory chapter presents the evidence which

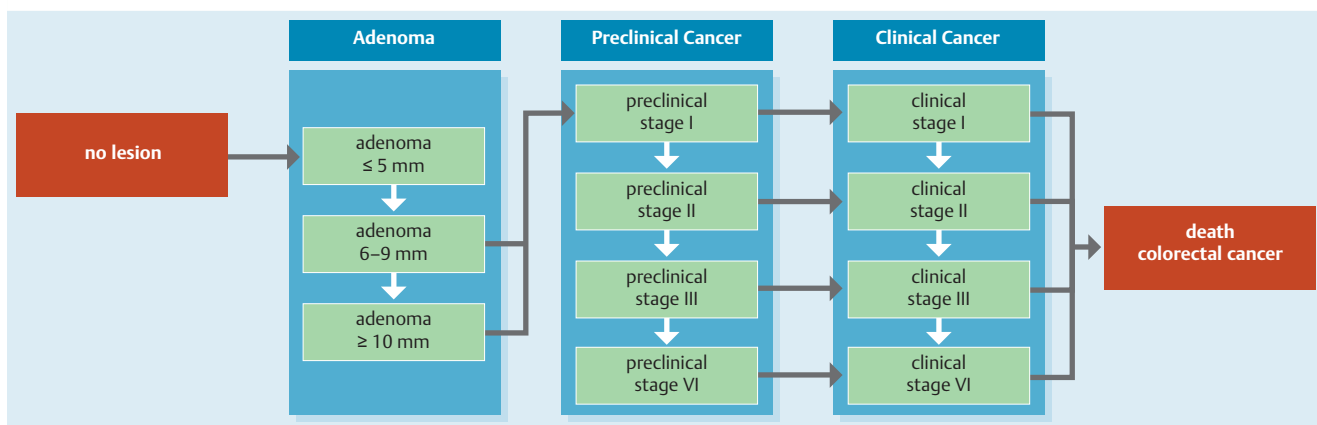


Fig. 1.1 Schematic overview of the adenoma-carcinoma sequence.

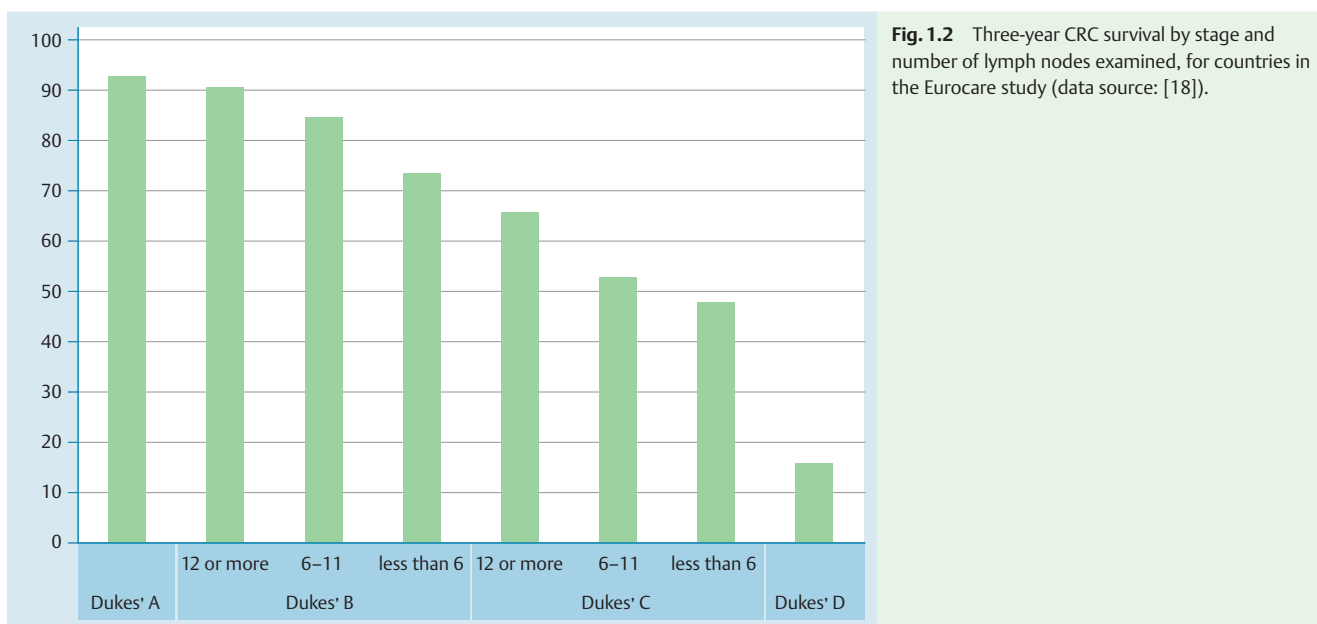


Fig. 1.2 Three-year CRC survival by stage and number of lymph nodes examined, for countries in the Eurocare study (data source: [18]).

confirms that CRC screening fulfils the above criteria established by the WHO. The subsequent chapters provide comprehensive recommendations and additional applicable evidence essential to ensuring that screening programmes also fulfil the principles of best practice and quality assurance mentioned above and elucidated in the Council Recommendation on Cancer Screening (see Sect. 1.1.4).

The European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis have been developed to inform European policymakers and public health specialists, and particularly also professionals, programme managers and any other staff involved in the provision of screening services, as well as advocates, individuals in the populations invited to attend screening, and any other interested people, about the essential issues, guiding principles, standards and procedures of quality assurance and best practice that should be taken into account in running and establishing colorectal cancer screening programmes in the EU Member States. We would like to stress that these guidelines are specifically developed for screening the average-risk population for CRC. High-risk individuals should be referred for high-risk protocols if available.

1.1.4 EU policy on cancer screening

A large body of knowledge on implementation of cancer screening programmes has been acquired through the screening networks established by the European Union in the Europe Against Cancer programme which have been consolidated under the subsequent EU Health programmes in the European Cancer Network. The EU networks have shown that overall screening outcome and quality depend on the performance at each step in the screening process. To achieve the potential benefit of cancer screening, quality must therefore be optimal at every step in the process, that includes information, identification and personal invitation of the target population; performance of the screening test; and, if necessary, diagnostic work-up of screen-detected lesions, treatment, surveillance and subsequent care. Screening is performed on predominantly healthy people; comprehensive quality assurance is also required to maintain an appropriate balance between benefit and harm in the large numbers of people eligible to attend cancer screening programmes. Achieving and maintaining high quality at every step in the screening process requires an integrated, population-based approach to health service delivery. This approach is essential in order to make screening accessible to those in the population who may benefit and in

order to adequately monitor, evaluate and continuously improve performance [4, 5, 25, 84–86, 130, 131].

Implementation of organised programmes is recommended because they include an administrative structure responsible for service delivery, quality assurance and evaluation. Population-based programmes generally require a high degree of organisation in order to identify and personally invite each person in the eligible target population. Personal invitation aims to give each eligible person an equal chance of benefiting from screening and to thereby reduce health inequalities. As with evidence-based screening for breast or cervical cancer, the population-based approach to programme implementation is also recommended for CRC screening because it provides an organisational framework conducive to effective management and continuous improvement of the screening process, such as through linkage with population and cancer registries for optimisation of invitation to screening and for evaluation of screening performance and impact. Nationwide implementation of population based screening programmes makes services performing to the high standards available to the entire population eligible to attend screening. Large numbers of professionals undertake further specialisation in order to meet the screening standards. Consequently, these nationwide efforts also contribute to widespread improvement in diagnosis and management of symptomatic disease [132].

On 2 December 2003, the Health Ministers of the European Union unanimously adopted a recommendation on cancer screening based on the developments and experience in the Europe Against Cancer programme [21]. The Recommendation of the Council of the European Union spells out fundamental principles of best practice in early detection of cancer and invites EU Member States to take common action to implement national cancer screening programmes with an organised, population-based approach and with appropriate quality assurance at all levels, taking into account European quality assurance guidelines for cancer screening, where they exist [131].

The adoption and subsequent implementation of the Council Recommendation on Cancer Screening has been repeatedly supported by vigorous initiatives of the European Parliament documented in parliamentary resolutions [28–30]. Continued, concerted efforts to implement the Council Recommendation including efforts to continuously update the European screening quality assurance guidelines have also been recommended by the Council at the conclusion of the Slovenian EU Presidency and more recently [22, 23]. These efforts, have also contributed to the adoption of the new European Partnership for Action Against Cancer which includes activities dedicated to improving implementation of the Council Recommendation [20].

The Council Recommendation and the EU guidelines also emphasise the need for effective communication in order to reach groups commonly found to have limited access to screening, such as less advantaged socioeconomic groups. This, in turn, should permit an informed decision about participation, based on objective, balanced information about the risks and benefits of screening [36, 37, 42, 130, 132] (see also Chapter 10 [9]).

In addition to the above-mentioned fundamental principles of quality assurance in implementation of cancer screening programmes, the Council Recommendation and the European quality assurance guidelines deal with other essential elements such as registration, monitoring and training. Of particular relevance to the new European Guidelines dealing with quality assurance in colorectal cancer screening are the recommended evidence-

based test for CRC and the recommended approach to introduction of novel screening tests.

The EU recommends implementation of new cancer screening tests in routine healthcare only after efficacy has been conclusively demonstrated in randomised controlled trials (RCTs) and other relevant aspects have been taken into account such as cost-effectiveness in the different healthcare systems of the Member States (items 6(a) to (d) in Council Recommendation [21]). Potentially promising new modifications of established screening tests may also be considered for introduction into routine healthcare once the effectiveness of the modification has been demonstrated, possibly using other epidemiologically validated surrogate endpoints (item 6 (e) in Council Recommendation [21]).

Only the FOBT for men and women aged 50–74 years has been recommended to date by the EU for CRC screening.² Any change in the recommended screening policy for predominantly healthy individuals should be prepared with the utmost rigour and should be based on an evidence base appropriate to the potential impact of the decision; it should also take into account the numerous other principles and standards of best practice laid down in the Council Recommendation.

The overwhelming majority of colorectal cancer screening examinations performed in the EU use the primary screening test recommended by the Council of the European Union (FOBT). The purpose of the European Guidelines for Quality Assurance in Colorectal Cancer Screening is not to provide recommendations on which other modalities might now be suitable for CRC screening in the EU. Instead, the new European Guidelines provide guiding principles and evidence-based recommendations on the quality assurance that should be followed when implementing CRC screening using the various modalities currently adopted in publically mandated programmes in the Member States.

1.1.5 Implementation of colorectal cancer screening in Europe

Because CRC risk varies across Europe, the benefit of screening will also vary. With a high-quality screening programme and sufficient participation, the percent mortality reduction is generally expected to be similar in all countries. However, the absolute number of CRC deaths prevented depends on the background risk of CRC mortality. Therefore each country should prioritise the benefit of CRC screening against the benefit of alternative programmes. Nevertheless, the levels of CRC incidence throughout Europe indicate that the potential benefit of CRC screening is significant in all European countries.

By the end of 2007, several EU Member States were in the process of implementing a national population screening programme [19, 131]. Population-based programmes were being rolled out nationwide in five countries (Finland, France, Italy, Poland and the United Kingdom). Furthermore, seven countries had established nationwide non-population-based programmes (Austria, Bulgaria, Czech Republic, Germany, Greece, Latvia and the Slovak Republic). Another five countries were planning or piloting a nation-wide population-based programme (Hungary, Cyprus, Por-

² Other evidence-based screening tests currently recommended by the Council of the European Union: pap smear screening (cervical cytology) for cervical cancer precursors starting not before the age of 20 and not later than the age of 30 years in accordance with European guidelines for quality assurance in cervical cancer screening (Council Recommendation 1(b)); mammography screening for breast cancer in women aged 50 to 69 years in accordance with European guidelines for quality assurance in breast cancer screening and diagnosis (Council Recommendation 1(b)).

tugal, Romania and Slovenia). Of these 17 countries, ten had adopted only FOBT, six used both FOBT and endoscopy and one only colonoscopy. In the meantime, 12 Member States have established or upgraded the status of their CRC screening programmes (Czech Republic, Denmark, France, Ireland, Lithuania, the Netherlands, Portugal, Slovak Republic, Slovenia, Spain, Sweden and the United Kingdom).

As mentioned above, the current EU screening policy only recommends faecal occult blood testing for population-based screening [21] (see Section 1.1.4). Currently, the guaiac FOBT is the only test for which extensive evidence of efficacy has been established in more than one RCT [43, 61, 68, 72].

1.2 Evidence for effectiveness of FOBT screening

With FOBT, stool samples are analysed for the presence of occult blood. FOBTs are either guaiac-based (gFOBT) or immunochemical tests (iFOBT). GFOBTs investigate the presence of any blood, whereas iFOBTs are specific for human blood (for more detailed information on test characteristics and clinical performance, see Chapter 4 [41]).

1.2.1 Guaiac FOBT³

1.2.1.1 Evidence for efficacy

Three systematic reviews have evaluated the evidence for the efficacy of gFOBT screening [44, 45, 58]. The reviews all included the RCTs of Minnesota, Nottingham and Funen which compare gFOBT screening with no screening [43, 61, 71]. In addition, the Cochrane review by Hewitson also included the then-unpublished results of the Goteborg study [68], whereas the Heresbach review also included the block-randomised trial from Burgundy [31]. All three reviews found a significant reduction in CRC mortality: the relative risk of dying from CRC in the screening arm compared to the control arm varies from 0.84–0.86, implying a 14–16% reduction in CRC mortality. GFOBT screening was not found to have an effect on overall mortality [45].

In a subgroup analysis, Heresbach showed that CRC mortality reduction was confined to the first 10 years of screening (six rounds) and that CRC mortality was not decreased during the 5–7 years after that, nor in the second phase (8–16 years after the onset of screening) of the Minnesota screening trial [44].

In conclusion, there is good evidence that gFOBT screening reduces CRC mortality by 14%–16% in people of appropriate age invited to attend screening. The observed, modest reduction in CRC mortality has not been shown to impact overall mortality (I).^{Rec 1.1}

1.2.1.2 Evidence for the interval

There are no specific trials investigating the best screening interval for programmes with gFOBT. One RCT conducted in the Minnesota area on healthy volunteers aged 50 to 80 years reported data on annual and biennial screening [71]. After 13 years of follow-up, a statistically significant 33% CRC mortality reduction was reported in the annual screening group compared to the control group. At that time, biennial screening resulted in a non-significant 6% mortality reduction. Two European trials (in England and in Denmark) subsequently showed statistically signifi-

Table 1.2 Age range and mortality reduction in the four randomised controlled trials on FOBT.

Study	Age range	RRR CRC mortality	Years of follow-up
Nottingham	45–75	13% (CI 0.78–0.97)	11 years
Funen	45–74	11% (CI 0.78–1.01)	17 years
Minnesota	50–80	21% (CI 0.62–0.97)	18 years
Goteborg	60–64	16% (CI 0.78–0.90)	15.5 years

RRR: Relative risk reduction.

cant 15% and 18% mortality reductions, respectively, with biennial screening [43, 61]. A second publication of the Minnesota trial provided updated results through 18 years of follow-up and reported a 21% CRC mortality reduction in the biennial screening group, while the reduction in CRC mortality for annual screening remained 33% [72].

In conclusion, both annual and biennial screening with gFOBT have been shown to be effective methods for significantly reducing CRC mortality (I). The results of the Minnesota trial imply that the benefit from annual screening appears to be greater than for biennial screening (II). No clear recommendation regarding the best time interval for offering screening by gFOBT can be drawn. To ensure effectiveness, the screening interval in a national screening programme should not exceed two years (II–B).^{Rec 1.2}

1.2.1.3 Evidence for the age range

There are no specific trials investigating the optimal age range for gFOBT screening. None of the RCTs investigating annual or biennial screening by gFOBT reported a formal subgroup analysis regarding efficacy of screening in different age groups [43, 61, 68, 71]. Data from the Nottingham trial at 11 years of follow up showed no difference in CRC mortality rates between subjects older and younger than 65 years [108].

Circumstantial evidence for the age range comes from the differences in age range of the RCTs. **Table 1.2** gives an overview of the age ranges of the four RCTs of Minnesota, Nottingham, Funen and Goteborg and the observed mortality reductions in these trials [45]. Goteborg investigated the narrowest age range from age 60 to 64, whereas the other trials have included individuals as young as 45 and as old as 80. Considering the limit of this indirect comparison, the table shows that CRC mortality reduction is significant for all age ranges and that the magnitude of the relative risk reduction is similar for all age ranges investigated.

In summary, the best age range for offering gFOBT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years (IV). The age range for a national screening programme should at least include 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. From there the age range could be expanded to include younger and older individuals, taking into account the balance between risk and benefit and the available resources (VI–B).^{Rec 1.3}

1.2.1.4 Evidence on risks vs. benefit and cost-effectiveness

GFOBT screening is a safe screening method with no direct adverse health effects. However, it is associated with false-positive test results, leading to anxiety and unnecessary follow-up colonoscopies. Approximately 1% of screened individuals in the Nottingham and Funen trials had a positive gFOBT and no adenomas or CRC detected at follow-up colonoscopy. In the UK pilot programme of gFOBT screening, a similar false positivity rate was

³ gFOBT is an evidence-based screening test for CRC recommended by the EU. The applicable item in the Council Recommendation of 2 December 2003 is 1(a) (see Sect. 1.1.4 and [21]).

found. Because of rehydration of the gFOBT, the rate of false-positive test results was almost 9% in the Minnesota trial.

Per 10000 follow-up colonoscopies after positive tests, approximately 7 perforations and 9 major bleeds were reported in the RCTs of Nottingham and Minnesota. In the UK pilot programme 5 perforations per 10,000 colonoscopies were reported. For unhydrated gFOBT, this means that there are approximately 16 major complications from unnecessary colonoscopies per 1 million persons screened. For rehydrated gFOBT these values are almost 10 times as high. No colonoscopy-related deaths were reported in any of the RCTs, or in the UK pilot programme.

In a well-organised, high-quality screening programme using unhydrated gFOBT, the risks of adverse effects are limited (**I**).

A systematic review [89] for the United States Preventive Services Task Force (USPSTF) compared the cost-effectiveness of the following CRC screening strategies: FOBT; sigmoidoscopy; the combination of FOBT and sigmoidoscopy; and colonoscopy. The included studies found that the cost-effectiveness of CRC screening with annual or biennial gFOBT varied from US\$ 5691 to US\$ 17805 per life-year gained [89]. The included studies differed with respect to what screening strategies were most cost-effective and the review concluded that no recommendation of one screening strategy over the others could be made based on the available evidence (**III–D**).^{Rec 1.17}

Two studies specifically investigated the cost-effectiveness of gFOBT screening in Europe [63, 136]. The first one estimated the cost-effectiveness of biennial FOBT screening over up to five screening rounds within the Nottingham trial [136]. The cost of screening was US\$ 8300 (£ 5290) per cancer detected (at 2002 prices). Under conservative assumptions, the incremental cost per life year gained as a result of screening was US\$ 2500 (£ 1584). A French cost-effectiveness analysis on a hypothetical cohort of 100 000 asymptomatic individuals aged 50 to 74 years confirmed that biennial FOBT screening for CRC was a cost-effective strategy [63]. Incremental costs per life-year gained of screening over no screening were US\$ 4600 (€ 3375) and US\$ 6400 (€ 4705) with a 20 and 10-year time horizon, respectively.

Costs per life-year gained with gFOBT screening are well below the commonly used cost-effectiveness threshold of US\$ 50 000 per life-year gained (**III**).^{Rec 1.15}

1.2.2 Immunochemical FOBT⁴

1.2.2.1 Evidence for efficacy

To date, there has been one RCT evaluating the efficacy of iFOBT screening. In this study, 94 423 individuals were offered a once-only iFOBT screen. After 8 years, the investigators found a statistically significant 32% reduction in rectal cancer mortality, but no reduction in colonic or overall CRC mortality [144]. There are two caveats concerning this study: Firstly, follow-up of positive iFOBT was performed by flexible sigmoidoscopy, which may explain the lack of effectiveness in the entire colon. Furthermore, randomisation was based on townships and not on individuals.

In addition, three Japanese case-control studies evaluated the efficacy of iFOBT [80, 104, 105]. All three studies found a significant reduction in CRC mortality from iFOBT screening, ranging from 23% to 81%, depending on the study and years since last iFOBT.

⁴ iFOBT is an evidence-based screening test for CRC that fulfils the requirements of the Council Recommendation of 2 December 2003. The applicable items in the Recommendation are 1(a) in combination with 6(e) (see Sect. 1.14 and [21]).

Clinical societies have argued that it might be appropriate to implement a new CRC screening test without an RCT on CRC mortality, if there is convincing evidence that the new test has: (1) at least comparable performance (e.g. sensitivity and specificity) in detecting cancers and adenomas; (2) is equally acceptable to patients and (3) has comparable or lower complication rates and costs [138]. This evidence is available for iFOBT: there have been 13 population-based screening studies comparing performance characteristics of gFOBT and iFOBT [2, 3, 16, 24, 39, 46, 50, 60, 102, 117, 128, 140, 142]. Although the studies used different tests and slightly different protocols, the results of all studies consistently showed that iFOBT has significantly higher sensitivity for advanced adenomas and cancer than the gFOBT (Hemoccult II). For some cut-off levels for referral, iFOBT was also more specific (see also Ch. 4 [41], Sect. 4.2.5 and 4.3.2).

There is reasonable evidence from an RCT (**II**) that iFOBT screening reduces rectal cancer mortality, and from case control studies (**IV**) that it reduces overall CRC mortality. There is additional evidence showing that iFOBT is superior to gFOBT with respect to detection rate and positive predictive value (**III**).^{Rec 1.4}

1.2.2.2 Evidence for the interval

The three case-control studies evaluating the efficacy of iFOBT showed that a reduction in risk of CRC death was only statistically significant for those subjects screened within three years prior to the diagnosis. No reduction in risk was observed after three years.

This circumstantial evidence suggests that the screening interval with iFOBT should not exceed three years (**III**). Due to lack of additional evidence, the interval for iFOBT screening can best be set at that for gFOBT, but should not exceed three years (**VI–C**).^{Rec 1.5}

1.2.2.3 Evidence for the age range

No evidence is available on the best age range for iFOBT screening. Given the similarities between the tests, the age range for a screening programme using iFOBT can best be based on the limited evidence for the optimal age range from gFOBT trials (see Rec. 1.3, Sect. 1.2.1.3) (**VI–C**).^{Rec 1.6}

1.2.2.4 Evidence on risks vs. benefit and cost-effectiveness

As with gFOBT, there are no serious adverse health effects directly attributable to iFOBT screening. Complications in an iFOBT screening programme occur from diagnostic colonoscopies after positive test results. Approximately 2–3% of individuals offered iFOBT screening in the Italian SCORE 2 and 3 trials [110, 112] and in the NORCCAP trial [38] had a positive iFOBT without adenomas or CRC detected at subsequent diagnostic colonoscopy. In the NORCCAP study, six perforations were reported after colonoscopy [38]. However, all of these complications occurred in therapeutic colonoscopies following polypectomy. There were no perforations in purely diagnostic colonoscopies without adenomas or cancer detected. In addition, there were four major bleeds and one burnt serosa syndrome. The total complication rate with colonoscopy was 4 per 1000 colonoscopies [38].

In a well-organised high-quality iFOBT screening programme, the risks of adverse effects are limited (**III**).

There were no studies specifically addressing the cost-effectiveness of iFOBT, but three studies that compared the cost-effectiveness of iFOBT to that of gFOBT [11, 64, 83]. Two studies concluded that iFOBT screening was at least as effective as gFOBT screening, but less costly [64, 83]. In the third analysis, the use of iFOBT for 20 years of biennial screening cost € 59 more than gFOBT per tar-

Outcome	Telemark, Norway	NORCCAP, Norway	UK FS trial, UK
Intention-to-treat analysis			
CRC incidence	80% reduction ¹	No difference	23% reduction ¹
CRC mortality	50% reduction	27% reduction	31% reduction ¹
Overall mortality	57% increase ¹	No difference	No difference
Per-protocol analysis			
CRC incidence	–	–	33% reduction ¹
CRC mortality	–	59% reduction ¹	43% reduction ¹

¹ significant; – not reported.

Table 1.3 CRC incidence and mortality reduction from three randomised controlled trials on sigmoidoscopy screening.

get individual, and led to a mean increase in individual life expectancy of 0.0198 years, which corresponds to an incremental cost-effectiveness ratio of US\$ 4100 (€ 2980) per years of life saved.

In conclusion, iFOBT seems to be a cost-effective alternative to gFOBT, either dominating gFOBT or providing incremental benefit at costs per life-year gained well below the commonly used threshold of US\$ 50 000 per life-year gained (III).^{Rec 1.15; 1.16}

1.3 Evidence for effectiveness of endoscopy screening

With endoscopy screening, a flexible tube is inserted into the anus to inspect the colorectum. With this procedure, the physician can detect abnormalities and remove them in one procedure. The two main endoscopy procedures are flexible sigmoidoscopy and colonoscopy. With sigmoidoscopy only approximately one-half of the colorectum can be inspected, whereas colonoscopy generally visualises the complete colorectum.

1.3.1 Sigmoidoscopy⁵

1.3.1.1 Evidence for efficacy

For sigmoidoscopy screening, evidence on the efficacy is available from three RCTs: the Telemark and NORCCAP studies in Norway and the large UK study in which 57 237 individuals were randomised to the screening group for once-only sigmoidoscopy alone (● Table 1.3). The UK study was the only study to find a significant 31% reduction in CRC mortality from sigmoidoscopy in an intention-to-treat analysis [8]. However, the Norwegian trials had considerably smaller sample sizes (13 823 individuals in the screening group in the NORCCAP study, and only 400 in the Telemark study); the NORCCAP study also had a shorter follow-up. Therefore these studies may have been underpowered [47, 123]. In per-protocol analyses, the NORCCAP study did find a significant reduction in CRC mortality. Both the Telemark and UK study found a significant reduction in CRC incidence. The disturbing finding in the very small Telemark study that sigmoidoscopy screening might increase overall mortality in the screening group was not corroborated by either the NORCCAP or UK study. The UK trial used a two-step invitation process in which only people who actively expressed their interest in being randomised were enrolled. Although CRC incidence in the trial control group was similar to what is expected in the general population, the results cannot be directly extrapolated to the general population. Future results from 2 other large RCTs in Italy and the US will be used to assess the findings of these trials [91, 111].

In addition, three case-control studies of good methodological quality have been published. In these studies, sigmoidoscopy was compared with no screening [78,81,113] while adjusting for the main confounding factors (family history of CRC, FAP, polyposis, ulcerative colitis and number of periodic health examinations). All three studies found a significant reduction in CRC mortality and two of them also in CRC incidence. Finally, a prospective cohort study including 24 744 asymptomatic men aged 40–75 years at average risk of CRC, showed a significant 42% reduction in overall CRC incidence and 56% in distal cancer incidence from screening endoscopy after 8 years of follow-up. The study did not find a significant difference in proximal cancer incidence or overall CRC mortality [57].

In conclusion, there is reasonable evidence that flexible sigmoidoscopy screening reduces CRC incidence and mortality, if performed in an organised screening programme with careful monitoring of the quality and systematic evaluation of the outcomes, adverse effects and costs (II).^{Rec 1.7}

1.3.1.2 Evidence for the interval

There are no studies directly assessing the optimal interval for sigmoidoscopy screening. Two studies have evaluated the detection rate of adenomas and cancer three and five years, respectively, after a negative sigmoidoscopy [90,106]. Both studies found a significantly lower detection rate at the second screening than at initial screening. The rates were 65–75% lower three years after a negative examination, [106] and 50% lower 5 years after a negative examination [90]. Nevertheless, the authors of the two studies arrived at different conclusions: Platell suggested that rescreening the average-risk population with flexible sigmoidoscopy at intervals longer than 5 years could be considered, whereas Schoen concluded that although the overall percentage of detected abnormalities is modest, the data raise concern about the impact of a screen interval longer than 3 years after a negative examination. The UK flexible sigmoidoscopy screening study showed that there was little attenuation of the protective effect of sigmoidoscopy after 11 years of follow-up [8], suggesting that the interval for rescreening should not be less than 10 years. This is in line with the evidence for colonoscopy screening (see Sect. 1.3.2.2).

In conclusion, the optimal interval for sigmoidoscopy screening was only assessed in two indirect studies that only considered intervals of three and five years. The UK flexible sigmoidoscopy study and evidence for colonoscopy screening seems to indicate that the optimal interval for endoscopy screening should not be less than 10 years and may even be extended to 20 years (see Sect. 1.3.2.2)

⁵ Flexible sigmoidoscopy is not a screening test for CRC recommended by the EU. The applicable items in the Council Recommendation of 2 December 2003 are 6(a) to 6(d) (see Sect. 1.14 and [21]).

Table 1.4 Major and minor complication rates in population-based sigmoidoscopy screening.

	SCORE [111]	SCORE 2 [110]	UK FS trial [125]	NORCCAP [38]
Sigmoidoscopy				
Severe complications	0.02%	0.02%	0.03%	0%
Minor complications	0.6%	0.5%	0.2%	0.2%
FU colonoscopy				
Severe complications	0.3%	0.3%	0.5%	0.4%
Minor complications	3.9%	3.9%	0.4%	1.6%

1.3.1.3 Evidence for the age range

Evidence on the age-specific prevalence of colorectal adenomas suggests that the best age range for flexible sigmoidoscopy screening is between 55 and 64 [112]. A significant reduction in incidence and mortality of CRC has recently been shown in this age range in a large RCT using flexible sigmoidoscopy performed once in a lifetime as the primary screening test [8].

There has been one cross-sectional study comparing safety, tolerability, completion, and endoscopic findings of sigmoidoscopy between individuals 50–74 years old and individuals 75 years and older [82]. The study demonstrated that elderly subjects ≥ 75 years old have an increased rate of endoscopist-reported difficulties and a higher rate of incomplete examinations compared to subjects aged 50–74 years. Complication rate and detection rate of adenomas and advanced adenomas were similar in both cohorts, while an increased detection of carcinomas in the elderly was observed.

In conclusion, there is limited evidence suggesting that the best age range for flexible sigmoidoscopy screening should be between 55 and 64 years (III–C). One study suggests that for screening in the elderly population (75 years and older) tolerability is an issue (V). Average-risk sigmoidoscopy screening should be discontinued after age 74, given the increasing co-morbidity in this age range (V–D).^{Rec 1.9}

1.3.1.4 Evidence on risks vs. benefit and cost-effectiveness

Four population-based screening trials reported on complication rates with flexible sigmoidoscopy (► Table 1.4). Severe complication rates from sigmoidoscopy varied from 0% to 0.03%. Minor complications occurred in 0.2–0.6% of sigmoidoscopies. Severe complication rates with follow-up colonoscopy were about 10 times as high as with sigmoidoscopy (0.3–0.5%). Minor complications occurred in 1.6–3.9% of follow-up colonoscopies.

In a well-organised high-quality flexible sigmoidoscopy screening programme the risk of severe complications is about 0–0.03% for sigmoidoscopies and 0.3–0.5% for follow-up colonoscopies (III). Six studies in the USPSTF review estimated the cost-effectiveness of sigmoidoscopy screening, [89]. One study showed that with favourable conditions sigmoidoscopy screening could be cost-saving. In the other studies the cost-effectiveness ratio varied from US\$ 12 477 to US\$ 39 359 per life-year gained. More recent cost-effectiveness analyses found similar ratios (US\$ 7407–US\$ 23 830) [87, 118, 129]. A recent study based in England also estimated that sigmoidoscopy screening could be cost-saving [122]. All cost-effectiveness analyses show that the cost-effectiveness of sigmoidoscopy screening is below the commonly used threshold of US\$ 50 000 per life-year gained. Some studies suggest that sigmoidoscopy screening could even be cost-saving (III).^{Rec 1.15}

1.3.2 Colonoscopy⁶

1.3.2.1 Evidence for efficacy

Until recently, there has been no RCT investigating the efficacy of colonoscopy screening; a large multicentre trial is currently underway in Norway, Poland, the Netherlands, Iceland, Sweden and Latvia comparing the efficacy of a once-only colonoscopy to no screening. Systematic reviews evaluating the efficacy of colonoscopy screening [88, 134] include one prospective observational study comparing CRC incidence in a population that underwent colonoscopy and removal of detected lesions with the incidence of three reference populations [139]. Incidence in the cohort under investigation was 76% to 90% lower than that of the reference populations. These results should be interpreted with caution because the study used historical controls that were not from the same underlying population. Recently, a second prospective observational study showed a 65% lower CRC mortality and 67% lower CRC incidence in individuals with a screening colonoscopy compared to the general population [56]. Two recent case–control studies also found a significant reduction of 31% in CRC mortality [10] and 48% in advanced neoplasia detection rates [15]. However, the reduction in these studies was limited to the rectum and left side of the colon. No significant reduction was found in right-sided disease.

Cross-sectional surveys have shown that colonoscopy is more sensitive than sigmoidoscopy in detecting adenomas and cancers and that this increased sensitivity could translate into increased effectiveness [134].

In conclusion, limited evidence exists on the efficacy of colonoscopy screening on CRC incidence and mortality (III). However, recent studies suggest that colonoscopy might not be as effective in the right colon as in other segments of the colorectum (IV).^{Rec 1.10} Results of at least one large RCT would permit more definitive conclusions about the efficacy of colonoscopy as a primary screening test.

1.3.2.2 Evidence for the interval

The optimal interval for colonoscopy screening has been assessed in a cohort study and a case-control study. The cohort study found that CRC incidence in a population with negative colonoscopy was 31% lower than general population rates and remained reduced beyond 10 years after the negative colonoscopy [116]. Similar results were obtained in the case–control study [14]: after adjustment for potential confounding variables, a previous negative colonoscopy was associated with a 74% lower risk of CRC. This risk reduction persisted up to 20 years. Several prospective studies found a risk of adenoma 5 years after a negative colonoscopy ranging from 2.1% to 2.7% and a risk of advanced adenoma or cancer ranging from 0.0% to 2.4% [26, 49, 67, 99, 141].

Evidence for the timing of colonoscopy intervals is limited. A cohort and case-control study suggest that screening colonoscopies do not need to be performed at intervals shorter than 10 years and that this time interval may even be extended to 20 years (III–C).^{Rec 1.11}

1.3.2.3 Evidence for the age range

Evidence on the age-specific prevalence of colorectal adenomas suggests that the best age range for colonoscopy screening is be-

⁶ Colonoscopy is not a screening test for CRC recommended by the EU. The applicable items in the Council Recommendation of 2 December 2003 are 6(a) to 6(d) (see Sect. 1.14 and [21]).

	Lieberman et al. 2000 [66]	Regula et al. 2006 [97]	Schoenfeld et al. 2005 [107]	Rainis et al. 2007 [94]	Kim et al. 2007 [59]
Severe complications	0.3 %	0.1 %	0 %	0.08 %	0 %

Table 1.5 Complication rates with screening colonoscopies.

tween 55 and 64 [112]. However, no studies have been published which directly investigated the optimal age range for colonoscopy screening. Two cross-sectional studies compared detection rates in a cohort of 40–49-year-olds with those in older cohorts [52, 103]. Although an increase in the prevalence of neoplasms in the 50–59 years age group compared with the 40–49 years age group was observed in the first study, this difference was not statistically significant [103]. The prevalence of CRC in the second study was significantly lower in the 40–49-year-old cohort than in the cohort older than 49 years ($p=0.03$) [52]. A German case-control analysis assessed the possible impact of colonoscopic screening history in different age groups [13]. For all screening schemes except those with a single endoscopy around age 50 or 70, strong, highly significant risk reductions between 70% and 80 % were estimated. The optimal age for a single screening endoscopy appeared to be around 55 years. The previously reported cross-sectional study on safety, tolerability, completion, and endoscopic findings of sigmoidoscopy screening (see Sect. 1.3.1.3) suggests that tolerability is also an issue in colonoscopy screening in individuals over 74 years of age [82].

There is no direct evidence confirming the optimal age range for colonoscopy screening. Indirect evidence suggests that the prevalence of neoplastic lesions in the younger population (less than 50 years) is too low to justify colonoscopic screening, while in the elderly population (≥ 75 years) lack of benefit could be a major issue. The optimal age for a single colonoscopy appears to be around 55 years (**IV–C**). Average-risk colonoscopy screening should not be performed before age 50 and should be discontinued after age 74 (**V–D**).^{Rec 1.12}

1.3.2.4 Evidence on risks vs. benefit and cost-effectiveness

Major complication rates with screening colonoscopy were obtained from five population-based studies and varied from 0–0.3% (Table 1.5) [59, 66, 94, 97, 107]. None of the studies reported minor complications. Complication rates with screening colonoscopies are considerably higher than for sigmoidoscopy, but slightly lower than for follow-up colonoscopies after a positive FOBT or sigmoidoscopy. The balance between benefit and harm for people attending screening colonoscopy may still be less favourable than for people attending FOBT screening, because relatively few people in the FOBT target population are exposed to the potential harm of follow-up colonoscopy.

In a well-organised high-quality colonoscopy screening programme, major complications occur in 0–0.3% of colonoscopies (**IV**).

Six studies in the USPSTF review estimated the cost-effectiveness of colonoscopy screening. The cost-effectiveness of colonoscopy screening varied in these studies from US\$ 9038 to US\$ 22012 per life-year gained. Recent studies found similar ratios (US\$ 8090–US\$ 20172) [62, 87, 118, 129]. One recent study in Germany estimated that a once-only colonoscopy screening could be cost-saving compared to no screening [114].

All cost-effectiveness analyses show that the cost-effectiveness of colonoscopy screening is below the commonly used threshold of US\$ 50000 per life-year gained (**III**).^{Rec 1.15}

1.4 Evidence for effectiveness of FOBT and sigmoidoscopy combined⁷

No trials have assessed the impact of combining sigmoidoscopy screening with annual or biennial FOBT on CRC incidence or mortality. One trial comparing a combination of flexible sigmoidoscopy and once-only FOBT with sigmoidoscopy alone did not find a lower post-screening CRC incidence in the group with the combination strategy than in the group with sigmoidoscopy alone [47].

A few studies reported diagnostic yield with a combination of once-only sigmoidoscopy and once-only FOBT, compared to FOBT and/or sigmoidoscopy alone [38, 65, 95, 96, 110]. The yield of the combination of once-only sigmoidoscopy with once-only FOBT was significantly higher than that of once-only FOBT alone, but not higher than that of once-only sigmoidoscopy alone.

When a once-only combination of sigmoidoscopy with FOBT was compared with biennial FOBT alone, the cumulative detection rates for cancer and advanced adenoma became similar among the two strategies after 5 rounds of biennial FOBT screening [95]. When the detection rate was calculated among the invited (as opposed to examinees) diagnostic yield was higher in the biennial FOBT programme because of the higher compliance with FOBT. These conclusions should be considered cautiously, however, because they are based on an indirect comparison of two trials and because sigmoidoscopy may prevent advanced adenomas and CRC. A comparison of cumulative detection rates of advanced adenomas and CRC may therefore be biased in favour of biennial FOBT screening.

Two studies evaluated the effect of offering combined once-in-a-lifetime testing on screening compliance [38, 110]. While one study showed a significantly lower compliance with the combination of sigmoidoscopy and FOBT compared to FOBT alone [110] the other did not find a difference between the combination, and sigmoidoscopy alone [38].

The impact on CRC incidence and mortality of combining sigmoidoscopy screening with annual or biennial FOBT has not yet been evaluated in trials. There is currently no evidence for extra benefit from adding a once-only FOBT to sigmoidoscopy screening (**II**).^{Rec 1.13}

1.5 New screening technologies under evaluation⁸

Besides the established FOBT and endoscopy tests, several new technologies are currently under development for CRC screening. The most important ones are CT colonography (CTC), stool DNA and capsule endoscopy screening. There currently is no evidence on the effect of these and other new screening tests under evaluation.

⁷ Combination of FOBT and sigmoidoscopy is not a screening approach for CRC recommended by the EU. The applicable items in the Council Recommendation of 2 December 2003 are 6(a) to 6(d) (see Sect. 1.14 and [21]).

⁸ New technologies under evaluation are not recommended for CRC screening by the EU. The applicable items in the Council Recommendation of 2 December 2003 are 6(a) to 6(d) (see Sect. 1.14 and [21]).

ation on CRC incidence and mortality (see Sections 1.5.1–3). New screening technologies are therefore not recommended for screening the average-risk population **(VI–D)**.^{Rec 1.14}

1.5.1 CT colonography

CTC is a potential technique for CRC screening. With CTC, two- and three-dimensional digital images are constructed to investigate the presence of lesions in the colon and rectum. Studies on the impact of CTC screening on CRC incidence or mortality have not yet been conducted. Seven systematic reviews have been published between 2003 and 2008 on CTC performance characteristics in comparison to colonoscopy [40,77,92,101,119,133,135]. All meta-analyses and primary studies [6,17,98] reported that sensitivity was low for small polyps and increased with polyp size. The incidence of adverse events was very low in all studies which assessed this outcome. Three studies also reported patient preferences and found that participants prefer CT colonography over colonoscopy, [55,100]. None of the retrieved studies considered the possible damage associated with radiation. All studies concluded that CT is not ready for routine use in clinical practice.

Before CTC can be recommended for average-risk screening, it must be demonstrated to be highly and consistently sensitive in a variety of settings and questions about the optimal technological characteristics of the technique must be settled. These questions include the appropriate threshold size for referral of findings, costs of the procedure in relation to its effectiveness and the potential risks from the radiation exposure **(VI–A)**.

1.5.2 Stool DNA

With stool DNA testing, faeces are investigated for the presence of disrupted or methylated DNA. There have been no studies evaluating the CRC incidence or mortality reduction from stool DNA testing. Systematic reviews of performance characteristics of stool DNA tests [12,69,135] included two prospective studies assessing diagnostic performance in an average-risk population [1,51]. Both studies found that stool DNA testing was more sensitive than Hemoccult II for advanced neoplasia, without loss of specificity. However, sensitivity of stool DNA was still only 50% and 20% in the respective studies [1,51].

A new version of the stool DNA test has been developed that incorporates only two markers. The use of only two markers will make the test easier to perform, reduce the cost, and facilitate distribution to local laboratories. In a case–control study of this test, Itzkowitz found a high sensitivity of 83% but the specificity was significantly worse than the older version at 82% [53].

An important issue which must be addressed before widespread implementation of stool DNA testing becomes possible involves costs. Two studies have shown that at current costs of approximately US\$ 350, stool DNA screening is not a cost-effective option for CRC screening [83,143]. According to one study, costs should be 6–10 times lower before stool DNA screening could compete with other available screening tests [143].

Stool DNA with version 1 testing has superior sensitivity over Hemoccult II, at similar levels of specificity **(III)**. Version 2 seems to have even better sensitivity, at the expense of worse specificity **(IV)**. The diagnostic accuracy of stool DNA needs to be confirmed by large multicentre prospective trials in the average-risk population, and costs need to be reduced before stool DNA testing can be recommended for CRC screening **(VI–D)**.

1.5.3 Capsule endoscopy

With capsule endoscopy, a camera with the size and shape of a pill is swallowed to visualise the gastrointestinal tract. No studies have reported on CRC incidence and mortality reduction from capsule endoscopy. Two reviews have evaluated its test performance characteristics compared to colonoscopy and/or CT colonography [34,124]. Since the reviews, four more studies on the diagnostic accuracy of capsule endoscopy have been published [27,35,115,127]. Sensitivity in the studies included in the review varied from 56–76%, and specificity from 64–69% [34,124]. The newer studies showed somewhat better estimates than the earlier studies, with sensitivity ranging from 72–78% and specificity from 53–78% [27,35,115,127]. However, these test characteristics are still inferior compared to colonoscopy.

Capsule endoscopy bears promise as an alternative to colonoscopy, because the examination can be realised without intubation, insufflation, pain, sedation or radiation; no serious adverse effects have been reported. However, accuracy data show inferior performance compared to colonoscopy **(III)**. Better diagnostic performance results from large multicentre prospective trials in the average-risk population are required before capsule endoscopy can be recommended for screening **(VI–A)**.^{Rec 1.14}

Conclusions

▼ In a multidisciplinary process, wide consensus has been achieved on a comprehensive package of evidence-based recommendations for quality assurance in colorectal cancer screening. Following these recommendations has the potential to enhance the control of colorectal cancer in Europe and elsewhere through improvement in the quality and effectiveness of the screening process that extends from systematic invitation to management of screen-detected cases.

Disclaimer

▼ The views expressed in this document are those of the authors. Neither the European Commission nor any person acting on its behalf can be held responsible for any use that may be made of the information in this document.

Competing interests: No competing interests reported.

Acknowledgements

▼ The comments and suggestions received from consultation of the European Cancer Network are gratefully acknowledged. The production of the Guidelines was supported by the European Union through the EU Public Health Programme, (grant agreement no. 2005317: Development of European Guidelines for Quality Assurance of Colorectal Cancer Screening). Partner institutions: Oxford University Cancer Screening Research Unit, Cancer Epidemiology Unit, University of Oxford, Oxford, United Kingdom; Unit of Cancer Epidemiology, Centre for Cancer Epidemiology and Prevention (CPO) and S. Giovanni University Hospital, Turin, Italy; Public Association for Healthy People, Budapest, Hungary; European Cancer Patient Coalition (ECPC), Utrecht, Netherlands ; Quality Assurance Group, Section of Early Detec-

tion and Prevention, International Agency for Research on Cancer, Lyon, France.

Financial support was also received through the Public Affairs Committee of the United European Gastroenterology Federation, and from a cooperative agreement between the American Cancer Society and the Division of Cancer Prevention and Control at the Centers for Disease Control and Prevention.

References

- Ahlquist DA, Sargent DJ, Levin TR et al. Stool DNA screening for colorectal neoplasia: prospective multicenter comparison with occult blood testing. *Gastroenterology* 2005; 128: 63
- Allison JE, Sakoda LC, Levin TR et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. *J Natl Cancer Inst* 2007; 99: 1462–1470
- Allison JE, Tekawa IS, Ransom LJ et al. A comparison of fecal occult-blood tests for colorectal-cancer screening. *N Engl J Med* 1996; 334: 155–159
- Arbyn M, Anttila A, Jordan J et al. European Guidelines for Quality Assurance in Cervical Cancer Screening. Second edition – summary document. *Ann Oncol* 2010; 21: 448–458
- Arbyn M, Anttila A, Jordan J et al. eds. European guidelines for quality assurance in cervical cancer screening. Second edition. Luxembourg: European Commission, Office for Official Publications of the European Communities; 2008
- Arnesen RB, von Benzon E, Adamsen S et al. Diagnostic performance of computed tomography colonography and colonoscopy: a prospective and validated analysis of 231 paired examinations. *Acta Radiol* 2007; 48: 831–837
- Atkin W, Valori R, Kuipers EJ et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition. Colonoscopic surveillance following adenoma removal. *Endoscopy* 2012; 44:
- Atkin WS, Edwards R, Kralj-Hans I et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet* 2010; 375: 1624–1633
- Austoker J, Giordano L, Hewitson P et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition. Communication. *Endoscopy* 2012; 44: SE164–1SE85
- Baxter NN, Goldwasser MA, Paszat LF et al. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med* 2009; 150: 1–8
- Berchi C, Bouvier V, Reaud JM et al. Cost-effectiveness analysis of two strategies for mass screening for colorectal cancer in France. *Health Econ* 2004; 13: 227–238
- Bluecross Blueshield Association Special Report. Special report: fecal DNA analysis for colon cancer screening. *Technol Eval Cent Asses Program Exec Summ* 2006; 21: 1–2
- Brenner H, Arndt V, Stegmaier C et al. Reduction of clinically manifest colorectal cancer by endoscopic screening: empirical evaluation and comparison of screening at various ages. *Eur J Cancer Prev* 2005; 14: 231–237
- Brenner H, Chang-Claude J, Seiler CM et al. Does a negative screening colonoscopy ever need to be repeated? *Gut* 2006; 55: 1145–1150
- Brenner H, Hoffmeister M, Arndt V et al. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. *J Natl Cancer Inst* 2010; 102: 89–95
- Castiglione G, Zappa M, Grazzini G et al. Immunochemical vs guaiac faecal occult blood tests in a population-based screening programme for colorectal cancer. *Br J Cancer* 1996; 74: 141–144
- Chaparro Sanchez M, del Campo V, Mate Jimenez J et al. Computed tomography colonography compared with conventional colonoscopy for the detection of colorectal polyps. *Gastroenterol Hepatol* 2007; 30: 375–380
- Ciccolallo L, Capocaccia R, Coleman MP et al. Survival differences between European and US patients with colorectal cancer: role of stage at diagnosis and surgery. *Gut* 2005; 54: 268–273
- Commission of the European Communities. Report from the Commission to the Council, the European Parliament, the European Economic and Social Committee and the Committee of the Regions – Implementation of the Council Recommendation of 2 December 2003 on cancer screening (2003/878/EC). Brussels: 2008: COM(2008) 882 final
- Commission of the European Communities. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Action Against Cancer: European Partnership. Brussels: European Commission; 2009: COM(2009) 291 final http://ec.europa.eu/health/ph_information/dissemination/diseases/docs/com_2009_291_en.pdf Accessed 11/2/2012
- Council of the European Union. Council Recommendation of 2 December 2003 on cancer screening (2003/878/EC). *Off J Eur Union* 2003; 34–38
- Council of the European Union. Council conclusions on reducing the burden of cancer. 2876th Employment, Social Policy, Health and Consumer Affairs Council meeting. Luxembourg, 9–10 June 2008 Brussels, Belgium: Press Office of the Council of the European Union; 10 June 2008; 2008: 10414/08 (Presse 166)
- Council of the European Union. Council conclusions on action against cancer. 3032nd General Affairs Council meeting. Brussels, 13 September 2010 Brussels, Belgium: Press Office of the Council of the European Union; 2010: 5021/09
- Dancourt V, Lejeune C, Lepage C et al. Immunochemical faecal occult blood tests are superior to guaiac-based tests for the detection of colorectal neoplasms. *Eur J Cancer* 2008; 44: 2254–2258
- de Wolf C, Perry N eds. European guidelines for quality assurance in breast cancer screening. Second edition. Luxembourg: European Commission, Office for Official Publications of the European Communities; 1996
- Ee HC, Semmens JB, Hoffman NE. Complete colonoscopy rarely misses cancer. *Gastrointest Endosc* 2002; 55: 167–171
- Eliakim R, Yassin K, Niv Y et al. Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. *Endoscopy* 2009; 41: 1026–1031
- European Parliament. European Parliament Resolution on Breast Cancer in the European Union. 2004: (2002/2279(INI)). *OJ C 68 E* (18 March 2004): 611–617
- European Parliament. European Parliament Resolution on Breast Cancer in the Enlarged European Union. 2006: P6_TA(2006)0449.
- European Parliament. European Parliament resolution of 10 April on combating cancer in the enlarged European Union. 2008: P6_TA-PROV(2008)0121.
- Faivre J, Dancourt V, Lejeune C et al. Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study. *Gastroenterology* 2004; 126: 1674–1680
- Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer* 2010; 46: 765–781
- Ferlay J, Shin HR, Bray F et al. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC. *CancerBase No. 10* [Internet]. 2010: <http://globocan.iarc.fr> Accessed 1/9/2011
- Fireman Z, Kopelman Y. The colon – the latest terrain for capsule endoscopy. *Dig Liver Dis* 2007; 39: 895–899
- Gay G, Delvaux M, Frederic M et al. Could the Colonic Capsule PillCam Colon Be Clinically Useful for Selecting Patients Who Deserve a Complete Colonoscopy?: Results of Clinical Comparison With Colonoscopy in the Perspective of Colorectal Cancer Screening *Am J Gastroenterol* 2010; 105: 1076–1086
- Giordano L, Webster P, Anthony C et al. Improving the quality of communication in organised cervical cancer screening programmes. *Patient.Educ.Couns* 2008; 72: 130–136
- Giordano L, Webster P, Segnan N et al. Guidance on breast screening communication. In: Perry N, Broeders M, de Wolf C et al., eds. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition. Luxembourg: Office for Official Publications of the European Communities; 2006: 379–394
- Gondal G, Grotmol T, Hofstad B et al. The Norwegian Colorectal Cancer Prevention (NORCCAP) screening study: baseline findings and implementations for clinical work-up in age groups 50–64 years. *Scand J Gastroenterol* 2003; 38: 635–642
- Guittet L, Bouvier V, Mariotte N et al. Comparison of a guaiac based and an immunochemical faecal occult blood test in screening for colorectal cancer in a general average risk population. *Gut* 2007; 56: 210–214
- Halligan S, Altman DG, Taylor SA et al. CT colonography in the detection of colorectal polyps and cancer: systematic review, meta-analysis, and proposed minimum data set for study level reporting. *Radiology* 2005; 237: 893–904

- 41 *Halloran S, Launoy G, Zappa M.* European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition. Faecal Occult Blood Testing. *Endoscopy* 2012; 44: SE65–SE87
- 42 *Hanselaar AG.* Criteria for organized cervical screening programs. Special emphasis on The Netherlands program. *Acta Cytol* 2002; 46: 619–629
- 43 *Hardcastle JD, Chamberlain JO, Robinson MH et al.* Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996; 348: 1472–1477
- 44 *Heresbach D, Manfredi S, D'halluin PN et al.* Review in depth and meta-analysis of controlled trials on colorectal cancer screening by faecal occult blood test. *Eur J Gastroenterol Hepatol* 2006; 18: 427–433
- 45 *Hewitson P, Glasziou P, Irwig L et al.* Screening for colorectal cancer using the faecal occult blood test, Hemoccult. *Cochrane Database Syst Rev* 2007
- 46 *Hoepffner N, Shastri YM, Hanisch E et al.* Comparative evaluation of a new bedside faecal occult blood test in a prospective multicentre study. *Aliment Pharmacol Ther* 2006; 23: 145–154
- 47 *Hoff G, Grotmol T, Skovlund E et al.* Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. *BMJ* 2009; 338: b1846
- 48 *Hofstad B.* Colon Polyps: Prevalence Rates, Incidence Rates, and Growth Rates. In: *Waye J, Rex DK, Williams CB*, eds *Colonoscopy: Principles and Practice*. Oxford: Blackwell Publishing Ltd; 2003: 358–376
- 49 *Huang EH, Whelan RL, Gleason NR et al.* Increased incidence of colorectal adenomas in follow-up evaluation of patients with newly diagnosed hyperplastic polyps. *Surg Endosc* 2001; 15: 646–648
- 50 *Hughes K, Leggett B, Del MC et al.* Guaiac versus immunochemical tests: faecal occult blood test screening for colorectal cancer in a rural community. *Aust N Z J Public Health* 2005; 29: 358–364
- 51 *Imperiale TF, Ransohoff DF, Itzkowitz SH et al.* Faecal DNA versus faecal occult blood for colorectal-cancer screening in an average-risk population. *N Engl J Med* 2004; 351: 2704–2714
- 52 *Imperiale TF, Wagner DR, Lin CY et al.* Results of screening colonoscopy among persons 40 to 49 years of age. *N Engl J Med* 2002; 346: 1781–1785
- 53 *Itzkowitz S, Brand R, Jandorf L et al.* A simplified, noninvasive stool DNA test for colorectal cancer detection. *Am J Gastroenterol* 2008; 103: 2862–2870
- 54 *Jemal A, Siegel R, Ward E et al.* Cancer statistics, 2008. *CA Cancer J Clin* 2008; 58: 71–96
- 55 *Jensch S, de Vries AH, Peringa J et al.* CT colonography with limited bowel preparation: performance characteristics in an increased-risk population. *Radiology* 2008; 247: 122–132
- 56 *Kahi CJ, Imperiale TF, Juliar BE et al.* Effect of screening colonoscopy on colorectal cancer incidence and mortality. *Clin Gastroenterol Hepatol* 2009; 7: 770–775
- 57 *Kavanagh AM, Giovannucci EL, Fuchs CS et al.* Screening endoscopy and risk of colorectal cancer in United States men. *Cancer Causes Control* 1998; 9: 455–462
- 58 *Kerr J, Day P, Broadstock M et al.* Systematic review of the effectiveness of population screening for colorectal cancer. *N Z Med J* 2007; 120: U2629
- 59 *Kim DH, Lee SY, Choi KS et al.* The usefulness of colonoscopy as a screening test for detecting colorectal polyps. *Hepatogastroenterology* 2007; 54: 2240–2242
- 60 *Ko CW, Dominitz JA, Nguyen TD.* Faecal occult blood testing in a general medical clinic: comparison between guaiac-based and immunochemical-based tests. *Am J Med* 2003; 115: 111–114
- 61 *Kronborg O, Fenger C, Olsen J et al.* Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996; 348: 1467–1471
- 62 *Ladabaum U, Chopra CL, Huang G et al.* Aspirin as an adjunct to screening for prevention of sporadic colorectal cancer. A cost-effectiveness analysis. *Ann Intern Med* 2001; 135: 769–781
- 63 *Lejeune C, Arveux P, Dancourt V et al.* Cost-effectiveness analysis of faecal occult blood screening for colorectal cancer. *Int J Technol Assess Health Care* 2004; 20: 434–439
- 64 *Li S, Wang H, Hu J et al.* New immunochemical faecal occult blood test with two-consecutive stool sample testing is a cost-effective approach for colon cancer screening: results of a prospective multicenter study in Chinese patients. *Int J Cancer* 2006; 118: 3078–3083
- 65 *Lieberman DA, Weiss DG.* One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. *N Engl J Med* 2001; 345: 555–560
- 66 *Lieberman DA, Weiss DG, Bond JH et al.* Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med* 2000; 343: 162–168
- 67 *Lieberman DA, Weiss DG, Harford WV et al.* Five-year colon surveillance after screening colonoscopy. *Gastroenterology* 2007; 133: 1077–1085
- 68 *Lindholm E, Brevinge H, Haglund E.* Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. *Br J Surg* 2008; 95: 1029–1036
- 69 *Loganayagam A.* Faecal screening of colorectal cancer. *Int J Clin Pract* 2008; 62: 454–459
- 70 *Malila N, Senore C, Armaroli P.* European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition. Organisation. *Endoscopy* 2012; 44: SE31–SE48
- 71 *Mandel JS, Bond JH, Church TR et al.* Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 1993; 328: 1365–1371
- 72 *Mandel JS, Church TR, Ederer F et al.* Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. *J Natl Cancer Inst* 1999; 91: 434–437
- 73 *Minozzi S, Armaroli P, Banzi R et al.* European guidelines for quality assurance in colorectal cancer screening and diagnosis – First edition. Appendix 1: Systematic evidence review 2010: <http://bookshop.europa.eu/en/european-guidelines-for-quality-assurance-in-colorectal-cancer-screening-and-diagnosis-pbND3210390/> Accessed 11/2/2012
- 74 *Minozzi S, Armaroli P, Segnan N.* European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition. Principles of evidence assessment and methods for reaching recommendations. *Endoscopy* 2012; 44: SE9–SE14
- 75 *Morson BC.* The evolution of colorectal carcinoma. *Clin Radiol* 1984; 35: 425–431
- 76 *Moss S, Ancelle-Park R, Brenner H.* European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition. Evaluation and interpretation of screening outcomes. *Endoscopy* 2012; 44: SE49–SE64
- 77 *Mulhall BP, Veerappan GR, Jackson JL.* Meta-analysis: computed tomographic colonography. *Ann Intern Med* 2005; 142: 635–650
- 78 *Muller AD, Sonnenberg A.* Protection by endoscopy against death from colorectal cancer. A case-control study among veterans. *Arch Intern Med* 1995; 155: 1741–1748
- 79 *Muto T, Bussey HJ, Morson BC.* The evolution of cancer of the colon and rectum. *Cancer* 1975; 36: 2251–2270
- 80 *Nakajima M, Saito H, Soma Y et al.* Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case-control study. *Br J Cancer* 2003; 89: 23–28
- 81 *Newcomb PA, Norfleet RG, Storer BE et al.* Screening sigmoidoscopy and colorectal cancer mortality. *J Natl Cancer Inst* 1992; 84: 1572–1575
- 82 *Pabby A, Suneja A, Heeren T et al.* Flexible sigmoidoscopy for colorectal cancer screening in the elderly. *Dig Dis Sci* 2005; 50: 2147–2152
- 83 *Parekh M, Fendrick AM, Ladabaum U.* As tests evolve and costs of cancer care rise: reappraising stool-based screening for colorectal neoplasia. *Aliment Pharmacol Ther* 2008; 27: 697–712
- 84 *Perry N, Broeders M, de Wolf C et al.* European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition – summary document. *Ann Oncol* 2008; 19: 614–622
- 85 *Perry N, Broeders M, de Wolf C et al.* European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition. Luxembourg: European Commission, Office for Official Publications of the European Communities; 2006
- 86 *Perry N, de Wolf C, Törnberg S et al.* (eds.) European guidelines for quality assurance in mammography screening. Third edition. Luxembourg: European Commission, Office for Official Publications of the European Communities; 2001
- 87 *Pickhardt PJ, Hassan C, Laghi A et al.* Cost-effectiveness of colorectal cancer screening with computed tomography colonography: the impact of not reporting diminutive lesions. *Cancer* 2007; 109: 2213–2221
- 88 *Pignone M, Rich M, Teutsch SM et al.* Screening for colorectal cancer in adults at average risk: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002; 137: 132–141

- 89 Pignone M, Saha S, Hoerger T et al. Cost-effectiveness analyses of colorectal cancer screening: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002; 137: 96–104
- 90 Platell CF, Philpott G, Olynyk JK. Flexible sigmoidoscopy screening for colorectal neoplasia in average-risk people: evaluation of a five-year rescreening interval. *Med J Aust* 2002; 176: 371–373
- 91 Prorok PC, Andriole GL, Bresalier RS et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials* 2000; 21: 273S–309S
- 92 Purkayastha S, Athanasiou T, Tekkis PP et al. Magnetic resonance colonography vs computed tomography colonography for the diagnosis of colorectal cancer: an indirect comparison. *Colorectal Dis* 2007; 9: 100–111
- 93 Quirke P, Risio M, Lambert R et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition. Quality assurance in pathology in colorectal cancer screening and diagnosis. *Endoscopy* 2012; 44:
- 94 Rainis T, Keren D, Goldstein O et al. Diagnostic yield and safety of colonoscopy in Israeli patients in an open access referral system. *J Clin Gastroenterol* 2007; 41: 394–399
- 95 Rasmussen M, Fenger C, Kronborg O. Diagnostic yield in a biennial Hemoccult-II screening program compared to a once-only screening with flexible sigmoidoscopy and Hemoccult-II. *Scand J Gastroenterol* 2003; 38: 114–118
- 96 Rasmussen M, Kronborg O, Fenger C et al. Possible advantages and drawbacks of adding flexible sigmoidoscopy to hemoccult-II in screening for colorectal cancer. A randomized study. *Scand J Gastroenterol* 1999; 34: 73–78
- 97 Regula J, Rupinski M, Kraszewska E et al. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. *N Engl J Med* 2006; 355: 1863–1872
- 98 Reuterskiold MH, Lasso A, Svensson E et al. Diagnostic performance of computed tomography colonography in symptomatic patients and in patients with increased risk for colorectal disease. *Acta Radiol* 2006; 47: 888–898
- 99 Rex DK, Cummings OW, Helper DJ et al. 5-year incidence of adenomas after negative colonoscopy in asymptomatic average-risk persons. [see comment] *Gastroenterology* 1996; 111: 1178–1181
- 100 Roberts-Thomson IC, Tucker GR, Hewett PJ et al. Single-center study comparing computed tomography colonography with conventional colonoscopy. *World J Gastroenterol* 2008; 14: 469–473
- 101 Rosman AS, Korsten MA. Meta-analysis comparing CT colonography, air contrast barium enema, and colonoscopy. *Am J Med* 2007; 120: 203–210
- 102 Rozen P, Knaani J, Samuel Z. Comparative screening with a sensitive guaiac and specific immunochemical occult blood test in an endoscopic study. *Cancer* 2000; 89: 46–52
- 103 Rundle AG, Lebwahl B, Vogel R et al. Colonoscopic screening in average-risk individuals ages 40 to 49 vs 50 to 59 years. *Gastroenterology* 2008; 134: 1311–1315
- 104 Saito H, Soma Y, Koeda J et al. Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. *Int J Cancer* 1995; 61: 465–469
- 105 Saito H, Soma Y, Nakajima M et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. *Oncol Rep* 2000; 7: 815–819
- 106 Schoen RE, Pinsky PF, Weissfeld JL et al. Results of repeat sigmoidoscopy 3 years after a negative examination. *JAMA* 2003; 290: 41–48
- 107 Schoenfeld P, Cash B, Flood A et al. Colonoscopic screening of average-risk women for colorectal neoplasia. *N Engl J Med* 2005; 352: 2061–2068
- 108 Scholefield JH, Moss S, Sufi F et al. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. *Gut* 2002; 50: 840–844
- 109 Segnan N, Patnick J, Karsa L von (eds.) European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition. Luxembourg: European Commission, Publications Office of the European Union; 2010
- 110 Segnan N, Senore C, Andreoni B et al. Randomized trial of different screening strategies for colorectal cancer: patient response and detection rates. *J Natl Cancer Inst* 2005; 97: 347–357
- 111 Segnan N, Senore C, Andreoni B et al. Baseline findings of the Italian multicenter randomized controlled trial of “once-only sigmoidoscopy”-SCORE. *J Natl Cancer Inst* 2002; 94: 1763–1772
- 112 Segnan N, Senore C, Andreoni B et al. Comparing attendance and detection rate of colonoscopy with sigmoidoscopy and FIT for colorectal cancer screening. *Gastroenterology* 2007; 132: 2304–2312
- 113 Selby JV, Friedman GD, Quesenberry CP Jr et al. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med* 1992; 326: 653–657
- 114 Sieg A, Brenner H. Cost-saving analysis of screening colonoscopy in Germany. *Z Gastroenterol* 2007; 45: 945–951
- 115 Sieg A, Friedrich K, Sieg U. Is PillCam COLON capsule endoscopy ready for colorectal cancer screening? A prospective feasibility study in a community gastroenterology practice. *Am J Gastroenterol* 2009; 104: 848–854
- 116 Singh H, Turner D, Xue L et al. Risk of developing colorectal cancer following a negative colonoscopy examination: evidence for a 10-year interval between colonoscopies. *JAMA* 2006; 295: 2366–2373
- 117 Smith A, Young GP, Cole SR et al. Comparison of a brush-sampling fecal immunochemical test for hemoglobin with a sensitive guaiac-based fecal occult blood test in detection of colorectal neoplasia. *Cancer* 2006; 107: 2152–2159
- 118 Song K, Fendrick AM, Ladabaum U. Fecal DNA testing compared with conventional colorectal cancer screening methods: a decision analysis. *Gastroenterology* 2004; 126: 1270–1279
- 119 Sosna J, Morrin MM, Kruskal JB et al. CT colonography of colorectal polyps: a metaanalysis. *AJR Am J Roentgenol* 2003; 181: 1593–1598
- 120 Steele RJC, Pox C, Kuipers E et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition. Management of lesions detected in colorectal cancer screening. *Endoscopy* 2012; 44: SE140–SE150
- 121 Steele RJC, Rey J-F, Lambert R. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition. Professional requirements and training. *Endoscopy* 2012; 44: SE88–SE105
- 122 Tappenden P, Chilcott J, Eggington S et al. Option appraisal of population-based colorectal cancer screening programmes in England. *Gut* 2007; 56: 677–684
- 123 Thiis-Evensen E, Hoff GS, Sauar J et al. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark Polyp Study I. *Scand J Gastroenterol* 1999; 34: 414–420
- 124 Tran K. Capsule colonoscopy: PillCam Colon. *Issues Emerg Health Technol* 2007; 1–4
- 125 UK Flexible Sigmoidoscopy Screening Trial Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. *Lancet* 2002; 359: 1291–1300
- 126 Valori R, Rey J-F, Atkin W et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition. Quality assurance in endoscopy in colorectal screening and diagnosis. *Endoscopy* 2012; 44: SE88–SE105
- 127 Van Gossum A, Munoz-Navas M, Fernandez-Urien I et al. Capsule endoscopy versus colonoscopy for the detection of polyps and cancer. *N Engl J Med* 2009; 361: 264–270
- 128 van Rossum LG, van Rijn AF, Laheij RJ et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. *Gastroenterology* 2008; 135: 82–90
- 129 Vijan S, Hwang I, Inadomi J et al. The cost-effectiveness of CT colonography in screening for colorectal neoplasia. *Am J Gastroenterol* 2007; 102: 380–390
- 130 von Karsa L. Mammographie Screening – umfassendes, populationsbezogenes Qualitätsmanagement ist hier gefragt! Mammography screening – comprehensive, population-based quality assurance is required! *Zeitschrift für Allgemeinmedizin* 1995; 71: 1863–1867
- 131 von Karsa L, Anttila A, Ronco G et al. Cancer Screening in the European Union. Report on the implementation of the Council Recommendation on Cancer Screening – First Report Luxembourg: European Commission; 2008: http://ec.europa.eu/health/archive/ph_determinants/genetics/documents/cancer_screening.pdf Accessed 11/2/2012
- 132 von Karsa L, Lignini TA, Patnick J et al. The dimensions of the CRC problem. *Best Pract Res Clin Gastroenterol* 2010; 24: 381–396
- 133 Waller S, Griffiths A, Lord SJ et al. What is the value of computerized tomography colonography in patients screening positive for fecal oc-

- cult blood? A systematic review and economic evaluation. *Clin Gastroenterol Hepatol* 2007; 5: 1439–1446
- 134 *Walsh JM, Terdiman JP*. Colorectal cancer screening: scientific review. *JAMA* 2003; 289: 1288–1296
- 135 *Whitlock EP, Lin JS, Liles E et al*. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2008; 149: 638–658
- 136 *Whynes DK*. Cost-effectiveness of screening for colorectal cancer: evidence from the Nottingham faecal occult blood trial. *J Med Screen* 2004; 11: 11–15
- 137 *Wilson JM, Jungner YG*. Principles and practice of mass screening for disease. World Health Organization; 1968: http://whqlibdoc.who.int/php/WHO_PHP_34.pdf Accessed 11/2/2012
- 138 *Winawer SJ, Fletcher RH, Miller L et al*. Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology* 1997; 112: 594–642
- 139 *Winawer SJ, Zauber AG, Ho MN*. The National Polyp Study Workgroup. et al. Prevention of colorectal cancer by colonoscopic polypectomy. *N Engl J Med* 1993; 329: 1977–1981
- 140 *Wong BC, Wong WM, Cheung KL et al*. A sensitive guaiac faecal occult blood test is less useful than an immunochemical test for colorectal cancer screening in a Chinese population. *Aliment Pharmacol Ther* 2003; 18: 941–946
- 141 *Yamaji Y, Mitsushima T, Ikuma H et al*. Incidence and recurrence rates of colorectal adenomas estimated by annually repeated colonoscopies on asymptomatic Japanese. *Gut* 2004; 53: 568–572
- 142 *Zappa M, Castiglione G, Paci E et al*. Measuring interval cancers in population-based screening using different assays of fecal occult blood testing: the District of Florence experience. *Int J Cancer* 2001; 92: 151–154
- 143 *Zauber AG, Lansdorp-Vogelaar I, Wilschut J et al*. Cost-effectiveness of DNA stool testing to screen for colorectal cancer. Report to AHRQ and CMS from the Cancer Intervention and Surveillance Modeling Network (CISNET) for MISCAN and SimCRC Models. December 20, 2007
- 144 *Zheng S, Chen K, Liu X et al*. Cluster randomization trial of sequence mass screening for colorectal cancer. *Dis Colon Rectum* 2003; 46: 51–58