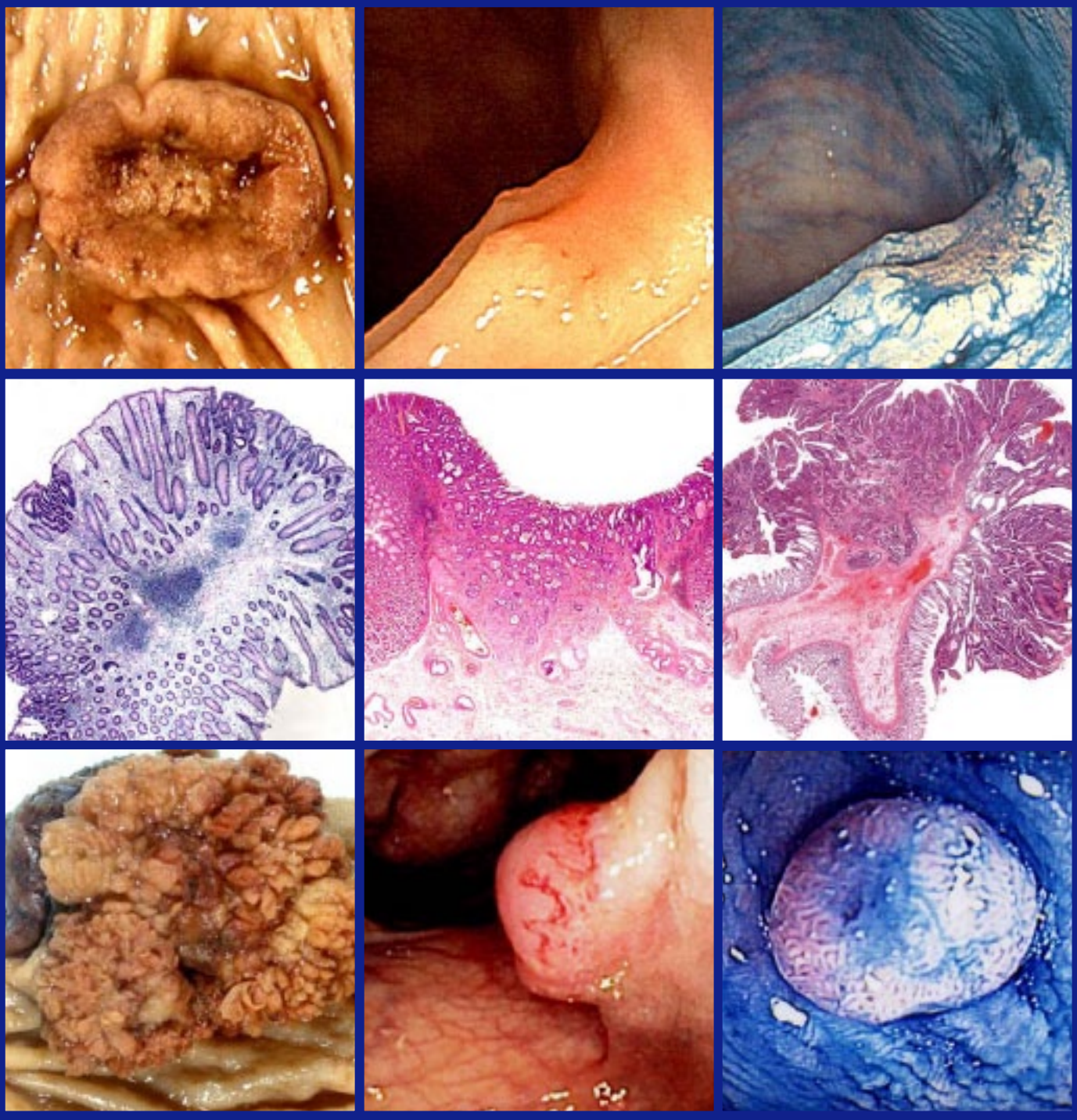

European guidelines for quality assurance in colorectal cancer screening and diagnosis

First Edition

European Commission

European Commission

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ERRATA Version 1.

The following errata apply to the first version of the Guidelines that was made available on the website of the European Union in February 2011. They have been corrected in the second version of the Guidelines.

p. VI	*Replace*: Henning Erfkampf *by*: Henning Erfkamp
pp. VII, 145 & 146	*Replace*: Ernst Kuipers *By:* Ernst J. Kuipers
p. XLVI, point 7	*Delete*: after positive FS
p.114, para. 7	*Replace*: PK isoenzyme type M2 has shown poor sensitivity and specificity when used alongside two immunochemical devices (Mulder et al 2007). *By*: When used alongside guaiac-based or immunochemical devices, PK isoenzyme type M2 has not shown adequate specificity for population screening (Shastri et al. 2006; Möslein et al 2010).
p. 141	*Insert*: Möslein G, Schneider C, Theilmeier A, Erckenbrecht H, Normann S, Hoffmann B, Tilmann-Schmidt D, Horstmann O, Graeven U & Poremba C (2010), [Analysis of the statistical value of various commercially available stool tests - a comparison of one stool sample in correlation to colonoscopy], *Dtsch.Med Wochenschr.*, vol. 135, no. 12, pp. 557-562.
p. 142, para. 3	*Delete*: Mulder SA, van Leerdam ME, van Vuuren AJ, Francke J, van Toorenenbergen AW, Kuipers EJ & Ouwendijk RJ (2007), Tumor pyruvate kinase isoenzyme type M2 and immunochemical fecal occult blood test: performance in screening for colorectal cancer, Eur.J.Gastroenterol.Hepatol. vol. 19, no. 10, pp. 878-882.
p. 143	*Insert*: Shastri YM, Naumann M, Oremek GM, Hanisch E, Rosch W, Mossner J, Caspary WF & Stein JM (2006), Prospective multicenter evaluation of fecal tumor pyruvate kinase type M2 (M2-PK) as a screening biomarker for colorectal neoplasia, *Int J Cancer*, vol. 119, no. 11, pp. 2651-2656.

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Addendum

For a journal publication, the authors, contributors, editors and reviewers were requested to review their declarations of interest based on the new IARC procedures adopted since publication of the original Guidelines book. The following revised declarations were received:

Dr Hermann Brenner is employed by The German Cancer Research Center (DKFZ) that has received significant research support from Eiken Chemicals (less than 40 000 €) for previously and currently running studies on colorectal cancer detection. The following companies have provided the DKFZ with faecal occult blood tests free of charge for previously and currently running evaluation studies: ulti med, Ahrensburg, Germany; DIMA, Gottingen, Germany; Beckman Coulter, Krefeld, Germany; CAREdiagnostica, Voerde, Germany; Preventis, Bensheim, Germany; Quidel, San Diego, California. The total value of the non-monetary support is less than 100 000 €.

Dr Christian Pox has received lecture honoraria and travel support of less than 7 000 € from the following manufacturers of pharmaceuticals, diagnostics, medical equipment and other health products: Dr Falk Pharma, Hitachi and Roche. He has also received consultancy fees of 1 500 € for attending an Advisory Board Meeting of the Abbot company, a broad-based health care manufacturer, and 2 100 € from the AQUA Institute, Germany, a private entity dedicated to quality assurance research and implementation that is mandated by the Federal Committee of the German Statutory Health Insurance System to implement a nationwide quality assurance scheme.

Dr Wolff Schmiegel is the holder of one patent and the co-holder of three patents covering technologies related to screening and diagnosis of colorectal tumours. He is also co-holder of a patent covering substances potentially suitable for prevention and treatment of colorectal polyps. He has received consultancy fees of less than 2 000 € from Astra Zeneca and consultancy fees, lecture honoraria and travel support totalling less than 16 000 € from Roche. He has also received lecture honoraria from Abbott, Pfizer and Falk. The Medical Faculty of the Ruhr University in Germany where he works has received institutional research funding of less than 165 000 € from Roche and the pharmaceutical manufacturer Sanofi Aventis for studies in colorectal cancer screening and diagnosis. Dr Schmiegel is the sole shareholder (25 000 €) of Medmotive GmbH, a holding that until 2010 controlled 25% of the company Westdeutsches Darm-Centrum GmbH with a capital investment of 25 000 €. The aim of these companies is to develop and coordinate a quality-assured network in colorectal oncology through such activities as consulting, development of therapeutic standards, specialized training and lobbying key stakeholders.

Dr Graeme Young has received consultancy fees (less than 10 000 €) from Quidel Corporation, a manufacturer of diagnostic products. Eiken Chemicals has provided Flinders University where he works with faecal occult blood tests free of charge for studies (total value less than 10 000 €).

Cover

Upper left: surgically excised pT2 adenocarcinoma of the rectum

Upper middle: depressed carcinoma (0-IIc), 7mm, submucosal invasion

Upper right: same lesion, chromoscopy with indigocarmine solution

Centre left: tubular adenoma at initial stage, 12 mm, HE stain

Centre middle: depressed carcinoma (0-IIa+IIc), 10 mm, massive submucosal invasion, HE stain

Centre right: tubulovillous adenoma giving rise to a pY1 adenocarcinoma invading the polyp stalk and showing vascular invasion. Completely excised

Lower left: Large colonic tubulovillous adenoma, surgically excised due to size

Lower middle: sessile adenocarcinoma (0-Is), 13 mm, superficial distorted vessels, submucosal invasion

Lower right: sessile adenoma (0-Is), 8 mm, chromoscopy with indocarmine solution

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Upper left, centre right and lower left: Images supplied by Professor P. Quirke, Leeds, United Kingdom.

Upper middle and right: images provided by Dr S. Tanaka, Hiroshima, Japan.

Centre left: image provided by Dr M. Vieth, Bayreuth, Germany.

Centre middle: image provided by Dr H. Watanabe, Niigata, Japan.

Lower middle and right: images provided by Dr A. Chavaillon, Lyon-Bourgoin, France.

European guidelines for quality assurance in colorectal cancer screening and diagnosis

First Edition

Editors
N. Segnan
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L. von Karsa

International Agency for Research on Cancer

World Health Organization

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Joan Austoker (1947 – 2010)

This edition is dedicated to the memory of our colleague and friend Joan Austoker who contributed substantially to the development of the European cancer screening guidelines through her pioneering work in communication in cancer screening and prevention.

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Minor pertinent interests are not listed. These include stock holdings valued at less than US$ 10 000 overall and occasional travel grants totalling less than 5% of time, and consulting on non-regulatory matters totalling less than 2% of time and compensation.

Conflicts of interest have been disclosed by the experts between October 2008 and October 2010. No other potential conflicts of interest relevant to this publication were reported.

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Prefaces

Preface

John Dalli*

Colorectal cancer is the second most common newly diagnosed cancer and the second most common cause of cancer death in the EU. Many of these deaths, however, could be avoided through early detection, by making effective use of screening tests followed by appropriate treatment.

For this reason, the evidence-based European Code Against Cancer recommends that men and women from 50 years of age should participate in colorectal screening. This has been given effect within the EU by the 2003 Council Recommendation on cancer screening. Making this screening effective, in turn, depends on appropriate quality assurance at all levels.

That is the aim of the "European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis". These guidelines, the result of tireless efforts over many years by a wide range of European experts, represent a major achievement, with the potential to add substantial value to the efforts of the Member States to improve control of colorectal cancer.

This, in turn, will save lives and help improve the quality of life of millions of EU citizens, their families and friends.

This publication will ensure that any organisation, programme or authority in the Member States, as well as every European citizen, can gain access to the recommended standards and procedures. It represents a concrete contribution by the European Commission to our shared European objective of preventing human illness and disease.

I should like to thank the editors, authors, contributors and reviewers of these guidelines for assembling, analysing and documenting the enormous quantity of evidence on which this volume has been based. I am confident that it will become an indispensable guide for colorectal cancer screening in the coming years.

Brussels, July 2010

*European Commissioner for Health and Consumer Policy

Preface

Christopher Wild*

Colorectal cancer is the third most common in incidence and the fourth most common cause of cancer death worldwide, with an estimated 1.2 million new cases and 609 000 deaths in 2008. Based on demographic trends, the annual incidence is expected to increase by nearly 80% to 2.2 million cases over the next two decades and most of this increase will occur in the less developed regions of the world. These regions are ill equipped to deal with the rapidly increasing demand for cancer treatment resulting from population growth and higher life expectancy. Even greater increases in the worldwide burden of the disease can be expected if less developed regions adopt a more “westernised” life style. Concerted efforts to control colorectal cancer are therefore of increasing importance worldwide.

Fortunately, experience in Europe has shown that systematic early detection and treatment of colorectal lesions before they become symptomatic has the potential to improve control of the disease, particularly if they are effectively integrated into an overall programme of comprehensive cancer control. Coordinated resources are needed not only for screening and primary prevention programmes but also for further development and capacity building in diagnosis and therapy of colorectal cancer, especially in the less developed regions of the world because of the expected changes mentioned above. Political commitment and appropriate investment at an early stage are not only likely to lower the future burden of disease, but also to save considerable resources when organised, population-based programmes are fully established.

The authors and editors of the new European quality assurance guidelines have taken care to point out that organised as opposed to “opportunistic” screening programmes are recommended because they include an administrative structure responsible for programme implementation, 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. These efforts should be supported by effective communication for groups with limited access to screening, such as less advantaged socio-economic groups. This, in turn, should permit an informed decision about participation, based on objective, balanced information about the risks and benefits of screening. The population-based approach to programme implementation is also recommended because it provides an organisational framework for effective management and continuous improvement of the screening process, such as through linkage with population registers and cancer registries for optimization of invitation to screening and for evaluation of screening performance and impact respectively. In this context research after implementation of screening should be an integral part of population-based programmes.

Crucial to the success of any cancer screening programme is the availability of comprehensive, evidence-based quality assurance guidelines, addressing all of the steps in the screening process, including not just performance of a test, but also information and invitation, diagnostic work-up of lesions detected in screening, treatment, surveillance and any other subsequent care. Widespread application of the standardised indicators recommended in the Guidelines will facilitate quality management and promote the international exchange of information and experience between programmes that is essential for continuous quality improvement.

Finally, as Director of an international agency I would like to highlight the outstanding international cooperation that has gone into the preparation of these Guidelines. But also, as the landscape of cancer occurrence evolves to cast the burden of colorectal cancer on new regions facing increasing incidence rates due to an aging population and “westernised” life style, it is vital that the excellence demonstrated here is pursued and translated to appropriate guidance for the widest possible audience on a global scale.

Lyon, October 2010

*Director, International Agency for Research on Cancer

Preface

Jean-François Rey, Colm O'Morain, René Lambert

Quality assurance has always been a key issue in digestive endoscopy. Fortunately, this important topic has recently also been placed high on the agenda of the health authorities, healthcare providers and patient associations. A major reason for this is the increasing awareness that effective screening programmes will have a vital role to play in helping to cope with growing problem of colorectal cancer in Europe. Effective screening should supplement ongoing efforts to improve primary prevention, as well as the diagnosis and therapy of symptomatic disease. However, the potential of screening to reduce the burden of the most common cancer in Europe will require an enormous expansion in the number of people attending national programmes. That in turn will require substantial resources and expanded efforts in the field of quality assurance.

Colonoscopy plays a key role in every colorectal cancer screening programme because it is the gold standard by which the status of people with positive screening tests is evaluated. The same applies to patients in a symptomatic service. As pointed out in the new European Guidelines, efforts to improve quality and expand screening should be well planned and should lead to improvement not just in screening, but also in symptomatic care. These efforts should also have a positive impact on the availability of high quality endoscopy for symptomatic services, by providing sufficient resources to achieve and maintain appropriate waiting times.

The international collaboration and cooperation in developing the new European Guidelines for quality assurance in colorectal cancer screening and diagnosis has also shown that additional tools are now being developed to assist gastroenterologists in evaluating their current level of performance in screening. It should be kept in mind, however, that these initiatives, though important, can only be effective if they stimulate action to continuously improve and maintain high levels of professional performance.

The following factors remain fundamental to achieving high quality in endoscopy:

Thorough cleansing of the large bowel is the first mandatory step. If the endoscopist's vision is obscured, small or flat lesions anywhere in the colon and particularly sessile lesions in the right colon may go undetected.

Patient tolerance and acceptance of the endoscopic examination is also of prime importance and can be increased by sedation. National or cultural differences in this domain should be taken into account.

Training, adequate equipment and external evaluation of endoscopy units has proved to be essential during the start-up of a national screening programme. Such activities are likely to play an increasingly important role in quality assurance of symptomatic endoscopy in the coming years.

Nice, Ireland, Lyon, October 2010

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Preface

J Patnick, N Segnan, L von Karsa (Editors)

The editorial board would like to thank all the authors, reviewers and other contributors who have worked so hard to develop these first Guidelines for the new colorectal screening cancer screening programmes which are emerging across the EU. This has been a major undertaking since many of these chapters broke new ground in European collaboration and challenged established practice. The chapters have been produced to a new evidence-based protocol that will, from now on, be used across all EU cancer screening guidelines and this also presented the authors and reviewers with fresh challenges.

It is, however, fair to say that the production has been a very stimulating experience to those involved, and the evolution of the guidelines created strong bonds for future joint working.

The guidelines are designed to ensure that in the future each Member State can deliver screening to a high standard even if they are at the beginning of a screening programme. There is another thank you due. This is to the citizens of the EU and those patients on whose past experiences of screening and endoscopy these guidelines are based.

Oxford, Turin, Lyon, October 2010

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Executive summary

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Role of screening in colorectal cancer control

Colorectal cancer (CRC) is the most common newly-diagnosed cancer and the second most common cause of cancer deaths in Europe. In the 27 Member States of the European Union, CRC ranks second in incidence and mortality in both sexes, with approximately 330 000 new cases and 149 000 deaths estimated for men and women combined in 2008 (Ferlay, Parkin & Steliarova-Foucher 2010). Even in those Member States in the lower range of age-standardised rates of CRC, the burden of disease is significant compared to other regions of the world (see Ferlay et al. 2010). CRC is therefore an important health problem across the EU.

The aim of screening is to lower the burden of cancer in the population by discovering disease in its early latent stages. This permits more effective treatment than if diagnosed later when symptoms occur. Early treatment of invasive lesions, for example by endoscopic resection of early CRC, can be generally less detrimental for quality of life. The endoscopic removal of pre-malignant lesions also reduces the incidence of CRC by stopping the progression to cancer. Randomised trials in people of average risk invited to attend screening have shown a reduction in CRC mortality (Hardcastle et al. 1996; Kronborg et al. 1996; Mandel et al. 1999; Atkin et al. 2010) and incidence (Mandel et al. 2000; Atkin et al. 2010).

Council Recommendation on cancer screening

The potential of screening for improving control of CRC has been recognised by the Council of the European Union. On 2 December 2003 the Council recommended implementation of population-based screening programmes using evidence-based tests for breast, cervical and colorectal cancer to the EU Member States (Council of the European Union 2003) (Appendix 2). The Council Recommendation fulfils the criteria for screening defined by the World Health Organization (Wilson & Jungner 1968) and takes into account the substantial experience in implementation of population-based cancer screening programmes in the EU. The Recommendation spells out fundamental principles of best practice in early detection of cancer. It invites EU Member States to take common action to implement cancer screening programmes with an organised, population-based approach and appropriate quality assurance at all levels, taking into account European quality assurance Guidelines for cancer screening, where they exist (von Karsa et al. 2008).

By the end of 2007, ten EU Member States were in the process of implementing national population-based CRC screening programmes (Cyprus, Finland, France, Hungary, Italy, Poland, Portugal, Romania, Slovenia and the United Kingdom) (see Appendix 3 (Commission of the European Communities 2008)). Furthermore, seven Member States had established nationwide non-population-based programmes. In the meantime, ten Member States have newly established or have upgraded the status of their existing CRC screening programmes (Czech Republic, France, Ireland, Lithuania, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom). In addition, Denmark and the Netherlands are currently in the decision process for implementing population-based CRC screening programmes.

Need for effective quality assurance

The potential harm caused by CRC screening includes the creation of unnecessary anxiety and morbidity, inappropriate economic cost, and exposure to the risk of invasive procedures for detection and diagnosis as well as for removal of lesions detected in screening. As demonstrated in implementation of breast and cervical cancer screening programmes, overall screening outcome and quality depend on the performance at each step in the screening process. To achieve the potential benefit of CRC screening, quality must therefore be optimal at each step in the process. This includes identification and personal invitation of the target population, performance of the screening test and, if necessary, diagnostic work-up, treatment, surveillance and aftercare of screen-detected lesions (Perry et al. 2008; von Karsa et al. 2010; Arbyn et al. 2010).

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. The Council of the European Union therefore recommends appropriate, comprehensive quality standards and best practice in the implementation of cancer screening programmes. European quality assurance Guidelines for breast and cervical cancer screening have been developed by experts and published by the EU (European Commission 2006; European Commission 2008). The availability of the new European guidelines for quality assurance in colorectal cancer screening and diagnosis will now make similar standards available to the Member States in which colorectal cancer screening programmes are currently running or being established.

Primary screening test recommended by the EU

The Council Recommendation calls for introduction of new cancer screening tests in routine healthcare only after they have been evaluated in randomised controlled trials (RCTs). To date, only the faecal occult blood test (FOBT) for men and women aged 50–74 years has been recommended by the EU for CRC screening (Appendix 2). In addition, any screening policy for colorectal cancer should take into account the available evidence and the numerous other principles and standards of best practice laid down in the Council Recommendation. Although the use of endoscopic screening methods is increasing, the majority of colorectal cancer screening examinations performed in the EU use the evidence-based test recommended by the Council of the EU.

Purpose of the EU quality assurance Guidelines

The purpose of the new EU Guidelines is not to recommend other modalities that might currently also be suitable for CRC screening in the EU. Instead, the Guidelines provide guiding principles and evidence-based recommendations on the quality assurance that should be followed when implementing screening programmes using the various modalities currently adopted in publicly mandated CRC screening programmes in the Member States.

The Editors have been conscious of the importance of raising and maintaining quality standards across all the EU Member States. While never abandoning those standards and recommendations that are crucial for mortality reduction, we have as far as possible attempted to achieve an equitable balance that can be used across a wide spectrum of cultural and economic healthcare settings. As with any standards and recommendations, these should be continuously reviewed in the light of future experience. It is not the purpose of these guidelines to promote recent research findings before they have been demonstrated to be of proven benefit in clinical practice. Neither should this edition be regarded as a textbook or in any way a substitute for practical clinical training and experience.

The Guidelines have been developed to inform European policymakers and public health specialists, and any other interested parties 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.

The Guidelines have been specifically developed for screening of the average-risk population in which most CRC develops. High-risk individuals should be referred for high-risk protocols if available. Since the relative variation in the moderate risk of developing CRC in most people with a family history of CRC is less than the geographic variation in average risk between the Member States, no attempt was made to develop recommendations tailored to this subgroup of the population. However, in the absence of hereditary syndromes people identified with a family history of CRC should not be excluded from average risk screening (see Chapter 2). The potential benefit and harm of screening recommendations tailored to people with a positive family history could be examined in greater depth in the preparation of the next edition of the Guidelines.

Process of guideline development

The Guidelines have been developed in an international collaborative project that was co-financed by the EU Public Health Programme.[10] The project involved over 90 experts serving as authors, contributors, editors or reviewers from 32 countries including 21 EU Member States 13 of which acceded to the EU before 2004 (Austria, Belgium, Denmark, Finland, France, Germany, Italy, Luxembourg, Portugal, Spain, Sweden, the Netherlands and the United Kingdom) and eight of which acceded later to the EU (Czech Republic, Hungary, Latvia, Lithuania, Malta, Poland, Romania and Slovenia), as well as one EU applicant country (Croatia). The other countries represented among the collaborators included Argentina, Australia, Canada, China, India, Israel, Japan, Korea, Norway and the United States of America.

The new EU quality assurance Guidelines build on the successful developments in previous editions of the other EU screening Guidelines. The comprehensive CRC Guidelines cover the entire screening process from invitation to management of screen-detected lesions. Although the Guidelines focus on elements essential to screening, it is recognised that certain principles are equally important in diagnosis. Training, multi-disciplinary teamwork, monitoring and evaluation, cost-effectiveness, minimising adverse effects, and timeliness of further investigations are referred to repeatedly throughout the chapters. The applicability of many of the recommended standards and procedures to quality assurance in both screening and diagnosis is therefore reflected in the title of the first edition. Variations in style and emphasis have been unavoidable given the diverse sources of the contributions. However, the editors have maintained a high degree of conformity of approach.

The process used for identifying and evaluating the relevant evidence and for developing respective recommendations in the new Guidelines is described in detail in the section on *Principles of evidence assessment and methods for reaching recommendations*. Briefly, scientific and editorial management was provided by an editorial board with extensive experience in development of best practice guidelines, in evaluation of strategies for CRC screening and in programme management. The editorial board drafted an initial comprehensive outline of the Guidelines and recruited a multidisciplinary group of experts from across Europe to collaborate in revising the outline and drafting the chapters of the guideline according to an agreed methodology.

Additional scientific support was provided by a Literature Group consisting of epidemiologists with special expertise in the field of CRC and in critical appraisal of clinical studies. The Literature Group worked closely with the authors and editors in preparing and conducting systematic reviews of the literature on clinical questions of key importance. Bibliographic searches were conducted for the time period extending from January 2000 to December 2008. Some articles published between 2000 and 2008 and not retrieved by the systematic search were considered to be relevant by the authors. Those references have therefore been included in the body of evidence with the agreement of the editorial board. In addition, articles published after December 2008 that were judged of high relevance by the authors and editors were also included in the Guidelines evidence base.

Preliminary versions of the draft guidelines were repeatedly reviewed and revised through multidisciplinary meetings of the authors, editors and the Literature Group, as well as in pan-European network meetings with participants from all of the EU Member States.

[10] 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 Detection and Prevention, International Agency for Research on Cancer, Lyon, France.

Guideline publication format

The print version of the Guidelines (400 pages) consists of 10 chapters each of which includes a list of key recommendations at the beginning of the chapter. The recommendations are graded according to the strength of the recommendation and the supporting evidence (for scale see below). The respective evidence is also summarised in the body of the chapters, with explicit citation of over 750 references in the Guidelines. In total, over 250 recommendations are provided.

The version of the Guidelines provided on the internet (web version) includes all of the elements in the print version, as well as an extensive Appendix 1 in digital format (1000 pages) with a complete record of the key clinical questions and corresponding bibliographic searches conducted by the Literature Group. The search results are documented in table format, and in summary documents. Altogether summary documents for over 100 clinical questions, and over 500 evidence tables are provided.

The level of evidence and the strength of each of the key recommendations presented in the front of each chapter is indicated using the following grading scales:

For the **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

For the **strength of the respective 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

Images illustrating the chapter on *Quality assurance in pathology in colorectal cancer screening and diagnosis* will be provided on a virtual pathology website at: http://www.virtualpathology.leeds.ac.uk.

Scope of recommendations in the Guideline chapters

The numerous guiding principles, evidence-based recommendations and conclusions presented in the new EU Guidelines for quality assurance in colorectal cancer screening and diagnosis cannot all be presented here. In addition to the key aspects of screening policy and methodology already mentioned above, the following points are highlighted in order to illustrate the scope and depth of the recommendations and conclusions in the first edition.

Chapter 1 - Evidence for the effectiveness of colorectal cancer screening

The first chapter deals with the currently available evidence for the effectiveness of CRC screening, key operational parameters (age-range, interval between two negative screening examinations, or

some combinations of tests) and cost-effectiveness. Among other things, the discussion of the 17 graded recommendations presented in the chapter reveals that the most evidence is available for the primary screening test (FOBT) recommended by the EU.

Chapter 2 - Organisation of colorectal screening programmes

The 29 recommendations and conclusions in Chapter 2 deal with key organisational aspects that influence the quality and effectiveness of CRC screening. There is a broad consensus in the EU on the fundamental principle that a colorectal cancer screening programme is a multidisciplinary undertaking. The effectiveness of the programme is a function of the quality of the individual components of the process.

It is also recognised that the provision of the screening service must account for the values and preferences of individuals as well as the perspectives of public health. The public health perspective in the planning and provision of screening services requires commitment to ensuring equity of access and sustainability of the programme over time. Taking into account the perspective of the individual requires commitment to promoting informed participation and to providing a high quality, safe service.

Successful implementation of a screening programme entails more than simply carrying out the screening tests and referring individuals to assessment whenever indicated. Specific protocols must also be developed for identifying and subsequently inviting the target population. Protocols are also required for patient management in the diagnosis, treatment, and surveillance phases in order to ensure that all individuals have timely access to the proper diagnostic and treatment options.

Irrespective of the organisational approach, it should be recognised that appropriate political and financial support is crucial to the successful implementation of any screening programme.

Chapter 3 - Evaluation and interpretation of screening outcomes

Chapter 3 includes 20 graded recommendations on the processes and procedures required for effective monitoring and evaluation of CRC screening programmes. Of fundamental importance is the complete and accurate recording of all relevant data on each individual and every screening test performed - including the test results, the decisions made as a consequence, diagnostic and treatment procedures and the subsequent outcome, including cause of death.

The chapter also provides an overview of performance measurements currently available from published trial results and population-based screening programmes. Based on this evidence and experience in implementation of population-based screening programmes, the authors and editors were able to reach a consensus on recommended standards of acceptable and desirable performance for a number of parameters. These initial standards, as well as the relevant standards available from other chapters are presented in a table at the end of the Executive Summary. The numbering of the standards is not indicative of importance. As explained elsewhere in the Guidelines, programmes should monitor numerous additional parameters in order to maintain and continuously improve quality. It is hoped that adherence to the other recommendations in the Guidelines will lead to development of a database that permits future expansion and improvement of the current standards.

Chapter 4 - Faecal occult blood testing

Chapter 4 includes 21 detailed and in some cases complex recommendations dealing with design and application of faecal occult blood tests in CRC screening. It is recognised that the ideal biochemical test for population-screening of colorectal cancer would use a biomarker, specific and sensitive for both cancer and pre-cancer, on an easily collected sample, that could be safely and cheaply transported to a centralised laboratory for accurate, reproducible, and inexpensive automated analysis. In addition to these factors which are important for test performance, other key aspects should be taken into account that may influence the acceptability of the test in the target population. These include

the design of the test kit, the instructions provided with the kit and the manner in which it is distributed. Laboratory quality assurance and external quality assessment also play an important role.

Chapter 5 - Quality assurance in endoscopy

Chapter 5 provides a comprehensive view of the many-faceted aspects of quality assurance in endoscopy in its use both for the follow-up of screen-positives as well as for primary screening.[11] The complexity of the relevant issues is reflected by the comparatively large number of specific recommendations dealing with planning and location of endoscopic services, infrastructure and equipment, preparation of the patient and aftercare, endoscopic technique, performance of endoscopists, quality improvement, policies and processes; a total of 50 recommendations.

The organisation of the chapter follows the patient journey to provide an explanation of the relevant issues of quality assurance that can also be used to improve the acceptability of CRC screening. This approach reflects the fundamental consensus of the authors and editors that everyone undergoing endoscopy, whether for primary screening, for assessment of abnormalities detected in screening, for assessment of symptoms, or for surveillance, should have as pleasant an experience as possible. A positive experience will help encourage people to recommend screening, assessment and surveillance to their friends, family and colleagues.

It is also recognised that the screening service must take into account the perspectives of endoscopy as well as public health to ensure that the experience is high-quality, safe and efficient as well as person-oriented. Furthermore, screening should take account of historic developments within different local and cultural contexts.

Although primary screening endoscopy is less complex than follow-up endoscopy (of screen-positives) primarily because of the lower frequency of high-risk lesions in primary screening endoscopy, care must be taken to ensure that the introduction of screening does not compromise endoscopy services for symptomatic patients and that screening and symptomatic (diagnostic) services achieve the same minimum levels of quality and safety. It is also recognised that, wherever possible, the quality assurance required for screening should have an enhancing effect on the quality of endoscopy performed for symptomatic patients and for other reasons. As for the other chapters in these Guidelines, the authors of chapter 5 have emphasised that screening and diagnosis of appropriate quality requires a multidisciplinary approach to diagnosis and management of lesions detected during endoscopy.

Chapter 6 - Professional requirements and training

Chapter 6 provides 23 graded recommendations dealing with the requisite competency of screening staff. As previously mentioned with regard to the other chapters in the Guidelines, the fundamental need for a multidisciplinary approach and hence the need for special training of the multidisciplinary team that is responsible for a colorectal screening programme is recognised.

All staff involved in the delivery of a colorectal cancer screening programme require knowledge of the basic principles of colorectal cancer screening. The need for specialist training in screening differs between the different disciplines and is most important for those involved in the delivery of the service and diagnosis, e.g. laboratory staff, endoscopists, radiologists, pathologists and nurses. The surgical treatment of screen-detected cancer and post-operative treatment is not performed differently according to whether a cancer is screen detected or symptomatic, but there are certain considerations for the surgeon to take into account when treating a screen-detected cancer. Professional requirements of oncologists are not discussed in this chapter because, stage for stage, their role in the treatment of screen-detected disease is no different from that in symptomatic disease.

[11] Note that although endoscopic screening programmes are running in some Member States, the FOBT is the only CRC screening test currently recommended by the EU (Appendix 2).

Chapter 7 - Quality assurance in pathology

The present chapter suggests practical guidelines for pathology within a colorectal screening programme. The pathology service plays a very important role in colorectal cancer screening since the management of participants in the programme depends on the quality and accuracy of the diagnosis. Pathology affects the decision to undergo further local and/or a major resection as well as surveillance after screening. The adoption of formal screening programmes leads to improvement not only in the management of early but also of advanced disease through the introduction of guidelines, quality standards, external quality assurance and audit. In screening programmes, the performance of individuals and programmes must be assessed and it is advantageous if common diagnostic standards are developed to ensure quality, recognise areas where sufficient evidence is still lacking, and initiate high-quality studies to gather the evidence required.

Chapter 7 includes 23 graded recommendations concentrating on the areas of clinical importance (Quirke et al. 2010). It is hoped that these recommendations will also help to standardise quality and performance across the European Union. The associated annex deals with some of the more difficult areas and suggests topics for future research (Vieth et al. 2010). Guidelines for the reporting and management of resected specimens have been included in an attempt to move towards agreed minimum European standards of pathology in these areas as well. This is the first edition of what will be a continuing process of revision as new data emerge on the pathology, screening and management of colorectal cancer. It is also hoped that by setting minimum standards, these will be followed in all programmes and that this will encourage the development of higher standards amongst the pathology community and screening programmes.

Chapter 8 - Management of lesions detected in colorectal cancer screening

The inclusion of a chapter with 32 graded recommendations on management of lesions detected in CRC screening recognises that reduction in CRC mortality is the main endpoint of any CRC screening programme. It is also recognised that all screening modalities will detect substantial numbers of individuals with adenomas (Levin et al. 2008) as well as a lesser number of lesions in the serrated pathway, some of which should be treated as adenomas (see Ch. 7). As adenomas are recognised to be pre-malignant (Leslie et al. 2002) screening has the potential to reduce the incidence of the disease if these lesions are adequately managed. To achieve the dual aims of mortality and incidence reduction it is essential that all the elements of the screening service achieve and maintain high levels of quality. The screening process can only be successful if it is followed by timely and appropriate management of screen-detected lesions.

In essence, the management of screen-detected adenomas and carcinomas does not differ, stage for stage, from that required for symptomatic disease. However, screening detects a different spectrum of disease compared with that diagnosed in the symptomatic population (i.e. higher proportion of early disease). Thus, there are some considerations in the management of screen-detected disease that should be emphasised. In this Chapter of the Guidelines the management of endoscopically detected pre-malignant lesions, pT1 cancers, as well as colon cancer and rectal cancer which is not limited to the submucosa are dealt with separately and discussion is focused on issues pertinent to screening. For these reasons, adjuvant chemotherapy and the management of advanced disease are not discussed.

Of prime general importance is the wide consensus that colorectal neoplasia is best managed by a multi-disciplinary team. The relevant disciplines include: surgery, endoscopy, pathology, radiology, radiotherapy, medical oncology, specialist nursing, genetics and palliative care (SIGN 2003), which should work in close collaboration with primary care. Furthermore, it is recognised that the interval between the diagnosis of screen-detected disease and the start of definitive management is a time of anxiety for the patient and affords the opportunity, if prolonged, for disease progression. For these reasons, standards have been set which aim at minimising delay (NHS 2007). Also of relevance in this regard is the recognition that colonoscopy is not merely a diagnostic procedure, but has therapeutic

capacity (Cotton & Williams 1996), and it is essential that the endoscopist carrying out screening colonoscopy has the necessary expertise to remove all but the most demanding lesions (see also Chapter 5).

Chapter 9 - Colonoscopic surveillance following adenoma removal

Chapter 9 includes 24 graded recommendations and a comprehensive strategy for surveillance after removal of adenomas in people taking part in screening programmes in any Member State. The recommendations in the EU Guidelines recognise that people with previous adenomas are at increased risk for recurrent adenomas and thus eventually colorectal cancer (Atkin, Morson & Cuzick 1992). The risk depends mainly on findings during baseline colonoscopy, in particular the number, size and histological grade of removed adenomas. This allows categorisation of patients into different risk groups. The indication and interval for surveillance is determined primarily by the presumed risk for recurrence of advanced adenomas and cancer, and secondarily by age, co-morbidity, and patient wishes.

The primary aims of colonoscopic surveillance are to reduce the morbidity and mortality from colorectal cancer by removing high risk adenomas before they have had a chance to become malignant, and by detecting invasive cancers at an early, curable, stage. It must be kept in mind however, that colonoscopy is a costly, invasive and scarce resource. Therefore, colonoscopy surveillance should be undertaken only in people at increased risk, and at a minimum frequency required to provide adequate protection against the development of cancer. If colonoscopy surveillance is undertaken, it should be performed to the highest standard.

Because surveillance colonoscopy consumes considerable endoscopic resources it may prevent a country that has difficulty meeting demand from sustaining reasonable waiting times. Screening programmes should therefore have a policy on surveillance with a hierarchy of action for different risk groups based on resource availability. The policy may limit surveillance to the high risk group if sufficient resources are not available to include people with lower risk.

Chapter 10 - Communication

Chapter 10 provides 35 recommendations dealing with communication in CRC screening. The large body of guidance reflects the essential goal of CRC screening programmes which is to reduce the burden of illness and death due to colorectal cancer. Screening programmes can only be successful if they ensure that as many people in the target population as possible receive the relevant information to be able to make informed decisions about whether or not they wish to attend CRC screening. As adverse effects are intrinsic to screening practice, participants should understand that a balance exists between benefits and harms associated with CRC screening (Holland, Stewart & Masseria 2006). A key component of CRC screening programmes, therefore, is the information and education provided about CRC, and CRC screening tests and procedures.

The recommendations in the EU Guidelines reflect the wide consensus that people who use CRC screening services should receive accurate and accessible information that reflects the most current evidence about the CRC screening test and its potential contributions to reducing illness as well as information about its risks and limitations. Achieving this goal is challenging, due to the complexity of CRC screening programmes compared to other established programmes such as screening for breast or cervical cancer. In CRC screening multiple tests are currently in use (FOBT in most, as well as flexible sigmoidoscopy (FS) and colonoscopy in some Member States). Furthermore, some screening tests are invasive, and have known adverse effects. Finally, some CRC screening procedures are generally undertaken without supervision from a healthcare professional (FOBT screening test and bowel cleansing procedure in preparation for follow-up colonoscopy or endoscopy screening). Therefore specific instructions on how to use the FOBT kit or perform the bowel cleansing procedure need to be communicated to the patient.

The recommendations in the chapter on Communication have therefore been developed to give people involved in providing and/or managing CRC screening (e.g. managers, decision-makers, health professionals etc.) an insight into the complexity of communication in CRC screening and its related critical issues. Pragmatic recommendations are also provided on information strategies/tools/interventions that can be used in current or future programmes. These recommendations mainly refer to an organised (and centralised) CRC screening programme, as this represents the gold standard to achieve (see Chapters 1 and 2). In the Communication chapter, the authors specifically provide guidance for screening programmes based on the primary screening test recommended by the EU, the faecal occult blood test (FOBT, see Chapter 4) which is also the most frequently used test in programmes implemented by the Member States. Most of the recommendations can be applied to endoscopy programmes as well.

Performance standards

The following Summary Table presents the performance standards in the first edition of these Guidelines. The numbering is not indicative of importance; more complete information regarding definition and context is provided in the sections indicated. As explained in the Guidelines, programmes should monitor numerous additional parameters in order to maintain and continuously improve quality. The standards listed in the present Summary Table are based on an overview of performance measurements currently available from published trial results and population-based screening programmes (see Chapter 3). In light of this evidence and experience in implementation of population based screening programmes, the authors and editors of the current version of the Guidelines were able to reach a consensus on the recommended targets across the EU. On occasions we have had to accept that different disciplines and different Member States show some variation of priorities and target levels. In all cases we have attempted to list what we regard as the most generally appropriate professionally agreed levels for usage in a pan-European setting. In any case, all targets should be constantly reviewed in the light of experience and revised accordingly with regard to results achieved and best clinical practice. As far as possible, targets given refer to men and women aged 50–74 years invited to and/or attending a CRC screening programme.

Summary Table of performance standards in colorectal cancer screening

	Indicator[1]	Acceptable level	Desirable level
1	Invitation coverage **Rec 3.7; Sect 3.3.1**	95%	>95%
2	Uptake rate **Rec 3.8; Sect 3.3.1**	>45%	>65%
3	Rate of inadequate FOBT **Rec 3.9; 4.21; Sect 3.3.2; 4.3.4**	<3%	<1%
4	Maximum time between test and receipt of result should be 15 days **Rec 3.15; Sect 3.3.4**	>90%	
5	Rate of referral to follow-up colonoscopy after positive test **Rec 3.10; Sect 3.3.2, 3.3.3**	90%	>95%
6	Maximum time between referral after positive screening (any modality) and follow-up colonoscopy should be 31 days **Rec 3.16, 5.19; Sect 3.3.4, 5.3.5**	>90%	>95%
7	Compliance with follow-up colonoscopy after positive FS **Rec 3.14; Sect 3.3.2, 3.3.3**	85%	>90%
8	Rate of complete colonoscopies. Follow-up and screening colonoscopies to be recorded separately **Rec 3.11; Rec 5.41, Sect 3.3.2, 3.3.3, 5.4.5.1**	>90%	>95%
9	Time interval between positive colonoscopy/FS and definitive management should be within 31 days **Rec 3.17, 8.2; Sect 3.3.4, 8.2**	>95%	
10	Endoscopists participating in a CRC screening programme should perform a minimum no. of procedures per year **Rec 5.38; Sect 5.4.5.1**	300	>300
11	Biopsies and lesions identified in the screening programme and the subsequent resection specimen should be reported on a proforma **Rec 7.11; Sect 7.6.5.2, 7.8**	>90%	
12	Rate of high-grade neoplasia reported by pathologists in a colonoscopy screening programme **Rec 7.21; Sect 7.7**	<5%	
13	Rate of high-grade neoplasia reported by pathologists in a FOBT screening programme **Rec 7.21; Sect 7.7**	<10%	

[1] **Sect** (superscript) refers to the section/s of the Guidelines dealing with the respective indicator.

Rec (superscript) refers to the number of the corresponding recommendation in the Guidelines.

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Principles of evidence assessment and methods for reaching recommendations

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Introduction

The evidence-based process for development of the recommendations in the first edition of the European Guidelines for quality assurance in colorectal cancer screening and diagnosis was established at the outset of the project in 2006 by an editorial board with extensive experience in development of best practice guidelines, in evaluation of strategies for colorectal cancer (CRC) screening and in programme management. In 2007 the editorial board drafted an initial comprehensive outline of the Guidelines and recruited a multidisciplinary group of experts in colorectal cancer screening and diagnosis across the European Union to collaborate in revising the outline and drafting the chapters, including guiding principles and recommendations. Additional scientific support was provided by a Literature Group consisting of epidemiologists with special expertise in the field of CRC and in performing systematic literature reviews.

The expert Literature Group provided technical and scientific support to the authors and editors in searching the relevant literature, assessing the methodological quality of retrieved studies, defining a grading system of the level of evidence and strength of the recommendations, and preparing evidence tables and summary documents for over 500 references identified through systematic reviews of the literature according to the priorities and procedures agreed with the editorial board and the authors.

The Literature Group was coordinated by N. Segnan at the Unit of Cancer Epidemiology, Department of Oncology of the Piedmont Centre for Cancer Prevention (CPO Piemonte) and S. Giovanni University Hospital, Turin, Italy, and was lead by S. Minozzi at the same institution. Other members of the Literature Group were based at the CPO in Turin and at the Oxford University Cancer Screening Research Unit, Cancer Epidemiology Unit, Oxford, United Kingdom. Additional scientific and technical support was provided by the International Agency for Research on Cancer, Quality Assurance Group, Section of Early Detection and Prevention, Lyon, France.

The principles of evidence assessment and the methods for developing the recommendations presented in the Guidelines are described below. The contribution of the Literature Group was crucial to the feasibility of this resource-intensive process. In addition to the above-mentioned activities, it included assistance to the chapter authors in defining relevant clinical questions of key importance.

The clinical questions for which evidence was collected by the Literature Group and the results of the literature search and analysis conducted by the group are presented in Appendix 1 to the Guidelines. The appendix is only available in electronic format, due to the extensive size of the records that correspond to approximately 1 000 printed pages.

The editors of the first edition of the Guidelines hope that this approach will promote regular updating of the evidence-based Guidelines and that resources will be available in the future to expand the current evidence base and the respective documentation, as well as to improve the methods that have been followed.

Definition of clinical questions

In multidisciplinary workshops conducted in 2007 and 2008 the chapter authors met with the editorial board and the Literature Group. At these meetings, the table of contents of the Guidelines was repeatedly revised and the methodology of evidence-based guideline development, including the process of identifying and evaluating the relevant evidence for each chapter based on the topics in the revised outline was agreed with the authors. Subgroups of authors responsible for each chapter also worked individually with members of the Literature Group to develop clinically relevant questions based on the revised chapter outlines, and the results for each chapter were subsequently discussed with the entire group of authors and editors and the Literature Group in plenary workshop sessions in order to ensure a common methodological approach and to reach a consensus on questions of key

importance requiring the support of the Literature Group in order to identify and assess the relevant evidence. This collaborative, multidisciplinary approach remained a guiding principle throughout the entire process up to completion of drafting and editing of the Guideline chapters.

The clinical questions initially formulated by the authors of each chapter and subsequently agreed with the editorial board and the other authors were developed according to the PICOS method (Greenhalgh 1997; O'Connor, Green & Higgins 2008; Richardson et al. 1995) modified slightly to take into account the aim of screening to lower the burden of the disease in the population:

P: **patients/population** characteristics

I: experimental **intervention** on which the question is focused

C: **comparison** intervention / control /reference group

O: **outcome** measure relevant for the clinical question

S: **study** design on which to base the evidence search

The extensive list of initial clinical questions was reduced to a feasible number, by prioritising questions of key importance for each chapter. In total, 113 clinical questions were prioritised. The PICOS components of each prioritised question were subsequently used by the Literature Group to define specific key words that were then employed in comprehensive bibliographic searches. The results of these activities were reported back to the authors and editors in subsequent workshops and electronically. This enabled the editors and authors to provide continuous professional and scientific support to the process of identifying and analysing the relevant evidence.

Bibliographic review

The Literature Group performed bibliographic searches on Medline, Embase, and the Cochrane library databases from January 2000 to December 2008 using mesh terms and free text words. Searches were conducted without date restrictions if the authors or editors who were experts in the field knew that there were relevant articles published before 2000. Published articles suggested by the authors and not retrieved by a systematic search, were also considered. 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 research is growing rapidly, high quality and updated systematic reviews, and large trials that make a significant contribution to the robustness of the results or allow upgrading of the level of evidence.

Inclusion criteria

The inclusion criteria applied by the Literature Group were based on the highest level of available evidence, taking into account study design. For primary studies, for each kind of question (e.g., effectiveness, diagnostic accuracy, acceptability and compliance) a hierarchy of the study designs and inclusion/exclusion criteria was developed by the epidemiologists in the Literature Group. For example, for effectiveness studies randomised controlled trials (RCT) were initially searched for. If RCTs were

retrieved, no other types of study design were considered. If no, or only a few and/or small RCTs were retrieved, quasi-experimental studies were considered. If no quasi-experimental studies were found, prospective or retrospective cohort and case-control studies were considered. If studies with none of the above designs were retrieved, cross-sectional studies and case series were included. For diagnostic accuracy questions, cross-sectional studies with verification by reference standard were considered as the best source of evidence.

Quality assessment

The methodological quality of the publications retrieved by the Literature Group was assessed using the following criteria obtained from published and validated check lists.

Systematic reviews - quorum checklist

A validated checklist for evaluating the manner in which systematic reviews have been conducted was not available when the methods for the present EU Guidelines were established. Therefore the QUOROM checklist that assesses the quality of reporting was used as a proxy to assess the methodological quality of systematic reviews. This approach reflects the view that the quality of reporting can be used as a criterion for the quality of the process of preparing a systematic review (Moher et al. 1999).

Randomised Controlled Trials

Randomised controlled trials were assessed using the following criteria suggested in the Cochrane Handbook {Higgins, 2008 754 /id} and by the Cochrane Effective Practice and Organisation of Care Review Group {EPOC, 2002 755 /id}:

- Unit of allocation (i.e. who or what was allocated to study groups: individuals or clusters);
- Unit of analysis (i.e. results analysed as events at the level of individuals or clusters);
- If unit of allocation and unit of analysis differ, was cluster analysis performed?
- Protection against selection bias (adequate sequence generation and allocation concealment);
- Protection against performance bias (blinding of providers);
- Protection against contamination (blinding of participants);
- Protection against attrition bias (intention to treat analysis, few lost at follow up balanced between groups); and
- Protection against detection bias (blinding of participants and outcome assessors).

Observational studies: cohort studies and case control studies

Observational studies were evaluated using the following criteria of the Newcastle-Ottawa Scale (for recent overview see: (Wells et al. 2010)

- Case control studies:
    - Adequate definition of the cases;
    - Representativeness of the cases;
    - Selection source of controls;
    - Definition of controls;
    - Comparability of cases and controls on the basis of the design or analysis;
    - Method of exposure assessment;

  - Same method of ascertainment for cases and controls;
  - Non-Response rate.
- Cohort studies:
  - Representativeness of the exposed cohort;
  - Selection source of the non-exposed cohort;
  - Method of exposure assessment;
  - Demonstration that outcome of interest was not present at start of study;
  - Comparability of cohorts on the basis of the design or analysis;
  - Method outcome assessment;
  - Adequacy of follow up of cohorts.

Interrupted time series studies

Studies based on interrupted time series were assessed using the following criteria suggested by the Cochrane Effective Practice and Organisation of Care Review Group (EPOC 2002):

- Clearly defined point in time when the intervention occurred.
  - A: Intervention occurred at a clearly defined point in time;
  - B: NOT CLEAR because not reported in the paper;
  - C: Intervention did not occur at a clearly defined point in time.
- At least three data points before and three after the intervention.
  - A: Three or more data points before and three or more data points recorded after the intervention;
  - B: NOT CLEAR because not reported in the paper;
  - C: Less than three data points recorded before, and less than three data points recorded after intervention.
- Protection against secular changes (the intervention is independent of other changes).
  - A: Intervention occurred independently of other changes over time;
  - B: NOT CLEAR because not reported in the paper;
  - C: Intervention was not independent of other changes over time.
- Protection against detection bias (intervention unlikely to affect data collection).
  - A: Intervention unlikely to affect data collection (for example, sources and methods of data collection were the same before and after the intervention);
  - B: NOT CLEAR because not reported in the paper;
  - C: Intervention likely to affect data collection (for example, any change in source or method of data collection before vs. after the intervention).
- Blinded assessment of primary outcome(s).
  - A: Explicit statement of authors that the primary outcome variables were assessed blindly OR the outcome variables are objective e.g. length of hospital stay, drug levels as assessed by a standardised test;
  - B: NOT CLEAR if not specified;
  - C: Outcomes were not assessed blindly.

- Completeness of data set.
  - A: Data set covers 80-100% of total number of participants or episodes of care in the study;
  - B: NOT CLEAR if not specified;
  - C: Data set covers less than 80% of the total number of participants or episodes of care in the study.

Diagnostic accuracy studies

The criteria used to evaluate diagnostic accuracy studies were obtained from the QUADAS checklist (Whiting et al. 2003):

- Study design: diagnostic cross-sectional studies with prospective or retrospective recruitment; case control;
- Spectrum of patients representative of the individuals who will receive the test in practice;
- Patients selection criteria clearly described;
- Verification by reference standard of all or a randomised sample of subjects (absence of verification bias);
- Execution of the index and comparator tests adequately described;
- Execution of the reference standard adequately described;
- Independent and blind interpretation of index test and reference standard results;
- Un-interpretable /intermediate test results reported;
- Withdrawals from the study explained.

Clinical guidelines

The quality of clinical guidelines evaluated by the Literature Group was assessed using the following most relevant criteria derived from the COGS checklist (Shiffman et al. 2003):

- Description of the clinical specialisation of the members of the panel of guideline authors;
- Search strategy described (databases, years covered, any language restriction);
- Inclusion criteria of primary studies stated;
- Method used to analyse and synthesise the evidence and to reach the consensus among the panellists to elaborate the recommendation described;
- Presence of a grading of level of evidence and/or of the strength of the recommendation; and
- Presence of a complete reference list.

Evidence tables and summary documents

The Literature Group prepared the following documents based on the publications retrieved for each clinical question or group of clinical questions. The documents were subsequently used by the authors in drafting respective chapters:

- An evidence table for each retrieved study with the main characteristics of the study (study design, objective of the study, comparisons, participant's characteristics, outcome measures, results, methodological quality, level of evidence);
- A summary document with a synthesis of the number, types and characteristics of the retrieved studies, their overall methodological quality, a description of the main methodological flaws, the study results and the conclusions and the overall level of evidence.

Evidence tables were not prepared for: additional publications cited in the background sections of the chapters; pathological and clinical classifications; technical instructions; narrative reviews; editorials and personal communications; and articles published before 2000 and cited by the authors after the systematic search of the literature.

Some articles published between 2000 and 2008 and not retrieved by the systematic search were considered to be relevant by the authors. Those references have therefore been included in the body of evidence in agreement with the editorial board. For these articles, evidence tables were prepared after December 2009, but the respective results were not included in the summary documents.

The above documents, together with the clinical questions and respective bibliographic literature searches for each chapter, are documented in Appendix 1.

Grading system

The key recommendations presented in each chapter of the Guidelines are listed at the front of the respective chapter together with a grading of the evidence on which each recommendation is based, and the strength of the recommendation. Only the highest level of evidence supporting a recommendation is reported. The following grading scales are used:

Level of the 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 the recommendations

The strength of recommendations was graded according to the following scale:

- **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

The strength of each key recommendation was determined by the authors of each chapter in agreement with the Guidelines editorial board.

Following the list of key recommendations at the beginning of each chapter, the rationale and the evidence on which the recommendations are based is summarised in the body of the chapter, including the respective levels of evidence.

In a number of chapters, in addition to the key recommendations, fundamental statements (Guiding Principles) defining the aims and scope of the recommendations presented in the chapter are provided at the front of the text. Most of the Guiding Principles are considered to be self-evident. All reflect the

consensus of the authors and editors on essential principles of best practice in screening and diagnosis of colorectal cancer. In addition to these principles, additional advisory statements are made in the body of the chapters that are not specifically graded. These statements also represent the consensus of the authors and editors on best practice.

Correspondence between level of evidence and strength of recommendation

This present grading of the strength of recommendations did not require a rigid correspondence with the levels of evidence. For example grade **A** was given to interventions for which there was evidence level **I** (multiple RCTs or SR of RCTs) but also to interventions that could not be assessed by RCTs, (e.g. psychological aspects, the importance of an accurate information to the patients, etc). Grade **B** was given to interventions with lower evidence level (**II** or **III**) but also for interventions with evidence level **I** but with uncertainty about their impact in the population or about practical implementation (e.g. lack of resources for implementation, social barriers, supposed lack of acceptability by the target population). Grade **C** level was given to interventions for which evidence was not available or was of low grade (i.e. **IV**, **V**) or that may not have been considered of high importance for other reasons (i.e. psychological or social aspects). Grades **D** and **E** were assigned to interventions for which there was evidence of no benefit for participants, or for which the harm outweighed the benefits.

Table 1 Correspondence between level of evidence and strength of recommendations

		Strength of recommendation				
Levels of evidence		A	B	C	D	E
	I	C	C		C	C
	II	Nc	C		C	C
	III	Nc	C	C	C	Nc
	IV	Nc	Nc	C	Nc	Nc
	V	Nc	Nc	C	Nc	Nc
	VI	Nc	Nc	C	Nc	Nc

C: Coherence between the level of evidence and the strength of recommendations

Nc: No coherence between the level of evidence and the strength of recommendations

Method of obtaining consensus between the chapter authors and editors and the internal peer review

Each subgroup of authors responsible for a chapter received all the evidence tables and summary documents relating to the respective clinical questions. The authors drafted each chapter by describing the relevant issues, summarising the evidence, and including recommendations and conclusions. The authors also proposed a grading for the strength of the evidence and the strength of the respective recommendations, based on the results of the literature search and on their clinical experience, as well as any additional pertinent scientific literature that was taken into account with agreement from the editorial board. The draft chapters and the proposed strength of each recommendation were discussed with the editorial board and the authors of all chapters to reach consensus.

External peer review

Chapter drafts were subsequently sent to international experts in their respective fields for external peer review. They were also made available for web consultation with restricted access by experts involved in screening programmes. Comments and criticisms were considered and a final version of the chapters was elaborated. Preliminary and nearly final versions of the Guidelines chapters were prepared and discussed at pan-European network meetings of screening experts, clinicians, advocates, healthcare planners and regulators from all of the EU member states and two EU applicant countries in 2008 and 2009.

Final editing

During 2010, final changes resulting from the network discussion in November 2009 were taken into account by the authors of respective chapters. The consistency of the recommendations between the individual chapters was reviewed by the editorial board and corrections were made where necessary.

The editors recognise that the approach to collection of the relevant evidence adopted for the Guidelines may have permitted introduction of bias if the authors or editors were not aware of significant publications after December 2008 because the systematic searches performed by the Literature Group were limited to this date. However, the relevant publications of studies published after 2008 that have been cited by the authors to justify recommendations have been evaluated by the Literature Group and respective evidence tables are included in Appendix 1. In view of the qualifications and experience of the authors and editors and the transparency of the process of guideline development, the editors have concluded that further efforts to limit this potential bias would have little or no impact on the content of the final recommendations. As mentioned in the introduction, the editors hope that the approach to evidence-based guideline development adopted for the first edition of the European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis will promote systematic discussion of the evidence base for the Guidelines and that resources will be available in the future to continuously update and expand the current evidence base and the respective documentation.

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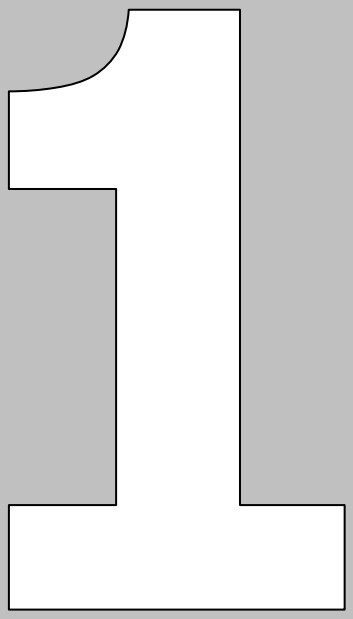

Introduction

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The comments and suggestions received from consultation of the European Cancer Network are gratefully acknowledged.

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 (Wilson & Jungner 1968). 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.
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 conclusions[1]

Guaiac 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, 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.

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 Background

1.1.1 Colorectal cancer in Europe

Colorectal cancer (CRC) is an important health problem in Europe. Each year approximately 435 000 people are newly diagnosed with CRC (Ferlay, Parkin & Steliarova-Foucher 2010). 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 (von Karsa et al. 2010).

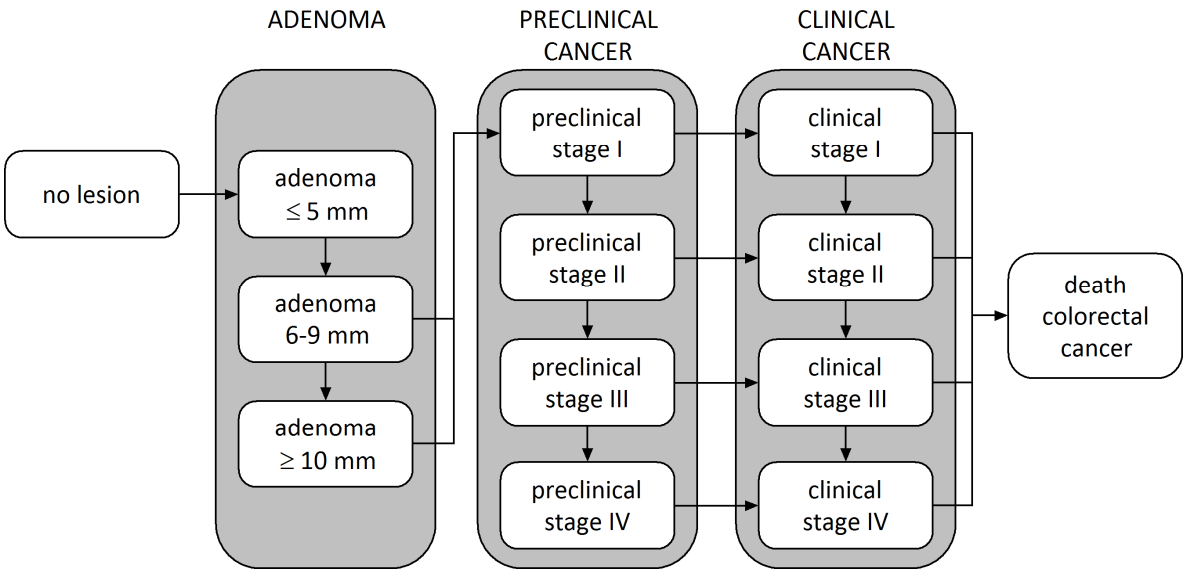
Table 1.1: Age-standardised (Europe) incidence and mortality rates for colorectal cancer by country and gender, rate per 100 000 in 2008 (data source: Ferlay, Parkin & Steliarova-Foucher 2010)

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

1.1.2 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 (Figure 1.1) (Muto, Bussey & Morson 1975; Morson 1984). 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 (Hofstad 2003). 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 (Hofstad 2003), but the majority of these adenomas will never develop into CRC. Only 5–6% of the population actually develop CRC (Jemal et al. 2008). The average duration of the development of an adenoma to CRC is unobserved, but is estimated to take at least 10 years (Winawer et al. 1997). This long latent phase provides an excellent window of opportunity for early detection of the disease.

Figure 1.1: Schematic overview of the adenoma-carcinoma sequence.

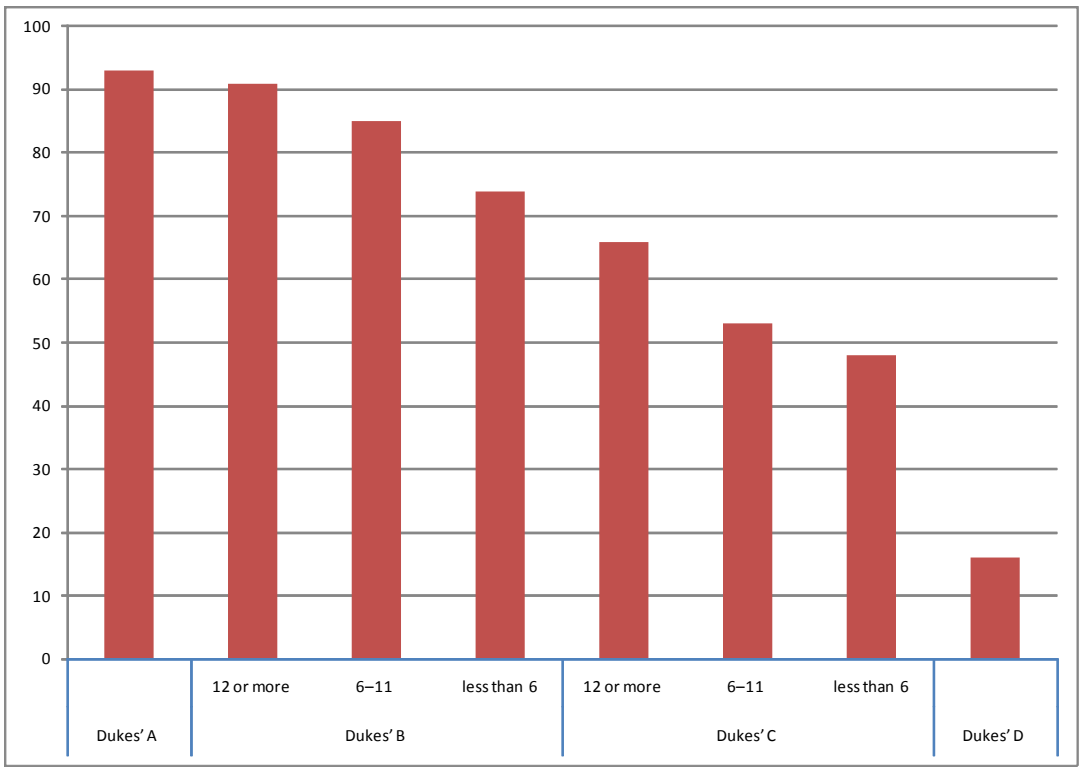


When detected in the adenoma-phase, removal of the adenoma can prevent the incidence of CRC (Winawer et al. 1993). But even when detected as an early-stage cancer, prognosis is considerably better than for late-stage cancer (Ciccolallo et al. 2005) as can be seen in Figure 1.2. Several screening tests 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 indi-

Figure 1.2: Three-year CRC survival by stage and number of lymph nodes examined, for countries in the Eurocare study (data source: Ciccolallo et al. 2005).



vidual and/or the community (Wilson & Jungner 1968). 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 (Wilson & Jungner 1968). 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 (Hanselaar 2002):

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 (Council of the European Union 2003) (see also Appendix 2). 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). This introductory chapter presents the evidence which 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 which 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 (European Commission 1996; European Commission 2001; European Commission 2006; von Karsa et al. 2008; European Commission 2008; Perry et al. 2008; Arbyn et al. 2010).

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 (von Karsa et al. 2010).

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 (Council of the European Union 2003) (Appendix 2). 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 (von Karsa et al. 2008).

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 (European Parliament 2004; European Parliament 2006; European Parliament 2008). 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 (Council of the European Union 2008; Council of the European Union 2010). 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 (European Commission 2009).

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 (Hanselaar 2002; Giordano et al. 2006; Giordano et al. 2008; von Karsa 1995; von Karsa et al. 2010) (see also Chapter 10).

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, Appendix 2). 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, Appendix 2).

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 which 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 (von Karsa et al. 2008; Commission of the European Communities 2008) (see Appendix 3). 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 nationwide population-based programme (Hungary, Cyprus, Portugal, 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, ten Member States have established or upgraded the status of their CRC screening programmes (Czech Republic, France, Ireland, Lithuania, Portugal, Slovak Republic, Slovenia, Spain, Sweden and the United Kingdom). In addition Denmark and the Netherlands are currently in the decision process for implementing a CRC screening programme.

[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)).

As mentioned above, the current EU screening policy only recommends faecal occult blood testing for population-based screening (Council of the European Union 2003) (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 (Hardcastle et al. 1996; Kronborg et al. 1996; Mandel et al. 1999; Lindholm, Brevinge & Haglind 2008).

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).

1.2.1 Guaiac FOBT[3]

1.2.1.1 Evidence for efficacy

Three systematic reviews have evaluated the evidence for the efficacy of gFOBT screening (Heresbach et al. 2006; Hewitson et al. 2007; Kerr et al. 2007). The reviews all included the RCTs of Minnesota, Nottingham and Funen which compare gFOBT screening with no screening (Mandel et al. 1993; Hardcastle et al. 1996; Kronborg et al. 1996). In addition, the Cochrane review by Hewitson also included the then-unpublished results of the Goteborg study (Lindholm, Brevinge & Haglind 2008), whereas the Heresbach review also included the block-randomised trial from Burgundy (Faivre et al. 2004). 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 (Hewitson et al. 2007).

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 (Heresbach et al. 2006).

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 (Mandel et al. 1993). After 13 years of follow-up, a statistically significant

[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. 1.14 and Appendix 2).

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 significant 15% and 18% mortality reductions, respectively, with biennial screening (Hardcastle et al. 1996; Kronborg et al. 1996). 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% (Mandel et al. 1999).

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 (Mandel et al. 1993; Hardcastle et al. 1996; Kronborg et al. 1996; Lindholm, Brevinge & Haglind 2008). 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 (Scholefield et al. 2002).

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 (Hewitson et al. 2007). 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.

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

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

Per 10 000 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 unrehydrated 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 unrehydrated gFOBT, the risks of adverse effects are limited **(I)**.

A systematic review (Pignone et al. 2002a) 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$ 5 691 to US$ 17 805 per life-year gained (Pignone et al. 2002a). 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 (Lejeune et al. 2004; Whynes 2004). The first one estimated the cost-effectiveness of biennial FOBT screening over up to five screening rounds within the Nottingham trial (Whynes 2004). The cost of screening was US$ 8 300 (£ 5 290) per cancer detected (at 2002 prices). Under conservative assumptions, the incremental cost per life year gained as a result of screening was US$ 2 500 (£ 1 584). 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 (Lejeune et al. 2004). Incremental costs per life-year gained of screening over no screening were US$ 4 600 (€ 3 375) and US$ 6 400 (€ 4 705) 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 FOBT[4]

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 mortal-

[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 Appendix 2).

ity (Zheng et al. 2003). 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 (Saito et al. 1995; Saito et al. 2000; Nakajima et al. 2003). 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.

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 (Winawer et al. 1997). This evidence is available for iFOBT: there have been 13 population-based screening studies comparing performance characteristics of gFOBT and iFOBT (Allison et al. 1996; Castiglione et al. 1996; Rozen, Knaani & Samuel 2000; Zappa et al. 2001; Ko, Dominitz & Nguyen 2003; Wong et al. 2003; Hughes et al. 2005; Hoepffner et al. 2006; Smith et al. 2006; Allison et al. 2007; Guittet et al. 2007; Dancourt et al. 2008; van Rossum et al. 2008). 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, 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 (Segnan et al. 2005; Segnan et al. 2007) and in the NORCCAP trial (Gondal et al. 2003) had a positive iFOBT without adenomas or CRC detected at subsequent diagnostic colonoscopy. In the NORCCAP study, six perforations were reported after colonoscopy (Gondal et al. 2003). 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 1 000 colonoscopies (Gondal et al. 2003).

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 (Berchi et al. 2004; Li et al. 2006; Parekh, Fendrick & Ladabaum 2008). Two studies concluded that iFOBT screening was at least as effective as gFOBT screening, but less costly (Li et al. 2006; Parekh, Fendrick & Ladabaum 2008). In the third analysis, the use of iFOBT for 20 years of biennial screening cost € 59 more than gFOBT per target 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$ 4 100 (€ 2 980) 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 Sigmoidoscopy[5]

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 (Atkin et al. 2010). 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 (Thiis-Evensen et al. 1999; Hoff et al. 2009). 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

[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 Appendix 2).

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 (Prorok et al. 2000; Segnan et al. 2002).

Table 1.3: CRC Incidence and mortality reduction from three randomised controlled trials on sigmoidoscopy screening

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

* significant - not reported

In addition, three case-control studies of good methodological quality have been published. In these studies, sigmoidoscopy was compared with no screening (Newcomb et al. 1992; Selby et al. 1992; Muller & Sonnenberg 1995) 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 (Kavanagh et al. 1998).

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 (Platell, Philpott & Olynyk 2002; Schoen et al. 2003). 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, (Schoen et al. 2003) and 50% lower 5 years after a negative examination (Platell, Philpott & Olynyk 2002). 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 (Atkin et al. 2010), suggesting that the inter-

val 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)

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 (Segnan et al. 2007). 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 (Atkin et al. 2010).

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 (Pabby et al. 2005). 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, (Pignone et al. 2002a). 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$ 7 407–US$ 23 830) (Song, Fendrick & Ladabaum 2004; Pickhardt et al. 2007; Vijan et al. 2007). A recent study based in England also estimated that sigmoidoscopy screening could be cost-saving (Tappenden et al. 2007).

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]

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

	SCORE (Segnan et al. 2002)	**SCORE 2** (Segnan et al. 2005)	**UK FS trial** (UK Flexible Sigmoidoscopy Screening Trial Investigators 2002)	**NORCCAP** (Gondal et al. 2003)
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%

1.3.2 Colonoscopy[6]

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 (Pignone et al. 2002b; Walsh & Terdiman 2003) 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 (Winawer et al. 1993). 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 (Kahi et al. 2009). Two recent case–control studies also found a significant reduction of 31% in CRC mortality (Baxter et al. 2009) and 48% in advanced neoplasia detection rates (Brenner et al. 2010). 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 (Walsh & Terdiman 2003).

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.

[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 Appendix 2).

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 (Singh et al. 2006). Similar results were obtained in the case–control study (Brenner et al. 2006): 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% (Rex et al. 1996; Huang et al. 2001; Ee, Semmens & Hoffman 2002; Yamaji et al. 2004; Lieberman et al. 2007).

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 between 55 and 64 (Segnan et al. 2007). 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 (Imperiale et al. 2002; Rundle et al. 2008). 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 (Rundle et al. 2008). 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), (Imperiale et al. 2002). A German case–control analysis assessed the possible impact of colonoscopic screening history in different age groups (Brenner et al. 2005). 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 (Pabby et al. 2005).

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) (Lieberman et al. 2000; Schoenfeld et al. 2005; Regula et al. 2006; Kim et al. 2007; Rainis et al. 2007). 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$ 9 038 to US$ 22 012 per life-year gained. Recent studies found similar ratios (US$ 8 090–US$ 20 172) (Ladabaum et al. 2001; Song, Fendrick & Ladabaum 2004; Pickhardt et al. 2007; Vijan et al. 2007). One recent study in Germany estimated that a once-only colonoscopy screening could be cost-saving compared to no screening (Sieg & Brenner 2007).

All cost-effectiveness analyses show that the cost-effectiveness of colonoscopy screening is below the commonly used threshold of US$ 50 000 per life-year gained **(III).**[Rec 1.15]

Table 1.5: Complication rates with screening colonoscopies

	Lieberman et al. 2000	Regula et al. 2006	Schoenfeld et al. 2005	Rainis et al. 2007	Kim et al. 2007
Severe complications	0.3%	0.1%	0%	0.08%	0%

1.4 Evidence for effectiveness of FOBT and sigmoidoscopy combined[7]

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 (Hoff et al. 2009).

Four studies reported diagnostic yield with a combination of once-only sigmoidoscopy and once-only FOBT, compared to FOBT and/or sigmoidoscopy alone (Rasmussen et al. 1999; Lieberman & Weiss 2001; Gondal et al. 2003; Rasmussen, Fenger & Kronborg 2003; Segnan et al. 2005). 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 (Rasmussen, Fenger & Kronborg 2003). 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.

[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 Appendix 2).

Two studies evaluated the effect of offering combined once-in-a-lifetime testing on screening compliance (Gondal et al. 2003; Segnan et al. 2005). While one study showed a significantly lower compliance with the combination of sigmoidoscopy and FOBT compared to FOBT alone (Segnan et al. 2005) the other did not find a difference between the combination, and sigmoidoscopy alone (Gondal et al. 2003).

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 evaluation[8]

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 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 (Sosna et al. 2003; Halligan et al. 2005; Mulhall, Veerappan & Jackson 2005; Purkayastha et al. 2007; Rosman & Korsten 2007; Walleser et al. 2007; Whitlock et al. 2008). All meta-analyses and primary studies (Reuterskiold et al. 2006; Arnesen et al. 2007; Chaparro Sanchez et al. 2007) 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, (Jensch et al. 2008; Roberts-Thomson et al. 2008). 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).**

[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 Appendix 2).

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 (Bluecross Blueshield Association Special Report: 2006; Whitlock et al. 2008; Loganayagam 2008) included two prospective studies assessing diagnostic performance in an average-risk population (Imperiale et al. 2004; Ahlquist et al. 2005). 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 (Imperiale et al. 2004; Ahlquist et al. 2005).

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% (Itzkowitz et al. 2008).

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 (Zauber et al. 2007; Parekh, Fendrick & Ladabaum 2008). According to one study, costs should be 6–10 times lower before stool DNA screening could compete with other available screening tests (Zauber et al. 2007).

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 (Fireman & Kopelman 2007; Tran 2007). Since the reviews, four more studies on the diagnostic accuracy of capsule endoscopy have been published (Eliakim et al. 2009; Gay et al. 2009; Sieg, Friedrich & Sieg 2009; Van Gossum et al. 2009). Sensitivity in the studies included in the review varied from 56–76%, and specificity from 64–69% (Fireman & Kopelman 2007; Tran 2007). The newer studies showed somewhat better estimates than the earlier studies, with sensitivity ranging from 72–78% and specificity from 53–78% (Eliakim et al. 2009; Gay et al. 2009; Sieg, Friedrich & Sieg 2009; Van Gossum et al. 2009). 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]

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2

Organisation

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Guiding principles for organising a colorectal cancer screening programme

1. A colorectal cancer screening programme is a multidisciplinary undertaking. The objective is to reduce mortality from and possibly incidence of colorectal cancer without adversely affecting the health status of those who participate in screening. The effectiveness is a function of the quality of the individual components of the process.
2. The provision of the service must account for the values and preferences of individuals as well as the perspectives of public health.
3. The public health perspective in the planning and provision of screening services requires commitment to ensuring equity of access and sustainability of the programme over time.
4. Taking into account the perspective of the individual requires commitment to promoting informed participation and to providing a high quality, safe service.
5. Implementation entails more than simply carrying out the screening tests and referring individuals to assessment whenever indicated. Specific protocols must be developed for identifying and subsequently inviting the target population. Protocols are also required for patient management in the diagnosis, treatment, and surveillance phase in order to ensure that all individuals have timely access to the proper diagnostic and treatment options.
6. Complete and accurate recording of all relevant data on each individual and every screening test performed, including the test results, the decision made as a consequence, diagnostic and treatment procedures and the subsequent outcome, including cause of death, should be ensured. This monitoring process is of fundamental importance.
7. The quality assurance required for screening should also enhance the quality of the service offered to symptomatic patients.
8. Appropriate political and financial support are crucial to the successful implementation of any screening programme.

Recommendations and conclusions[1]

Organised vs. non-organised screening

2.1 In order to maximise the impact of the intervention and ensure high coverage and equity of access, only organised screening programmes should be implemented, as opposed to case-finding or opportunistic screening as only organised programmes can be properly quality assured **(III - A).**[Sect 2.2.1; 2.2.2; 2.2.3]

2.2 When organising a screening programme, several fundamental aspects should be considered: the legal framework, the availability and accuracy of epidemiological and demographic data, the availability of quality-assured services for diagnosis and treatment, promotional efforts, a working relationship with the local cancer registry, and follow-up for causes of death at individual level **(VI - A).**[Sect 2.2.3]

Implementing the screening programme

2.3 A population registry should be implemented for screening if not yet available, combining the most accurate and updated information about the target population **(VI - A).**[Sect 2.3.1]

2.4 If the screening policy allows for exclusions, the exact definition of the criteria should be given. Exclusions should be carefully and routinely monitored for appropriateness and quality **(VI - A).**[Sect 2.3.1.1]

2.5 In the absence of hereditary syndromes people with a positive family history should not be excluded from CRC screening programmes **(III - B).**[Sect 2.3.1.2]

2.6 Subjects belonging to families with hereditary syndromes, identified at the time of screening, should be referred to special surveillance programmes or family cancer clinics, if available **(III - B).**[Sect 2.3.1.2]

Participation in screening

2.7 Access to screening and any follow-up assessment for people with abnormal test results should not be limited by financial barriers. In principle, screening should be free of charge for the participant **(I - A).**[Sect 2.4.2.1]

2.8 In the context of an organised program, personal invitation letters, preferably signed by the general practitioner, should be used. A reminder letter mailed to all non-attenders increases attendance rate and is therefore recommended (see also Chap. 10, Rec. 10.7) **(I - A).**[Sect 2.4.3.1; 2.4.3.2; 10.4.1.2]

2.9 Although more effective than other modalities, phone reminders may not be cost-effective (see also Chap. 10, Rec. 10.8) **(I - B).**[Sect 2.4.3.2; 10.4.1.2]

2.10 Provision of information is necessary to enable subjects to make an informed choice, but it is not sufficient to enhance participation. Organisational measures enabling people to attend screening should be implemented **(I - A).**[Sect 2.4.3.3.1]

2.11 Primary health care providers should be involved in the process of conveying information to people invited for screening (see also Chap. 10, Rec. 10.6) **(II - A).**[Sect 2.4.3.4; 2.4.3.4.1; 10.4.1.1]

[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.

2.12 General practitioners or family physicians (or primary health care practitioners, where preventive services are not primarily based on primary care physicians) should be involved in the implementation of organised programmes **(I - A).**[Sect 2.4.3.4.2]

2.13 Reducing organisational barriers to physicians' advice should be a priority for interventions aimed at promoting GPs' involvement in organised screening programmes **(I - B).**[Sect 2.4.3.4.2]

Testing protocol

2.14 For FOBT-based screening programmes, the choice of the kit provider should aim to maximise accessibility for the target population **(II - A).**[Sect 2.5.1.1]

2.15 Mailing of FOBT kits may be a good option, taking into account feasibility issues (such as reliability of the mailing system and test characteristics) as well as factors that might influence cost-effectiveness (such as the expected effect on the participation rate) (see also Chap. 10, Rec. 10.9) **(II - B).**[Sect 2.5.1.1; 10.4.1.3]

2.16 Clear and simple instructions should be provided with the kit (see also Chap. 10, Rec. 10.10) **(V - A).**[Sect 2.5.1.1; 10.4.1.3]

2.17 In order to enhance compliance, testing procedures that require no or only minor dietary restrictions are preferred **(I - A).**[Sect 2.5.1.2]

2.18 Systematic (preferably automated) check protocols should be implemented in order to ensure correct identification of the screenee's test results and recognition of incomplete or erroneous data **(VI - A).**[Sect 2.5.1.3]

2.19 Protocols should be in place to ensure standardised and reliable classification of the test results **(VI - A).**[Sect 2.5.1.3]

2.20 Bowel preparation for screening sigmoidoscopy should preferably involve a single procedure. Cultural factors should be taken into account and population preference should be assessed. **(II - B).**[Sect 2.5.2.2]

2.21 For screening sigmoidoscopy, several providers should be available that are close to the target population. Organisational options include the possibility of having the enema administered at the endoscopy unit. Clear and simple instructions should be provided with the preparation **(II - B).**[Sect 2.5.2.2]

2.22 To date no single bowel preparation for colonoscopy has emerged as consistently superior over another in terms of efficacy and safety **(I)** although sodium phosphate may be better tolerated and it has been shown that better results are obtained when the bowel preparation is administered in two steps (the evening before and on the morning of the procedure) **(II)**. It is therefore recommended that there should be colonic cleansing protocols in place and the effectiveness of these should be monitored continuously (see Ch. 5, Rec. 5.22) **(VI - A).**[Sect 2.5.2.3; 5.3.3]

2.23 For colonoscopy, several providers should be available that are close to the target population. Clear and simple instructions should be provided with the preparation **(VI - B).**[Sect 2.5.2.2 ;2.5.2.3]

Management of people with positive test results and fail-safe mechanism

2.24 In order to ensure timely and appropriate assessment, an active follow-up of people with an abnormal screening test result should be implemented, using reminders and computerised systems for tracking and monitoring management of these patients **(II - A).**[Sect 2.5.3]

2.25 The cost charged to the participant undergoing assessments should be as low as possible in order to promote equity of access **(II - A).**[Sect 2.5.3]

Screening policy within the healthcare system

2.26 Gender and age-specific screening schedules deserve careful attention in the design and implementation of screening interventions **(III - C).**[Sect 2.6.3.1]

2.27 The costs of screening organisation (including infrastructure, information technology, screening promotion, training and quality assurance), the occurrence of adverse effects and the likelihood that patients will actually complete the tests required for any given strategy represent additional important factors to be taken into account in the design and implementation of screening interventions and in the choice of the screening strategy **(III - A).**[Sect 2.6.1-3; 2.6.3.2-5]

Implementation period (step-wise)

2.28 Ideally, any new screening programme should be implemented using individual level randomisation into screening and control groups in the phase in which resources and practical limitations prohibit the full coverage of the target population **(VI - A).**[Sect 2.6.4]

Data collection and monitoring

2.29 In order to be able to evaluate the effectiveness of screening, the data must be linked at the individual level to several external data sources including population register, cancer or pathology registries, and registries of cause of death in the target population. Therefore, legal authorisation should be put in place when the screening programme is introduced in order to be able to carry out programme evaluation by linking the above-mentioned data for follow-up **(VI - A).**[Sect 2.6.5.1; 2.6.5.2]

2.1 Introduction

National and organised, population-based cancer screening programmes have been in place since the early 1960s, when cervical cancer screening was first implemented in Finland. In fact, the concept of organised screening has largely been built on this experience. The effectiveness of a programme can be measured by the reduction of mortality from the specific cancer site, and this depends on the extent of organisation, i.e. how well different factors in the screening process can be linked together. These factors include the identification of the target population, the performance of the test, and diagnostics and treatment of those who need further assessment or treatment after the primary screening test (Läärä, Day & Hakama 1987; Quinn et al. 1999).

The effectiveness of screening with regard to its impact on mortality and incidence of CRC is a function of the quality of the individual components of the process, from the organisation and administration up to the assessment, treatment and follow-up of screen-detected lesions.

Fundamental to the success of a screening programme is that people in the target population are actually screened. The uptake rate is a critical determinant of the impact of screening on the reduction of CRC incidence and mortality at the population level. Equity of access to screening is clearly as important a challenge as is high compliance in new screening programmes. Understanding the reasons for non-participation is helpful in the planning phase when considering factors that should be taken into account in the design of the screening programme.

Concerns have been raised about the potential conflict between advocating high uptake rates and the intention to promote informed uptake, i.e. enabling people to make an informed choice about whether or not they want to be screened. The purpose of screening should be to benefit the whole community, while at the same time respecting the individual's autonomy that includes the right to refuse screening. Interventions aimed at increasing uptake should try to identify ways to minimise barriers to participation among those who have understanding of its likely benefits, limitations and harms.

2.2 Organised vs. non-organised screening

The specific policy of a screening programme determines the target age and gender and possibly the geographical area, the screening test and screening interval, and further diagnostics and treatment for those who need them.

The implementation of a population based screening programme is characterised by the definition of a specific population (by target age and geographical area), with eligible subjects being actively invited following an explicit and pre-defined protocol specifying the planned screening interval, as well as the testing and assessment procedures. Screening tests and the related assessments are usually free of charge for the target population in this context.

This policy may be implemented within different organisational contexts, but in all options a predefined organised protocol is required that takes into consideration the entire process.

2.2.1 Opportunistic screening or case-finding

Case-finding may take place outside an organised programme in which case it is referred to as opportunistic screening. This type of screening may be the result of a patient request or a recommendation made during routine medical consultation for unrelated conditions, or on the basis of a possible increased risk of developing colorectal cancer (family history or other known risk factors). Opportunistic screening is less efficient and more costly both in terms of resources and harms, and thus it is not recommended as an alternative to organised screening.

2.2.2 Comparison of coverage and effectiveness

Two cross-sectional surveys have assessed the increase in coverage (17% and 23%) resulting from the introduction of organised cervical cancer screening versus the pre-existing opportunistic approach (Ronco et al. 1997; Bos et al. 1998). Both in the United Kingdom and Norway the introduction of an organised screening programme was associated with a decrease in the incidence rate of invasive cervical cancer and an increase in the target population coverage, as compared to the period preceding the start of the programme when opportunistic screening was already widespread (Quinn et al. 1999; Nygard, Skare & Thoresen 2002). A decrease in the incidence rate of invasive cervical cancer in women who received organised screening compared to opportunistic screening was also observed in a cohort study (Lynge et al. 2006) and a case control study (Nieminen et al. 1999). A 20% decrease in incidence of invasive cervical cancer was observed in Turin, Italy, among women invited to an organised programme, compared with those not invited, after introduction of the organised programme in an area in which intensive opportunistic screening was already established (Ronco et al. 2005).

Similar findings have been reported by studies conducted in the context of breast cancer screening. Organised screening programmes can ensure better coverage of hard-to-reach populations, as suggested by a recent survey: compared to women undergoing opportunistic screening, participants in an organised programme were more likely to have never been screened, tended to ignore screening efficacy and were at risk of abandoning screening, as a result of their less-favourable attitudes towards prevention (Chamot, Charvet & Perneger 2007). A recent case–control study conducted in Italy showed that the introduction of breast cancer screening programmes was associated with a reduction in breast cancer mortality attributable to the additional impact of the organised programmes over and above the background spontaneous mammography activity. Compared to those not yet invited, women invited to the organised programmes showed a 25% (OR:0.75; 95%CI:0.62–.92) reduction of the risk of death from breast cancer (Puliti et al. 2008).

Available data from studies conducted in the context of CRC screening indicate that the introduction of organised programmes can have a similar impact, at least on target population coverage. A nationwide observational telephone survey, conducted in France (Eisinger et al. 2008), showed that greater compliance with reduced inequalities in the distribution across social groups was achieved in geographical departments where CRC screening was organised by health authorities.

2.2.3 Prerequisites for organised screening

The International Agency for Research on Cancer (IARC) has defined an organised screening programme as one that has the following features: 1) an explicit policy with specified age categories, method and interval for screening; 2) a defined target population; 3) a management team responsible

for implementation; 4) a health-care team for decisions and care; 5) a quality assurance structure; and 6) a method for identifying cancer occurrence and death in the population (IARC 2005).

When organising a new screening programme the following fundamental aspects should therefore be considered:

1. the legal framework for identification and follow-up of the population;
2. the availability and accuracy of the necessary epidemiological data upon which the decision to begin screening is based;
3. the availability and accessibility of essential demographic data to identify the target population and set up an invitation system;
4. the availability and accessibility of quality-assured services for diagnosis and treatment of colorectal cancer and its precursors;
5. promotional efforts to encourage participation in the programme;
6. a working relationship with the local Cancer Registry[2], if available, and causes of death registry, and maintenance of population and screening registers, to include adjustments to the programme and to ensure evaluation of the effects and follow-up for causes of death at individual level.

The evaluation of outcomes and interpretation of results from the entire screening programme are affected by these aspects, therefore the feasibility of an effectively managed programme should be piloted or built up gradually in the phase in which resources and practical limitations prohibit the full coverage of the target population. It is recognised that the context and logistics of screening programmes will differ by country and even by region. For example the prior existence of a population registry facilitates the issuing of personalised invitations, whereas the absence of a population register may encourage recruitment by open invitation. Many of these contextual differences will explain the differences in outcomes. In opportunistic screening programmes or case-finding, the aforementioned aspects are overlooked and evaluation of the benefits and possible harms will not be possible. The disadvantages also include many unnecessary screenings per person and low coverage of the entire target population, leading to low impact at the public health level. Compared with opportunistic screening, organised screening permits much greater attention to the quality of the screening process including follow-up of participants (Miles et al. 2004). Consequently, organised screening provides greater protection against the harms of screening, including over-screening, poor quality and complications of screening, including poor follow-up of participants with positive test results.

Summary of evidence

- Organised screening programmes achieve better coverage of the target population including hard-to-reach or disadvantaged groups **(IV - V)**.
- Organised screening is more effective, and hence likely to be more cost-effective than opportunistic screening or case-finding. The available evidence indicates that organised screening results in a larger reduction of invasive cancer incidence (cervical cancer) or mortality (breast cancer) **(III - IV)**.
- Organised screening provides greater protection against the harms of screening, including over-screening, poor quality and complications of screening, and poor follow-up of participants with positive test results **(III)**.

Recommendations

- In order to maximise the impact of the intervention and ensure high coverage and equity of access, only organised screening programmes should be implemented as opposed to case-finding or

[2] If a cancer registry is lacking, registration of the target cancer should be initiated with the screening programme.

opportunistic screening as only organised programmes can be properly quality-assured **(III - A).**[Rec 2.1]

- When organising a screening programme several fundamental aspects should be considered: the legal framework, the availability and accuracy of epidemiological and demographic data, the availability of quality-assured services for diagnosis and treatment, promotional efforts, a working relationship with the local Cancer Registry, and follow-up for causes of death at individual level **(VI - A).**[Rec 2.2]

2.3 Implementing the screening programme

Organised CRC screening is a multi-step process including:

- Identification of the target population;
- Recruitment of eligible subjects;
- Delivery of screening test;
- Reporting of screening test results;
- Reassurance of people with normal results and information on the timing of the next test;
- Recall of people with unsatisfactory/inadequate screening test
- Follow-up of people with positive tests, i.e. diagnostic procedures and treatment needed, including a fail-safe system to make sure this actually happens; and
- Registration, monitoring and evaluation of the entire programme.

Issues related to programme implementation are discussed in Section 2.6.4.

2.3.1 Identifying and defining the target population

Catchment areas and target populations must be clearly defined. The necessary data include unique identification for each person, such as name, date of birth, relevant health insurance or social security numbers, general practitioner (GP) where appropriate, and contact address. Population registers or registries can in general provide such data, but they must be updated regularly to account for population migration, deaths and changes in personal details. In those countries in which population registries are based on administrative areas of small size, communication between registries is essential. Suitable registries might include population, electoral, social security, screening programme, and health service registries. Incomplete or inaccurate registries can result in certain groups (such as transients or ethnic minorities) not being invited for screening.

If an accurate, complete and regularly-updated register of the whole target population does not exist, an administrative database that combines information from available registries for all people to be included in screening should be implemented for the purposes of the programme. The legal basis for access to such registries must be set up and all data protection measures should be implemented according to the national and European legislation.

Recommendation

- A population registry should be implemented for screening if not yet available, combining the most accurate and updated available sources **(VI - A).**[Rec 2.3]

2.3.1.1 Inclusion and exclusion criteria

The target population for a CRC screening programme includes all people eligible to attend screening on the basis of age and geographical area of residence. However, each programme may apply additional exclusion/inclusion criteria to identify the population eligible for screening. Potential reasons for excluding a subject from screening might include conditions in which offering the screening test is not appropriate, such as terminal illness (no benefit could be attained through screening), recent (the relevant period should be specified and justified) screening test (the expected benefit achievable by repeating the test might not outweigh the risks associated with the procedure), previous diagnosis of CRC or pre-malignant lesions (these patients should already be followed-up according to specific surveillance protocols, and their inclusion in screening might result in the offer of conflicting management options).

The extent to which such individuals can be identified and excluded from the target population will vary by screening programme: for some programmes it may not be feasible or desirable to identify every category of potential exclusion prior to invitation.

The necessary information may be collected at the first personal contact with the screenee, i.e. at the time of a possible colonoscopy assessment in the case of FOBT programmes, or at the time of the screening exam for FS or colonoscopy programmes.

Exclusion might alternatively be based on the information gathered through the GPs or other primary care providers, who may be requested to check the eligibility of their patients ear-marked for invitation.

If the screening policy allows for exclusions, the exact definition of the respective criteria should be given and exclusions should be carefully and routinely monitored for appropriateness and equity.

Recommendation

If the screening policy allows for exclusions, the exact definition of the criteria should be given. Exclusions should be carefully and routinely monitored for appropriateness and equity **(VI - A).**[Rec 2.4]

2.3.1.2 Family history

People with a positive family history for CRC are sometimes considered for exclusion from screening programmes targeting average-risk people.

Implementing this option requires the adoption of procedures for identifying people with a positive family history and accurately collecting the information that is relevant to assess an individual's level of risk. It is also necessary to ensure that an alternative organised programme is in place for this group of people.

Specific surveillance protocols based on colonoscopy at shorter intervals and starting at a younger age have been shown to be effective and are recommended for members of families with hereditary syndromes. However, it is still not clear if more intensive surveillance for people at moderate risk can achieve a favourable cost-benefit ratio (Sondergaard, Bulow & Lynge 1991; Benhamiche-Bouvier et al. 2000; Nakama et al. 2000; Johns & Houlston 2001; Church 2005; Baglietto et al. 2006; Butterworth, Higgins & Pharoah 2006; Menges et al. 2006; Cottet et al. 2007) **(III)**.

If an alternative option (i.e. access to a specific surveillance protocol) is not available, people with positive family history should not be excluded from a population-based screening programme as screening offers the opportunity of access to an intervention that may ensure protection for people who would not be otherwise be covered.

Furthermore, family history, in the absence of hereditary syndromes, does not represent an indication for changing standard surveillance protocols (see Ch. 9, Sect. 9.2.3.2, Rec. 9.13). In a recent study, the characteristics of the neoplasm rather than individual's family history were found to be associated with the risk of recurrence among subjects not fulfilling the Amsterdam criteria. This suggests that these people could be considered at moderate risk of developing CRC and that surveillance intervals of more than five years may be appropriate in these cases (Dove-Edwin et al. 2005). Therefore, family history should not represent a criterion for exclusion from the screening programme, even for patients identified at the time of assessment.

Summary of evidence

Members of families with hereditary syndromes should follow specific surveillance protocols based on colonoscopy at shorter intervals and starting at a younger age **(III)**.

Recommendations

- In the absence of hereditary syndromes people with a positive family history should not be excluded from CRC screening programmes **(III - B).**[Rec 2.5]
- Subjects belonging to families with hereditary syndromes identified at the time of screening should be referred to special surveillance programmes or family cancer clinics, if available **(III - B).**[Rec 2.6]

2.4 Participation in screening

The planning and implementation of screening programmes should take into account cultural, behavioural, economic and organisational factors.

2.4.1 Barriers

Several factors influencing participation have been identified related to individual's characteristics, the setting and the organisation of the intervention and the knowledge, attitudes and practice of the provider (Vernon 1997; Jepson et al. 2000). The findings concerning the relative weight of these factors are not consistent across studies assessing determinants and barriers to participation. However, the variability of the reported findings is probably related to the different conditions under which the examined screening interventions have been implemented.

The organisation of screening within health services appears, in most countries, to be a major determinant of participation rate. Lack of insurance coverage and cost of the test have been identified as the main negative influences on participation for all screening interventions and tests. Also, lack of resources is the most likely explanation for the negative association of lower socio-economic status with completion of CRC screening tests (Sutton et al. 2000; McCaffery et al. 2002; Cokkinides et al.

2003; Slattery, Kinney & Levin 2004; Dassow 2005; Wardle, Miles & Atkin 2005). Other factors related to service organisation which were fairly consistently related to poor screening attendance are the amount of time required to perform screening, distance from the test provider and lack of physician recommendation **(III - V)**.

Knowledge and perceived benefits of screening, perceived risk of CRC and health motivation were associated with higher participation in most of the studies assessing the influence of these determinants. Worry about pain, discomfort, or embarrassment associated with the test, or fear of test results were also consistently associated with a lower attendance (James, Campbell & Hudson 2002; Montano et al. 2004; Weinberg et al. 2004; Wardle, Miles & Atkin 2005; Lawsin et al. 2007) **(V)**.

Gender and age differences in participation to CRC screening have also been reported; most studies have shown a trend to decreased participation among older people, although these findings have not been confirmed by all investigators. It has been reported that participation may be higher among women for FOBT screening and among men for endoscopy screening (James, Campbell & Hudson 2002; McCaffery et al. 2002; Menon et al. 2003; Slattery, Kinney & Levin 2004; Wardle, Weinberg et al. 2004; Dassow 2005; Miles & Atkin 2005; Segnan et al. 2005; Lawsin et al. 2007) **(V)**.

Support from a partner probably explains the positive association of marriage with screening uptake. This is more prominent in males. One reason for these findings could be that women have prior experience of screening (breast, cervix) and may therefore need less support to participate (Sutton et al. 2000; Menon et al. 2003; Wardle, Miles & Atkin 2005; Malila, Oivanen & Hakama 2008) **(V)**.

2.4.2 Interventions to promote participation

A systematic review (Stone et al. 2002), assessed the effectiveness of the following on improving screening participation: regulatory and legislative actions (outside the medical care organisation), financial incentives for providers or patients, organisational change (changes in clinical procedures or facilities and infrastructures), reminders for providers and screenees, provider feedback, education and visual materials. The most effective was the implementation of organisational changes that made delivery of these services a routine part of patient care (establishing separate clinics devoted to screening, involving nursing or clerical staff in the delivery of services, adoption of monitoring and quality improvement approaches), reducing, or eliminating costs for the individual or establishing a system of reminders.

2.4.2.1 Removing financial barriers

Experimental studies conducted in the context of breast cancer screening showed that reduced charges for screening are effective in encouraging uptake among disadvantaged groups (Jepson et al. 2000). Sending an FOBT with a postage-paid envelope for returning the sample resulted in a significantly higher uptake, compared to non-postage (Jepson et al. 2000). The return rate was highly significant for medically uninsured people in one of the studies (Miller & Wong 1993). Offering a free FOBT in addition to educational intervention was superior to the educational intervention alone in promoting completion of screening (Plaskon & Fadden 1995). Offering financial incentives to subjects invited for screening was not found to have an impact on participation (Jepson et al. 2000).

Summary of evidence

- Free-of-charge screening is associated with increased participation, including participation of disadvantaged groups **(I)**.

- The implementation of organisational changes that make delivery of screening a routine part of health care (establishing a system of reminders, establishing separate clinics devoted to screening, involving nursing or clerical staff in the delivery of services, adoption of monitoring and quality improvement approaches) represent the most effective interventions to enhance participation rate **(I)**.

Recommendation

- Access to the screening tests and to the follow-up assessment for individuals with abnormal test results should not be limited by financial barriers. In principle access should be free of charge for the participant **(I - A).**[Rec 2.7]

2.4.3 Invitation

2.4.3.1 Invitation letter

Strong evidence indicates that receiving a letter signed by the GP increases screening uptake, compared to receiving letters signed by other figures of authority (Jepson et al. 2000; Cole et al. 2002; Federici et al. 2005).

A personal invitation letter from the GP is also associated with increased participation when the FOBT kit is delivered by mail (Cole et al. 2002).

It should be considered however that individuals can be encouraged to participate through support provided by other trusted health care professionals. In the Nordic countries, for example, invitation letters are not signed, but refer to the local authorities, and the observed participation rates are very high (70%) (Malila, Oivanen & Hakama 2008).

A positive impact on participation due to the offer of a pre-fixed appointment has been reported by several studies of breast and cervical cancer screening (IARC handbook vol 10, (IARC 2005) and has also been confirmed among people invited for FS screening. Inviting people to obtain the FOBT kit within a pre-defined time interval, or offering a pre-defined appointment for kit delivery has been adopted in some programmes, but comparative data on the impact of these strategies are lacking.

Data from a recent trial (Cole et al. 2007) indicate that an advance notification letter significantly increases participation in FOBT screening (from 39.5% to 48.3%). The effect was explained by a population shift in readiness to undertake screening.

2.4.3.2 Reminders

In the English NHS Screening Programme over 50% of participants only respond after receiving a reminder about 28 days after receiving their initial postal invitation. A well-conducted review (Jacobson & Szilagyi 2005) that assessed the effectiveness of different kinds of reminders (reminder and recall systems delivered by letter; postcard; telephone; auto-dialler; or in person, e.g. a provider gives face-to-face reminder) concluded that all kinds of reminders are effective, with telephone reminders being the most effective, but also the most costly.

Summary of evidence

- A personalised letter signed by the general practitioner or by another trusted primary health care provider is more effective than an impersonal letter sent by a central screening centre **(I)**.
- An advance notification letter may increase participation **(II)**.

- Any kind of reminder is effective in increasing participation, with telephone reminders being the most effective although the most costly option **(I)**.

Recommendations

- In the context of an organised programme, personal invitation letters, preferably signed by the GP, should be used. A reminder letter should be mailed to all non-attenders to the initial invitation **(I - A).**[Rec 2.8]
- Although more effective than other modalities, phone reminders may not be cost-effective **(I - B).**[Rec 2.9]

2.4.3.3 Delivering information about screening

Although the organisation of screening within health services emerges as the most important determinant of uptake, factors related to culture, values and beliefs may still play a role. Also, provision of information is clearly necessary to enable subjects to make an informed choice.

Data from the National Health Interview Survey (NHIS) consistently indicate that lack of awareness of CRC represents one of the main determinants of the underutilisation of screening.

Data from people recruited in the UK sigmoidoscopy trial (Wardle et al. 2004) who were requested to express their intention to attend screening suggest that part of the explanation of the socio-economic status (SES) gradient may be the difference in beliefs and expectations. Lower social groups evaluated the offer of a screening test, which had been publicised identically and was provided free of charge , at a convenient location and time, to all social groups, as being more frightening and less beneficial, than higher social groups. In England, with overall population participation at 60% despite free testing, the uptake rate of the FOBT programme is lower in deprived areas and among ethnic minorities (von Wagner et al 2009). Rural areas were shown to have a lower participation rate than urban areas (Launoy et al. 1993; Giorgi Rossi P. et al. 2005).

Therefore, the way the population is informed about the potential benefits and harms of screening is of particular importance. Strategies aimed at improving population knowledge and awareness of CRC and screening should target health professionals as well as individuals (see also Chapter 10).

Most programmes provide written information in the form of leaflets to people invited for screening. (see also Chapter 10).

Mass-media campaigns are also implemented, to support enrolment in organised programmes (see also Chapter 10).

Interventions aimed at promoting health professionals practice and communication with people invited for screening is discussed in Section 2.4.3.4.1 when considering the role of GPs/family physicians (see also Chapter 10).

2.4.3.3.1 Information conveyed with the invitation (see also Chapter 10)

A systematic review of methods aimed at enhancing screening rates concluded that educational interventions are less effective than organisational changes and should not be the first choice (Stone et al. 2002). Findings from more recent studies (Harris et al. 2000; Lipkus, Green & Marcus 2003; Robb et al. 2006; Costanza et al. 2007) support such a conclusion. When individuals interested in screening were requested to actively seek further information and a referral to screening from their providers, an information brochure was observed to have no impact, but the number of screening requests in-

creased significantly when the GP delivered an FOBT request form together with the information pamphlet.

The content and format of the information material sent with the invitation may influence a subject's decision to undertake screening (see also Chapter 10). An individually tailored interactive multimedia programme at the physician's office seemed more efficacious in increasing readiness to undergo screening, as compared to the same intervention not individually tailored (Jerant et al. 2007). Interventions that use visual instruments to enhance appeal and clarity are more effective: adding illustrations about the polyp-cancer process and the removal of the polyps during FS to written material was associated with a significant increase in knowledge and understanding (Brotherstone et al. 2006). Culturally and linguistically appropriate approaches promoting FOBT can enhance screening practice in groups of low-income and less acculturated minority patients (Tu et al. 2006).

Summary of evidence

- The impact of information conveyed with the invitation is greater if the invitation is signed by an individual's physician. Involvement of GPs also shows a positive influence on the impact of more tailored and structured information methods **(II)**.

Recommendations

- Provision of information is necessary to enable subjects to make an informed choice, but it is not sufficient to enhance participation. Organisational measures should be implemented in order to enhance participation in screening **(I - A).**[Rec 2.10]

2.4.3.4 The role of primary care providers

Primary health care providers can be effective media for improving awareness of the risk of cancer and of the benefits of screening, for increasing confidence in the screening test method and for countering the reluctance to collect faecal samples. In many European countries this provider is the general practitioner (GP), but other trusted health professionals, such as community nurses for example, may play a similar role.

Primary health care providers should be trained to deliver evidence-based information on screening and there should be a consensus on the programme protocol before starting the programme.

2.4.3.4.1 Role of GPs/family physicians

The involvement of GPs in screening can be very effective in improving compliance, according to the findings of several studies from different countries (Launoy et al. 1993; Tazi et al. 1997; Grazzini et al. 2000; Brawarsky et al. 2004; Federici et al. 2006; Sewitch et al. 2007; Seifert et al. 2008), but the effect is dependent upon the GP's own willingness to get involved. The findings of studies conducted in the context of opportunistic screening showed that the probability of not receiving a GP recommendation for CRC screening was highest among those with a low socioeconomic status (SES) (Brawarsky et al. 2004; Wee, McCarthy & Phillips 2005; Klabunde, Schenck & Davis 2006; Schenck, Klabunde & Davis 2006). These findings suggest that inadequate provider counselling represents an important determinant of the SES gradient in screening uptake. Compliance was shown to be closely linked to practitioner motivation also in the context of organised programmes (Launoy et al. 1993; Federici et al. 2006).

Knowledge of GP attitudes and preferences is therefore crucial in enhancing participation. A study based on semi-structured questionnaires addressed to 32 GPs in England (Woodrow et al. 2006) indicated that for GPs to effectively promote screening they must have adequate information prior to the start of a screening programme. The evidence should be based specifically on the effectiveness of the

screening programme, and information on the proportion of false negatives and the proportion of false positives.

Summary of Evidence

- The implementation of organisational measures aimed at facilitating participation in screening is required in order to achieve the expected impact of educational interventions **(II)**.

Recommendation

- Primary health care providers should be involved in the process of conveying information to people invited for screening **(II - A).**[Rec 2.11]

2.4.3.4.2 Interventions aimed to promote provider involvement (See also Chapter 10)

Provider education has been identified as a potentially effective intervention to promote CRC screening utilisation, even if the implementation of organisational measures may be necessary to achieve an impact of educational efforts (Stone et al. 2002). This conclusion is supported by the results of recent experimental studies: educational seminars offered to physicians did not show an effect on rates of CRC screening (Walsh et al. 2005), while a reminder note to the physician to direct his patients to perform an FOBT was more effective than a mail reminder and as effective as a phone reminder for the patients.

Even if GPs are not delivering kits, or not collecting or reading the test cards, they should be aware of how the programme, and in particular the invitation scheme, is structured. They can advise non-compliers about screening, which is important for older people, or for those with lower socio-economic status, and they can offer counselling for patients with positive tests. To facilitate this task, GPs should receive the results of screening and assessment tests performed by their patients.

Summary of evidence

- Primary health care providers appear to be effective media for improving awareness of the risk of cancer and the benefits of screening, and increasing confidence in and countering the reluctance to take the screening test **(I)**.
- Educational interventions are less effective than organisational changes in improving the impact of physicians' counselling on their patients' screening rates **(I)**.

Recommendations

- GPs or family physicians (or primary health care practitioners where preventive services are not primarily based on primary care physicians) should be involved in the implementation of organised screening programmes **(I - A).**[Rec 2.12]
- Reducing organisational barriers to physician's advice should be a priority for interventions aimed at promoting GP involvement in organised screening programmes **(I - B).**[Rec 2.13]

2.5 Testing protocol

2.5.1 FOBT

2.5.1.1 Delivery of kits and collection of stool samples (see also Chapter 4)

The test kit may be delivered by mail, at GPs' offices or outpatient clinics, by pharmacists, or in other community facilities, and in some cases with the support of volunteers. There is no evidence that any of these strategies may have an impact on the proportion of inadequate samples, provided that clear and simple instruction sheets are included with the kit (Courtier et al. 2002; UK Colorectal Cancer Screening Pilot Group 2004; Zorzi et al. 2007).

The choice of the provider should aim to maximise accessibility, taking into account local conditions, settings and cultural factors.

Mailing of the FOBT kit with instructions, together with the invitation letter and the information leaflet, is effective in increasing participation rates (Church et al. 2004; Segnan et al. 2005). These results are consistent with previous reports indicating that the GP's letter and mailing of FOBT kits represent the most important factors for improving compliance (King et al. 1992). Mailing of the FOBT kit might not always represent a cost-effective strategy, if the baseline participation rate and the expected increase in participation are low. Compared to mailing a second FOBT kit to all non-responders, mailing a recall letter with a test order coupon resulted in a substantial decrease in the programme costs, but also in a significant decrease in participation (Tifratene et al. 2007). The authors of the trial suggested, however, that the spared costs might be allocated more efficiently to communication interventions that might have a higher impact on compliance.

Several test providers close to the target population should be available when the subject is required to reach health or community facilities to get the kit. A recent study (Federici et al. 2006) showed that the time required to reach the test provider was the strongest determinant of compliance: OR (<15 minutes versus 15–30 or >30 minutes):0.8 (0.5–1.3) and 0.3 (0.2–0.7) respectively.

Volunteers or non-health professionals may also be involved in the distribution and collection of kits. Delivery of kits may represent in this case an additional opportunity for counselling, for conveying information about the programme and for providing instructions for test utilisation. Subjects contacted at home by a trained non-health professional who delivered the kit and collected the sample from the participant's home showed a substantially higher completion rate of iFOBT, as compared to the group who received the kit by mail with an invitation from their primary care physician, (Courtier et al. 2002).

Community volunteers, who have received some general training by the programme staff, have been involved in the kit distribution in the context of ongoing organised programmes and their involvement has been consistently associated with high participation rates (Zorzi et al. 2007). As no randomised comparison is available, it is difficult to dissociate their specific effect from other characteristics of the communities or target populations involved. Sustainability over time represents an important issue to be taken into account when planning to use volunteer support.

The modalities adopted for stool collection, storage and shipping of the sample to the laboratory are mainly dependent on the characteristics of the test adopted, i.e. its stability at environment temperature. Based on these considerations mailing of the samples may be an option that can be implemented more easily for guaiac than for immunochemical tests, which need to be processed faster. Accessibility of the collection facilities remains an important goal, but the logistics of the sample han-

dling may promote reducing the number of collection facilities in order to ensure an appropriate storage or timely shipping to the laboratories.

See also Chapter 4 for tests characteristics and storage requirements.

Summary of evidence

- There is no evidence that the proportion of inadequate samples may be affected by the provider used to deliver the kit, if clear and simple instruction sheets are provided with the kit **(II - V)**.
- The time required to reach the test provider represents a strong determinant of compliance **(II)**.
- Sending the FOBT kit together with the invitation letter may be more effective than sending a letter alone, but this strategy may not be cost-effective **(II)**.

Recommendations

- The choice of the kit provider should aim to maximise accessibility of the target population **(II - A).**[Rec 2.14]
- Mailing of FOBT kit may be a good option, taking into account feasibility issues (such as reliability of the mailing system and test characteristics), as well as factors that might influence cost-effectiveness (such as the expected impact on participation rate) **(II - B).**[Rec 2.15]
- Clear and simple instruction sheets should be provided with the kit **(V - A).**[Rec 2.16]

2.5.1.2 Performing the test: dietary restrictions and number of samples

In order to reduce the probability of a false positive result, dietary restrictions are usually recommended when guaiac-based tests are used. Retesting of subjects with a positive test (possibly with dietary restrictions being recommended) represents an alternative option adopted in some programmes to deal with this problem. A review of 5 trials (10 359 participants overall) comparing Guaiac FOBT with and without dietary restriction found a significant difference in compliance in favour of testing without dietary restrictions only in the trial where restrictions were particularly extensive. Authors concluded that advice to restrict the diet and avoid NSAIDs and vitamin C does not substantially reduce completion rate except perhaps when the dietary restrictions are particularly extensive (Pignone et al. 2001). More recent randomised trials (Cole et al. 2003; Federici et al. 2005; van Rossum et al. 2008) have demonstrated that better compliance can be achieved using iFOBT compared to a guaiac-based test. These results are not explained by the nature of the test but by lack of dietary and drug restrictions and easier and more pleasant sampling methods. Indeed, dietary restriction was associated with a significant decrease in participation also among people offered iFOBT test, compared to controls receiving the same test who where not advised to control their diet (Cole & Young 2001).

Summary of evidence

- Compliance is affected by dietary restriction and number of stool samples to be collected. Compliance is found to be consistently higher when the test adopted does not require modification of a subject's diet and sampling is limited to one bowel movement **(I)**.

Recommendation

- In order to enhance compliance, testing procedures that require no or only minor dietary restrictions are to be preferred **(I - A).**[Rec 2.17]

2.5.1.3 Examination of the samples, test interpretation and reporting

Detailed protocols on handling the stool samples must be available and followed. Identification and tracing of the sample through the entire process should be ensured by adopting appropriate labelling

allowing the sample and patient's ID code to be linked. Automated check protocols should be implemented in order to avoid mismatching of the results. All data, including test results, should have a regular backup system.

Guidelines for the equipment, organisation, quality assurance (within and between laboratories) to be adopted for different FOB tests, as well as the professional requirements for the staff, are described in Chapters 4 and 6.

An operational definition for an inadequate screening test should be made explicit in the programme protocol, taking into account the characteristics of the test (i.e. the stability and the storage requirements of the tests) as well as the testing procedure adopted (i.e. the number of samples or of cards required) (see Sect. 2.5.4.2.1 and 2.5.4.2.2).

Protocols should be in place to define the appropriate test and the algorithm used to classify a test result (as negative or positive). For quantitative or semi-quantitative iFOBTs, an explicit definition of cut-off levels for haemoglobin concentration should be defined. Protocols or rules for combining results when using multiple samples, the number of samples that are needed to evaluate the test result, etc. must be in place. When using a quantitative test, provision should be made to record the information concerning the actual amount of haemoglobin, both for tests classified as negative and for those classified as positive.

Some people may present with clinical conditions such as inflammatory bowel disease (Crohn's disease or haemorrhagic recto-colitis), which may explain a positive FOBT result. In such cases, if no cancers were detected, then the screening result should be classified as negative for the purposes of the screening programme. These patients should then be referred for treatment in the appropriate clinical setting.

See Chapter 10 for a discussion of information about negative test results.

Recommendations

- Systematic (preferably automated) check protocols should be implemented in order to ensure correct identification of the screenee's test results and recognition of incomplete or erroneous data **(VI - A).**[Rec 2.18]
- Protocols should be in place to ensure standardised and reliable classification of the test results **(VI - A).**[Rec 2.19]

2.5.2 Endoscopy

2.5.2.1 Obtaining bowel preparation for endoscopy screening

The bowel preparation may be obtained from the office of the primary health care provider (e.g. GP), from endoscopy units or other screening facilities, or from pharmacists. There is no evidence concerning the impact of any of these strategies on participation rate, or on the proportion of inadequate exams. The aim should be to maximise accessibility taking into account local conditions, setting and culture. Several providers close to the target population should be available. The bowel preparation should be provided with clear and simple instruction sheets (see also Chapter 5).

2.5.2.2 Bowel preparation for sigmoidoscopy (see also Chapter 5)

The acceptability of different types of preparations is influenced by cultural factors, which should be considered together with the evidence concerning the effect of the preparation, when choosing among different options. No difference in the proportion of inadequate exams was observed when comparing a single enema regimen to a preparation using two enemas or to oral preparation (Senore et al. 1996; Atkin et al. 2000).

Summary of evidence

- A bowel preparation regimen using a single enema self-administered at home two hours before the endoscopy has been reported as the most acceptable option **(II)**.
- Using two enemas may not decrease participation, while a preparation using both oral preparation and enema has a negative effect on compliance **(II)**.

Recommendations

- Bowel preparation for screening sigmoidoscopy should involve a single procedure, either enema or oral preparation. A single self-administered enema seems to be the preferred option, but cultural factors should be taken into account, and population preference should be assessed **(II - B).**[Rec 2.20]
- Several providers of bowel preparation close to the target population should be available when the subject is required to reach health or community facilities to get the preparation. Organisational options include the possibility of having the enema administered at the endoscopy unit. Clear and simple instruction sheets should be provided with the preparation **(II - B).**[Rec 2.21]

2.5.2.3 Bowel preparation for colonoscopy (see also Chapter 5)

Data on the impact of different preparation regimens in the context of population screening with colonoscopy are lacking. A recent systematic review (Belsey, Epstein & Heresbach 2007) concluded that no single bowel preparation emerged as consistently superior, but sodium phosphate was better tolerated. The authors identified a need for rigorous study design to enable unequivocal conclusions to be drawn on the safety and efficacy of bowel preparations (see Ch. 5, Sect. 5.3.3).

Timing of administration of the recommended dose appears important, as it has been established that split dosing (the administration of at least a portion of the laxative on the morning of the examination) is superior to dosing all the preparation the day before the test, both for sodium-phosphate and poly-ethylene glycol (Aoun et al. 2005; Parra-Blanco et al. 2006; Rostom et al. 2006; Cohen 2010) **(II)**

Summary of evidence

- To date no single bowel preparation for colonoscopy has emerged as consistently superior over another in terms of efficacy and safety **(I)** although sodium phosphate may be better tolerated and it has been shown that better results are obtained when the bowel preparation is administered in two steps (the evening before and on the morning of the procedure) **(II).**

Recommendations

- Preparation regimes used for colonoscopy seem equivalent in terms of efficacy and safety, although sodium phosphate may be better tolerated **(I)** and it has been shown that better results are obtained when the bowel preparation is administered in two steps (the evening before and on the morning of the procedure) **(II)**. It is therefore recommended that there should be colonic cleansing protocols in place and the effectiveness of these should be monitored continuously (see also Ch. 5, Rec. 5.22, Sect. 5.3.3) **(VI - A).**[Rec 2.22]

- Several providers close to the target population should be available when the subject is required to reach health or community facilities to obtain the preparation. Clear and simple instruction sheets should be provided with the preparation **(VI - B).**[Rec 2.23]

2.5.2.4 Test interpretation and reporting

2.5.2.4.1 Inadequate test

As mentioned above (Sect. 2.5.1.3), an operational definition for an inadequate screening test should be made explicit in the programme protocol, taking into account the characteristics of the test as well as the testing procedure adopted .

2.5.2.4.2 Defining a negative test and episode result

An explicit protocol defining the conditions for classifying a test as negative should be adopted, specifying the criteria for referral to colonoscopy assessment (in FS-based programmes) or surveillance (TC-based programmes).

Also, an operational definition for a negative screening episode should be made explicit in the programme protocol. A screening episode should be classified as negative when, based on the results of the primary test or of the recommended assessments (if any), the subject is referred again to the standard screening protocol. The rationale for having such pragmatic definition is to avoid the risk of labelling people detected with lesions that do not have clinical and prognostic significance (see also Chapter 10). This approach allows concomitant measurement of the detection rates for various types of lesions that are included among the performance indicators listed in Chapter 3.

See Chapter 10 for details on how to communicate information about negative and positive test results.

2.5.3 Management of people with positive test results and fail-safe mechanisms

The potential reduction of mortality through cancer screening can only be achieved if subjects with abnormal findings receive timely and appropriate follow-up for detected abnormalities.

The findings of a recent US survey indicated that less than 15% of health plans monitor receipt of appropriate follow-up care by patents with abnormal results. This lack of organised tracking systems probably explains the low proportion of people with abnormal screening findings who receive adequate follow-up (Yabroff et al. 2003). In particular, among patients receiving FOBT screening in the Veterans health administration, 41% of those with a positive test failed to receive appropriate assessment (Etzioni et al. 2006). The negative implications of follow-up failures are substantial, including at the population level. A previous analysis of the screening history of invasive cervical cancers identified by a population-based cancer registry showed that about 20–25% of women with invasive cancer had been recommended for an early repeat smear, but had not received adequate follow-up (Bucchi & Serafini 1992).

Effective interventions targeting the screen-positive individuals include (Bastani et al. 2004): reducing financial and other barriers for further investigations or eliminating the costs for the patients, mail or telephone reminders, and providing written information material or telephone counselling addressing

fears related to abnormal findings. All these interventions were found to be successful in increasing the proportion of people receiving timely follow-up. Few interventions have been assessed at the practice/provider level. The offer of same-day follow-up on-site colposcopy for abnormal Pap-smears (Holschneider et al. 1999) or an on-site colonoscopy following a positive sigmoidoscopy (Stern et al. 2000), has led to improved patient compliance. In a predominantly minority and indigent population targeted for cervical cancer screening, subjects managed through a specialised clinic, including nurse case manager, tracking system, reminder calls, rescheduling of missed appointments and clinical staffing with on-site colposcopy, achieved a significantly increased follow-up compared to a randomly assigned control group (Engelstad et al. 2001). The implementation of infrastructure (computerised systems for tracking and monitoring of screening abnormalities) and organisational changes (multidisciplinary team work) are required to ensure sustainability over time of effective interventions.

Treatment and after-care service following evidence-based guidelines should be offered to all patients detected with cancer or pre-invasive lesions at the time of assessment of abnormal screening findings.

Summary of evidence

- Reducing the financial barriers for further investigations, utilisation of mail or telephone reminders, written information material or telephone counselling addressing fears related to abnormal findings, implementation of computerised systems for tracking and monitoring of screening abnormalities and organisational changes (multidisciplinary team work) were found to be successful in increasing timely follow-up **(II)**.

Recommendations

- In order to ensure timely and appropriate assessment, active follow-up of people with screening abnormalities should be implemented, using reminders and computerised systems for tracking and monitoring management of these patients **(II - A).**[Rec 2.24]
- The cost to the participant undergoing assessments should be as low as possible in order to promote equity of access **(II - A).**[Rec 2.25]

2.5.4 Follow-up of population and interval cancers (see also Chapter 3)

The ascertainment of interval cancers represents a key component of the evaluation of a screening programme. The documentation and evaluation process requires forward planning and linkage between screening registries and cancer registries, including data on causes of death, with no losses to follow-up. Data collection and reporting should cover all cancers appearing in the target population.

Methods of ascertainment and follow-up may differ across countries and screening programmes depending on the availability and accessibility of data and of existing data sources: cancer/pathology registries, clinical or pathology records or death records/registries. See Chapter 3 for a description of the indicators and the data requirements.

2.6 Screening policy within the healthcare system

There should be a national and governmental context for planning of CRC screening. The programme needs political support with sustainable funding to succeed. If appropriate structures in the healthcare system are lacking, screening should not be implemented until they are developed, for example using the implementation phase to build up the needed structures.

It is essential that the programme is integrated into the healthcare system and is accepted by both the population and health professionals involved in the diagnostic process for CRC. Organisation of the screening programme should integrate the structures of the entire health care system appropriately and it should comply with national guidelines and protocols. Within the organisational framework of the programme, the target population should be defined as well as the frequency of screening. Provisions should be made for the financing of the programme, including evaluation costs.

The professional and organisational managers of a screening programme must have sufficient authority and autonomy, including an identified budget and sufficient control over the use of resources to effectively control the quality, effectiveness and cost-effectiveness of the programme and the screening service. The institutional structure must facilitate effective management of quality and performance.

Process and outcome indicators should be constantly evaluated to serve the needs of the individual and the health service.

Adequate protection of all data should be ensured, following requirements set by European directives concerning data protection and national privacy legislation.

2.6.1 Local conditions at the start of a programme

Before implementation of a screening programme, an inventory of baseline conditions including information on opportunistic screening rates, background CRC incidence rates and availability of endoscopic resources should be made.

In order to run a successful programme, adequate resources, in terms of both staff and facilities must be available, and an adequate infrastructure must be in place.

Colonoscopy is the final common denominator of all the CRC screening strategies. Therefore, as the implementation of any form of population screening for CRC will place greater demands on colonoscopy resources, the feasibility of CRC screening also depends on the availability of colonoscopy services. There may also be limitations to access for subjects in rural or remote areas and in the public health sector. Clearly, CRC screening is only feasible if access can be guaranteed to individuals who participate in screening.

In many European countries, CRC early detection activity exists in some form, e.g. testing personally initiated by patients, or as a component of private health care. According to the findings of a recent survey conducted in 10 European countries and in Canada, about 10% of colonoscopies are performed for screening (Burnand et al. 2006). However a wide variation was found in the occurrence and in the appropriateness of the exams. The inappropriateness rates ranged between 0% and 50%. Similarly the proportion of colonoscopies performed following clinical indications which were judged to

be inappropriate was about 25%, suggesting overuse of the exam. Even if screening exams should be delivered within dedicated sessions (see also Chapter 5), promoting a more appropriate use of colonoscopy might therefore increase quality of care and favour an efficient use of available resources. As suggested by simulations conducted in the US (Seeff et al. 2004) a more efficient use of colonoscopy resources may result in an increase in the capacity to meet the demand of screening-induced colonoscopies.

It is unlikely, however, that simply providing funds to increase existing activity will enable the programme or screening policy to be successful. In parallel with introducing the general principles of organised screening, governments should consider the introduction of administrative measures (i.e. not paying for unnecessary exams) and implementing educational interventions aimed at enhancing appropriateness of colonoscopy referrals. In some countries, re-allocation of resources already used for opportunistic screening activities will be sufficient to cover the entire target population within a defined screening interval.

2.6.2 Defining the relevant healthcare professional and facilities

Depending on each country's health system and culture, different health professionals can be involved in kit delivery and stool sampling collection or in delivering bowel preparation for endoscopy screening (i.e. GPs, nurses, paramedics, pharmacists, volunteers from no-profit organisations, etc.), as well as in performing sigmoidoscopy when offered as a screening test (i.e. GPs, nurses gastroenterologists,). Each country should follow quality assurance standards for the facilities and establish minimum training requirements for each type of professional, fulfilling the present guidelines (see Chapter 6).

2.6.2.1 Diagnostic and treatment centres

Screening will be neither effective nor efficient if patients with a positive FOBT or FS are not followed up with a proper evaluation of the entire colon and appropriate management, if needed. Trained endoscopists are essential, and each programme should establish and monitor validated training for colonoscopy, following the guidelines in Chapter 6. To help in the planning of location of endoscopic services for screening, five levels of competency are proposed in Chapter 5 (see 5.3.1). The definitions of the proposed levels take into account the facilities and the level of competency which are necessary to remove screen-detected lesions, and consequently how often the patients should be referred elsewhere in order to have the detected lesions safely and expertly removed. If all resources are not available in a given area, large centres, particularly for diagnosis and treatment, can serve more than one area, provided that adequate communication is established.

2.6.2.2 Public health specialists

Considering the different healthcare environments, public health specialists with adequate epidemiological knowledge or equivalent expertise are recommended. These professionals are needed from the onset, to ensure that the programme includes a population-based information system that monitors each step of the screening process. They will then be responsible for gathering data and for ongoing monitoring in order to identify problems that need intervention. These public health specialists can be based at a national or regional level, whereas the other health professionals who are providing screening services are needed in each area. Public health specialists should have training in and an understanding of basic epidemiology, statistics and communication. A European training programme on monitoring and evaluation of screening programmes would be desirable (see also Chapter 6).

2.6.3 What factors should be considered when deciding which primary test to use?

According to the findings of a survey of the International ColoRectal Cancer Screening Network (ICRCSN) describing CRC screening protocols adopted in various countries, a number of diverse screening initiatives have been implemented with a wide variation in various aspects of programme implementation including the tests used for primary screening. Currently FOBT is the only primary test recommended by the EU for CRC screening (Council of the European Union 2003, Appendix 2, see Ch. 1, Sect. 1.1.4) (Benson et al. 2008).

Today there is a range of options for CRC screening in the average-risk population. The tests commonly adopted in screening interventions include tests for occult blood (either guaiac or immunochemical), sigmoidoscopy (FS) and total colonoscopy (TC). Whether one method is superior to the other is not clear from several analyses (Pignone et al. 2002; Zauber et al. 2008). Although clear experimental evidence is available only for FOBT, FS and TC are commonly considered as reasonable alternatives (see Chapter 1). It has been suggested that a country's screening initiative should be adapted to suit population size, healthcare system and methods of funding, and should be individualised to practice settings and if possible to people (Benson et al. 2008; Whitlock et al. 2008). Thus, when deciding which primary test to use, several factors should be considered. Some of them are connected with country-specific conditions.

2.6.3.1 Gender and age differences (see also Chapter 1)

CRC incidence and mortality are consistently lower among women than among men, and they show an increasing trend with age, although age-specific CRC incidence and mortality vary strongly within Europe. Comparative analyses of age- and gender specific CRC incidence and mortality in 38 European countries indicate that the differences across countries translate to wide age ranges at which comparable levels of risk are reached. The risk advancement attributable to these geographical differences in age-specific incidence and mortality rates across Europe has been estimated to be up to 10 years or more, while the lower incidence and mortality among women quite consistently translates to an age difference of approximately 4–8 years at which comparable levels of risk are reached (Regula et al. 2006; Brenner et al. 2007b; Brenner, Hoffmeister & Haug 2008). CRC incidence and mortality represent important parameters affecting potential benefits of screening, which must be weighed against costs and potential adverse side effects when choosing the age of screening initiation.

Cost-effectiveness modelling of different strategies was generally consistent in evaluating as efficient to begin screening between 50 and 60 (Eddy 1990; Ness et al. 2000); decreasing the stop age from 85 to 75 yielded a small reduction in life-years gained with a large reduction in the number of tests. Another important factor when assessing the age at which to stop screening is the remaining life expectancy.

2.6.3.2 Participation

Acceptability of the proposed strategy and test represents a critical determinant of the impact of an organised programme. It influences the cost-effectiveness of the most commonly recommended tests due to different levels of participation (Zauber et al. 2008). The effectiveness of an intervention is therefore influenced by the compliance level that can be achieved, and ultimately the best option for a patient is the one he or she will attend. It has been suggested that the relevant information when comparing different strategies should be the estimate of the level of relative adherence to different tests which provide comparable levels of life-years gained per number of colonoscopies. More accept-

able tests would pick up a higher proportion of prevalent lesions, even if their sensitivity were low, because more people would attend screening (Segnan et al. 2007).

Differences in exclusion criteria, if any, should be taken into account.

Thus the availability of different screening methods that would allow individuals in the target population to choose their preferred strategy based on their preferences and values does not seem to be an effective option. The offer of a choice between two tests was not associated with increased coverage in a recent trial (Segnan et al. 2005). Offering an alternative test to people refusing the main screening strategy of a screening programme might represent a feasible option (Zorzi et al. 2007). However, the sustainability and the organisational impact of such strategy should be assessed at the local level.

2.6.3.3 Screening interval and neoplasia detection rates according to the site distribution (see also Chapter 1)

Evidence from randomised trials indicates that annual guaiac FOBT is associated with a higher mortality reduction compared to biennial screening. Observational studies (Saito et al. 1995; Zappa et al. 2001) support the indication of biennial screening with iFOBT (see also Chapter 4). The recommended interval for colonoscopy screening is usually 10 years, although evidence from observational studies would indicate that the protective effect may be longer. A five-year interval is usually recommended for FS screening, although available evidence does not support such a recommendation: observational studies have indeed suggested that the protective effect of the exam for CRC arising in the distal colon may last for more than 10 years and it would justify the adoption of a protocol offering the test once in a lifetime (Selby et al. 1992; Newcomb et al. 2003).

The expected impact of endoscopic tests is also related to the site distribution of the neoplastic lesions in the colon and on their natural history (see also Chapter 1).

According to the results of a population-based case–control study, about 75–80% of colorectal cancer cases could be prevented by colonoscopy, with stronger effect for distal than for proximal CRCs (Brenner et al. 2007a). Recent cohort studies of people examined with colonoscopy confirm a protective effect of colonoscopy but suggest that the protective effect for proximal lesions might be overestimated (Lakoff et al. 2008; Baxter et al. 2009).

2.6.3.4 Cost-effectiveness (see also Chapter 1)

Available evidence from cost-effectiveness analysis suggests that all commonly considered CRC screening strategies (FOBT, FlexiSig, TC total colonoscopy) are nearly equivalent for prevention of colorectal cancer mortality (assuming 100% adherence) (Zauber et al. 2008) and they therefore represent reasonable alternatives. Compared with no screening, nearly all analyses found that any of the common screening strategies for adults 50 years of age or older will reduce mortality from colorectal cancer. The cost per life-year saved for colorectal cancer screening (US$ 10 000 to US$ 25 000 for most strategies compared with no screening) compares favourably with other commonly endorsed preventive health care interventions, such as screening mammography for women older than 50 years of age or treatment of moderate hypertension.

The costs of a screening programme are strongly affected by the organisation of screening, including the costs of infrastructure, information technology, screening promotion, training and quality assurance, and by the characteristics of the health system. These same factors represent the main determinants of the cost of the screening test, which influences the estimates of the relative costs of different strategies. The timing of the costs and benefits should be considered as well: for example, endoscopy costs are met at the beginning, while those of FOBT spread over 10 years.

Also, the advantage in terms of risk reduction must be weighed not only against the programme costs, but also against the inconvenience for the patient and the adverse effects (some of them causing death, potentially, thus mortality evaluation is also key in cost-effectiveness) associated with each strategy. These factors will influence the likelihood that patients will actually complete the tests required for any given strategy and therefore these factors also have a strong impact on the costs of the tests.

2.6.3.5 Resources and sustainability of the programme

A recent resources-use analysis of the strategies considered for the UK bowel cancer screening programmes found considerable differences between screening strategies in terms of endoscopy staffing and capital requirements. Limited availability of endoscopy services would favour the adoption of strategies using highly specific tests targeting older age groups, while a sigmoidoscopy-based strategy would be preferred if the financial resources are constrained. Also, the high number of cases detected when adopting a strategy using biennial FOBT for people aged 50 to 69 would have a significant impact on surgical services. Resource constraints, mainly related to availability of highly qualified personnel (Vijan et al. 2004) represent a strong barrier to the adoption of colonoscopy as a primary screening tool.

Summary of evidence

- The balance in favour of screening is likely to be reached at rather different ages in the various European countries, and several years later among women than among men **(III)**.
- Offering people the option to choose a preferred strategy based on individual preferences and values does not result in increased coverage **(II)**. Offering an alternative test to people refusing the main screening strategy adopted by a screening programme might represent a feasible and effective option **(V)**.
- The relative effectiveness in terms of incidence and mortality reduction of TC compared to FS might be overestimated **(IV)**.
- The costs of a screening programme are strongly affected by the organisation of screening, by the characteristics of the health system. Different strategies involve different timing of the expected costs and of the achievable benefits **(III)**.
- The impact of each specific strategy is strongly affected by its acceptability in the target population **(III)**.

Recommendations

- Gender- and age-specific screening schedules deserve careful attention in the design and implementation of screening interventions **(III - C).**[Rec 2.26]
- The costs of screening organisation (including infrastructure, information technology, screening promotion, training and quality assurance), the incidence of adverse effects and the likelihood that patients will actually complete the tests required for any given strategy represent additional important factors to be taken into account in the design and implementation of screening interventions and in the choice of the screening strategy **(III - A).**[Rec 2.27]

2.6.4 Implementation period (step-wise)

From an epidemiological perspective implementation entails more than simply carrying out the screening process and onward referral for assessment whenever required. The particular epidemiological concerns at the early, implementation phase focus on the complete and accurate recording of all indi-

vidual data pertaining to every participant, the screening test, its result, the decisions made as a consequence and their eventual outcome in terms of diagnosis and treatment and monitoring the causes of death.

Pilot demonstration projects have been carried out in some European countries to assess the feasibility of national programmes and their impact on routine services and to test whether the short-term outcomes of RCTs could be achieved in a context of routine care by a programme covering the whole target population (UK Colorectal Cancer Screening Pilot Group 2004; Goulard et al. 2008).

A new screening programme should be implemented in such a way that effectiveness can be evaluated. This can be achieved using individual-level randomisation into screening and control groups at the phase when the programme is new and resources and practical limitations prohibit the full coverage of the target population. This step-wise implementation, in which the target population is gradually taken into the programme as available resources expand, is both feasible and accepted when the available resources are used to their full extent.

A randomised screening design is helpful in the start-up phase when all the healthcare services and the infrastructure have not been evaluated within the screening programme, and since there cannot be certainty that the desired outcome and quality will be reached in that particular programme. In the first years of screening, an invitation scheme that gradually expands to cover more regions and age groups over the years can be used. Individuals in the control group will be offered screening later after the first years. This provides an unbiased comparison group.

A model from Finland is based on individual-level randomisation over the first six years (Malila, Anttila & Hakama 2005). For a six-year implementation phase it was expected that the number of colorectal cancer deaths will accumulate during 10 years from launching the programme in a population of around 3 million and a colorectal cancer mortality rate of approximately 15/100 000. Meanwhile, feasibility can be studied and the programme monitored with various process indicators such as attendance rates, proportion of test positives, detection rates, and positive predictive values.

A randomised screening design can also be used to assess the impact of alternative policies, such as different methods of invitation, or different target age groups. The randomised approach may also represent an acceptable and feasible alternative to assess the impact of a new screening test or to compare cost-effectiveness of different screening strategies, when a clinical randomised trial to evaluate the reduction in cancer occurrence or mortality is deemed impractical.

For other aspects relevant to implementation of screening programmes, see Sect. 2.3.1.

Recommendation

- Ideally, any new screening programme should be implemented using individual-level randomisation into screening and control groups in the phase when resources and practical limitations prohibit the full coverage of the target population **(VI - A).**[Rec 2.28]

2.6.5 Data collection and monitoring (see also Chapter 3)

2.6.5.1 Data sources

To determine whether a programme has been effective with respect to its impact on mortality and morbidity requires continuous follow-up of the target population over an extended period of time, and ascertainment and recording of the outcomes of the screening process and of the indicators of programme impact.

There is a special need to monitor performance of programmes using new tests.

The monitoring and evaluation of the programme therefore require that adequate provision be made in the planning process for the complete and accurate recording of all the relevant data. Achieving this goal is dependent on the development of comprehensive systems for documentation of the screening process, monitoring of data acquisition and quality, and accurate compilation and reporting of the results.

The information system should be designed to support the implementation of the different steps of screening, to record screening findings of each individual, to identify those detected with abnormalities, to monitor that the recommended action has been taken and to collect information about assessments and treatment.

For the purposes of impact evaluation this information should be linked to several external data sources, and legal authorisation to be able to achieve this should be secured: population registries, for estimating population coverage and to identify people in the target population in relation to their screening history; cancer or pathology registries, for cancer follow-up and for quality assurance purposes and feed-back to clinicians; and cause of death register for individuals in addition to population statistics, for assessing vital status and cause of death for final effectiveness evaluation.

2.6.5.2 How to respond to outcomes of monitoring

The design of the information system should take into account the views and data requirements of all groups involved in the screening programme. A wide range of consultation and participatory planning is important to improve programme evaluation, through common definition of data elements, indicators and standards. The programme should ensure that professionals involved in screening receive timely feedback on programme and individual performance. Rapid publication of the monitoring results is important as screening units and other actors need the information to run their activity and to implement quality assurance and training efforts. (See also Chapter 6).

In order to achieve these aims it is recommended to identify a coordination board that is responsible for regularly auditing the programme and taking necessary actions (including indications about the specific organisational changes which are necessary to meet the desired quality standards).

Recommendation

- In order to be able to evaluate effectiveness of screening, the data must be linked to several external data sources including population registries, cancer or pathology registries, and registers of the cause of death at the individual level in the target population. Therefore, legal authorisation should be put in place in order to be able to link the aforementioned data for follow-up when screening is introduced **(VI - A).**[Rec 2.29]

2.7 References

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3

Evaluation and interpretation of screening outcomes

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Recommendations[1]

3.1 The development of comprehensive systems for documentation of the screening processes, monitoring of data acquisition and quality, and accurate compilation and reporting of results are essential to the evaluation of population screening programmes **(VI - A).**[Sect 3.1]

3.2 Detailed eligibility criteria should be predefined, based on a pre-specified protocol (see also Ch. 2, Rec. 2.4, Sect. 2.3.1.1) **(VI - B).**[Sect 3.2.1]

3.3 A database consisting of individual records (one record per person for each screening episode) is essential in order to produce results on screening performance **(VI - A).**[Sect 3.2.1]

3.4 Quality control procedures for the database should be available and run regularly to check the quality of the data and to correct data entry errors **(VI - A).**[Sect 3.2.1]

3.5 For monitoring the programme, tables presenting performance indicators should be produced at regular intervals (at least annually) by age and gender and by type of screening test using the collected data **(VI - A).**[Sect 3.2.5]

3.6 All indicators should be calculated and reported for age-gender subgroups **(VI - A).**[Sect 3.3]

3.7 Invitation coverage should be high (95%) in order to maximise screening impact **(VI - A).**[Sect 3.3.1]

3.8 A minimum uptake of 45% is acceptable **(III - A)**, but it is recommended to aim for a rate of at least 65% **(III - A).**[Sect 3.3.1]

3.9 Rates of inadequate FOBTs should remain low. These reflect the understanding of the people who are using the test and therefore the quality of the information given to the population. Less than 3% is acceptable, less than 1% is desirable (See Ch. 4, Rec. 4.21) **(III - A).**[Sect 3.3.2; 4.3.4]

3.10 High rates of referral to follow-up colonoscopy should be achieved for people with a positive screening test or examination requiring follow-up (90% is acceptable, >95% is desirable) **(VI - A).**[Sect 3.3.2; 3.3.3]

3.11 The proportion of screening and follow-up colonoscopies that are incomplete should be recorded separately. A completeness rate of >90% is acceptable, >95% is desirable (see also Ch. 5, Rec. 5.41) **(III - A).**[Sect 3.3.2; 3.3.3; 5.4.5.1]

3.12 A favourable stage distribution in screen-detected cancers compared to clinically diagnosed cancers should be observed. In absence of this condition a screening programme could not be effective **(I - A).**[Sect 3.3.2]

3.13 The rate of serious adverse effects should be monitored carefully **(III - A).**[Sect 3.3.2; 3.3.3]

3.14 High rates of compliance with follow-up colonoscopy should be achieved (85% is acceptable, >90% is desirable) **(III - A).**[Sect 3.3.2; 3.3.3]

3.15 The time in days, between completion of a screening test and receipt of results by the participant should be as short as possible: acceptable standard >90% within 15 days **(VI - A).**[Sect 3.3.4]

3.16 Follow-up colonoscopy after positive screening (any modality) should be scheduled within 31 days of referral (acceptable standard is >90%, desirable >95%). (See Ch. 5, Rec. 5.19) **(VI - B).**[Sect 3.3.4; 5.3.5]

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[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.

3.17 The time interval between positive FS or colonoscopy and definitive management should be minimised and in 95% of cases should be no more than 31 days (acceptable standard) (see Ch. 8, Rec. 8.2) **(VI - B).**[Sect 3.3.4; 8.2]

3.18 The evaluation of surrogate outcome measures requires rigorous data collection of colorectal cancer registrations and stage of disease in the target population. Such data should also be collected for the time period leading directly up to the introduction of a screening programme to allow trends to be analysed **(VI - A).**[Sect 3.4]

3.19 Data on interval cancers should be collected and reported **(VI - A).**[Sect 3.4.1]

3.20 Evaluation of interval cancer rates requires careful linkage of cancer registrations with screening history to allow cancers to be classified (i.e. as screen detected, interval, non-responders, other). A link with the cancer registry should be established **(VI - A).**[Sect 3.4.1]

3.1 Introduction

Evaluation and interpretation of screening outcomes are essential to recognising whether a colorectal cancer screening programme is achieving the goals for which it has been established. It is recognised that the context and logistics of screening programmes will differ by country and even by region. For example, the prior existence of a population register facilitates issuing personalised invitations, whereas the absence of such a register may lead to recruitment by open invitation. Many of these contextual differences will affect the measured outcomes.

The effectiveness of a programme is a function of the quality of its individual components. Success of the programme is measured not only by its impact on public health, but also by its organisation, implementation, and acceptability.

The organisational aspects of a screening programme, described in Chapter 2 of these Guidelines influence the evaluation and interpretation of screening outcomes. Therefore all aspects of the programme should be monitored and evaluated.

To determine whether a programme has been effective with regard to its impact on morbidity and mortality requires continuous follow-up of the target population over an extended time-frame. Therefore early-performance indicators using standard definitions, available early in the lifetime of a screening programme are essential to measure the quality of the programme and its potential longer-term impact.

A key component in the evaluation of population screening programmes is data collection. Colorectal cancer screening can be performed using various tests or techniques. Data collection necessary for evaluation can be common to all tests or specific to particular tests. The examples given in these Guidelines refer to in vitro stool tests based on detection of faecal occult blood (FOBT) that are currently the most widely used, and to endoscopic tests i.e. flexible sigmoidoscopy (FS) or colonoscopy (CS). In the text, gFOBT refers to guaiac-based FOBTs, and iFOBT to immunological FOBTs.

This chapter includes only the minimum data variables and indicators that should be collected and measured for the purposes of programme evaluation. It does not discuss quality indicators such as those used to measure endoscopist performance or patient satisfaction; a number of such indicators are described elsewhere in the Guidelines.

It should be noted that in a setting where opportunistic screening (for example by colonoscopy) has been taking place for some time, the uptake and performance of an organised programme may differ markedly from those in a setting where no such screening has been taking place. The majority of the values of the indicators described below will relate to the latter setting.

Recommendation

- The development of comprehensive systems for documentation of the screening processes, monitoring of data acquisition and quality, and accurate compilation and reporting of results are essential to the evaluation of a population screening programme (Day, Williams & Khaw 1989) **(VI - A).**[Rec 3.1]

3.2 Data items necessary for evaluation

This section describes the data items and information that must be collected, recorded and stored in order to generate the indicators, analyses and reports required for evaluation.

3.2.1 Programme conditions

Programme type

As mentioned above, the organisational aspects of a screening programme influence the evaluation and interpretation of screening outcomes. Population-based programmes are recommended because they require an infrastructure that is conducive to implementation of quality assurance and evaluation, such as through linkage of screening data and cancer registry data (Karsa et al. 2010). It is therefore important to document the type of programme (population-based or non-population-based) and to describe the sources of population data used for identification and invitation of the eligible target population (e.g. population registry). Data on screening outcomes should be linked with data from other registries in order to monitor and evaluate the programme.

Primary screening test

Currently only the faecal occult blood test (FOBT) is recommended by the EU for CRC screening. However endoscopic screening programmes with flexible sigmoidoscopy (FS) or colonoscopy (CS) as primary screening tests are currently running in a number of Member States. Given the potential impact of the type of primary screening test or tests used in a programme on the respective results and performance, the type of primary screening test should always be indicated when documenting results and reporting.

Population base

A screening programme is population based when every member of the target population in the area designated to be served by the programme is known to the programme, and when the eligible members of the target population are individually invited to participate.

The availability and reliability of target population data will depend on the existence, quality and accessibility of population registers in the region where the programme is being set up. Population registers are not always available and demographic data for identifying the target population might be obtained from various sources, e.g. census data, electoral registers, private or statutory health care registers or health insurance funds registers. The choice of the target population database for issuing invitations will depend on the completeness of the database and on the individuals or variables included, e.g. electoral registers might not include eligible foreigners or dates of birth.

A database consisting of individual records (one record per person for each screening episode) is essential in order to produce results on organisational aspects of the programme (coverage, participation) and screening performance. The data collected should respect a logical order and follow the development of the screening process (identification of person [date of birth, gender], date of invitation, date of reminder, date of test, test results, date of the examination performed during assessment, results, colonoscopy date, results, adverse effects, treatment). The location in the bowel of any detected lesions or cancers (Tumour site) should also be recorded [Rectum, sigmoid, descending colon (distal colon) transverse colon, splenic flexure, ascending colon].

Each variable should be precisely defined. All data collected for each round should be kept and updated information should not overwrite data provided during preceding rounds. All information on the

timing of events during each screening episode, including invitation history, should be recorded as calendar dates. This ensures maximal flexibility of the database for future evaluation efforts and participation in multi-centre studies. It also permits distinguishing between the first and subsequent screening episodes and between participants with different patterns of attendance (see Section 3.3).

- **Self registrations**

Self registrations are defined as eligible residents of the designated area served by the programme, who request screening but who are not identified by the target population register used to generate invitations. Their number should be reported separately.

- **Self referrals**

Self referrals are defined as people requesting screening before receipt of an invitation or outside the invited age-range. They should not be included in coverage by invitation, or in participation rate if in the relevant age range, but their number should be reported separately.

Recommendations

- Detailed eligibility criteria should be pre-defined based on a pre-specified protocol (see also Ch. 2, Rec. 2.4, Sect. 2.3.1.1) **(VI - B).**[Rec 3.2]
- A database consisting of individual records (one record per person for each screening episode) is essential in order to produce results on screening performance **(VI - A).**[Rec 3.3]
- Quality control procedures for the database should be available and run regularly to check the quality of the data and to correct any data entry errors. **(VI - A).**[Rec 3.4]

3.2.2 Invitation variables

Target population

The target population are those people of eligible age according to the programme policy residing in the area designated to be served by the screening programme.

Eligible population

The eligible population are those people in the target population who fulfil the eligibility criteria specified in the programme policy.

Invited

The invited are those members of the eligible population who have received an invitation for screening according to the programme policy/process; e.g. invited by mail, by primary care practitioner. N.B. Not all invitations sent may be received.

3.2.3 Process variables of primary screening and follow up

3.2.3.1 Process variables in screening with the faecal occult blood test (FOBT) and other in vitro tests

The following process variables are described in the context of screening with faecal occult blood testing because FOBT is the only screening test currently recommended by the EU. In principle, the same

definitions apply to other in vitro tests. It is recommended that the type of test used for screening is indicated when reporting data

- **Screened/tested**

The group of screened or tested participants are those who have used and returned an FOBT irrespective of the result. This includes people with inadequate/incomplete results. Note that each person is counted once regardless of the number of tests performed.

- **Inadequate test**

An inadequate FOBT is a test returned by a participant, the results of which cannot be reliably determined (see Chapter 4). The quality is insufficient for processing and the test cannot be used for recording a result according to the programme policy.

- **Positive test**

A positive i.e. abnormal FOBT result is a result based on the last adequate test that according to the programme policy leads directly to referral to follow-up colonoscopy.

- **Referral to follow-up colonoscopy[2]**

This variable refers to participants with a positive FOBT who require an appointment for follow-up colonoscopy. Ideally all participants with positive FOBTs would be referred to follow-up colonoscopy.

3.2.3.2 Variables in endoscopic screening

The following process variables are described in the context of CRC screening in which either flexible sigmoidoscopy (FS) or colonoscopy (CS) is used as the primary screening test.

- **Screened**

The group of screened participants comprises those people who have attended the FS or CS screening examination, irrespective of the result. This includes people with inadequate/incomplete results. Note that each person is counted once regardless of the number of exams performed.

- **Inadequate test**

This group comprises those participants who attended the FS or CS screening examination, the results of which could not be interpreted because of inadequate preparation, and who do not have an adequate screening FS or CS in the reporting period. In such cases a new screening examination should be performed.

- **Positive test**

A positive i.e. abnormal screening FS or CS is one resulting either directly in diagnosis of cancer or removal of an adenoma or other lesion, or in referral for further investigation according to the programme policy (see Chapters 2 and 5).

- **Referral to follow-up colonoscopy**

Included in this group are the participants with a positive screening FS or CS who require a medical appointment for follow-up colonoscopy.[3]

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[2] The process variables related to performance of follow-up colonoscopy as a result of a positive FOBT test are the same as for follow-up colonoscopy as a result of a positive FS or CS screening examination. They are therefore described in Section 3.2.3.2 ("referral to surgery or tertiary endoscopy", "severe complications requiring hospitalisation", "30-day mortality").

[3] In rare cases in which follow-up colonoscopy is not possible, other follow-up examinations may be performed. Those patients should be included in the group referred to follow-up CS but should also be counted separately.

- **Referral to surgery or tertiary endoscopy**

This group of participants includes those who require an appointment for surgery or tertiary endoscopy for removal of challenging lesions following a positive screening FS or CS (or as a consequence of follow-up colonoscopy after primary screening with FS or CS).

- **Severe complications requiring hospitalisation**

A very small number of participants will develop severe complications such as hospitalisation within 30 days due to serious haemorrhage involving transfusion, or due to perforation, vagal syndrome or peritonitis-like syndrome as a consequence of primary screening with FS or CS (or as a consequence of follow-up colonoscopy for any primary screening test).

- **30-day mortality**

In a much smaller number of participants than those experiencing severe complications requiring hospitalisation, death may occur within 30 days after having undergone primary screening with FS or CS or follow-up colonoscopy, whether diagnostic or therapeutic, for any screening test. If the death is attributed to complications caused by the endoscopy, the participant should be counted in this group.

3.2.4 Programme outcome variables

The following outcome variables apply to CRC screening performed with any of the currently available primary screening tests.

Follow-up colonoscopy

Participants in the group on which diagnostic or therapeutic colonoscopy[4] has been performed to follow-up primary screening according to programme policy include participants, the screening endoscopy of which was inadequate or incomplete. Note that each person is counted once regardless of the number of follow-up colonoscopies that were performed. Where more than one colonoscopy or other follow-up investigation is performed, the reported result should be that of the complete diagnostic or therapeutic work-up.

Definitions of what is included in the reported result (e.g. grade of neoplasia,[5] TNM stage, other lesions) are given in Chapter 7 (Sect. 7.2, Table 7.1, Rec. 7.1-7.5, 7.8).

If more than one lesion is found, then the lesion with the worst prognosis (see Chapter 7) should be indicated as the outcome of screening.

In the event of more than one detected lesion in a person where it is not possible to determine difference in prognosis, then the lesion requiring the most invasive procedure (see Ch. 7 and Ch. 8) should be recorded.

Lesions

Any lesion removed or biopsied at endoscopy or surgery (whether or not they were diagnosed as adenomas) should be recorded.

Adenomas

Pathological specimens removed at endoscopy or surgery that have been reported by a pathologist to be adenomatous should be recorded.

[4] See previous footnote on follow-up colonoscopy.

[5] In screening programmes the use of the term “advanced adenoma” has developed and is sometimes used to categorise adenomas for management. In the present context an advanced adenoma is one that is either ≥10 mm or contains high-grade mucosal neoplasia or a villous component (Ch. 7).

Advanced adenoma

If it is not possible to collect such details for organisational reasons, the programme should at least focus on collecting and reporting data on adenomas ≥10 mm in size (see Ch. 9, Sect. 9.1). For definition, see Ch. 7, Sect. 7.2, and footnote 5 on previous page.

Cancers

Colorectal cancer diagnosed by the screening programme, or diagnosed as a direct result of participating in the screening programme (see Ch. 7, Sect 7.2 for definition).

Severe complications requiring hospitalisation

For definition, see Sect. 3.2.3.2.

30 day mortality

For details, see Sect. 3.2.3.2.

3.2.5 Data tables

Recommendation

- For monitoring the programme, tables presenting performance indicators should be produced at regular intervals (at least annually) by age and gender and by type of screening test using the collected data **(VI - A).**[Rec 3.5]

Tables should present data for people, not data for tests, and therefore each person is counted once regardless of the number of tests performed (see Table 3.1).

They should present the participation in the programme, the main results of testing, and the main detection outcomes. When processing the data, decisions should be made regarding age. Age can be calculated according to different events (age at invitation, age at time of screening, age at time of diagnosis). Age at time of screening is preferable for indicators pertaining to the testing procedure, results and outcome. Age should be presented in 5-year groups.

Table 3.1: List of recommended data tables to be produced by CRC screening programmes

1. Targeted
2. Eligible
3. Invited
4. Screened/tested at first screening and at subsequent screening episodes
5. Inadequate tests
6. Positive test or screening
7. Follow-up colonoscopy examination attended (diagnostic assessment and/or treatment)
8. Negative follow-up colonoscopy examination (diagnostic assessment and/or treatment)
9. Positive follow-up colonoscopy examination (diagnostic assessment and/or treatment)
10. Lesion detected (at least one)
11. Adenoma detected (at least one)
12. Non-advanced adenoma detected (at least one)
13. Advanced/high-risk adenoma detected (at least one)
14. Cancer detected by stage

Tables should record the number of people by age, sex and type of screening test in the respective reporting period. Where applicable, data should be broken down by initial and subsequent screening episodes.

3.3 Early performance indicators

Several rounds of screening are required before the impact of a screening programme on CRC mortality in the target population can be measured. Early performance indicators using standard definitions must therefore be used early in the lifetime of a screening programme to measure the quality of the screening process and to assess its potential longer-term impact. The accumulating experience in piloting and implementing population-based screening programmes provides an evidence base that can be used to establish and refine standards and set performance targets.

Factors affecting performance indicators

Coverage and uptake, i.e. participation, are organisational parameters that apply to CRC screening programmes using any kind of primary screening test. They have a substantial impact on the potential effectiveness of any screening programme because they reflect the degree to which the population is exposed to the screening intervention. Coverage and uptake in turn will be affected by the age and gender distribution of the target population due to differential uptake rates. Screening performance indicators will be affected by the age and gender distribution of the population screened due to variation in underlying incidence of disease.

Recommendation

- All indicators should be calculated and reported for age-gender subgroups **(VI - A).**[Rec 3.6]

In addition, age-gender standardised measurements should be developed for comparative purposes.

Age should be recorded as the age of the person at the time of the invitation (for measurement of coverage/participation) or at time of screening (for measurement of screening outcome) for the respective screening round. The outcome of the screening examination for a person should thus be recorded in the same age category throughout a particular screening episode.

Screening performance indicators will also be affected by the background incidence in the target population in the absence of screening. Efforts should therefore be made to document age-gender specific incidence rates in the target population for the period immediately prior to the introduction of the screening programme.

If high-risk subjects are identified, managed, and/or excluded from the programme and reported separately, this should be stated.

Performance indicators will also vary according to whether the screen is a prevalent (first) screen for those invited for the first time, an incident (repeat) screen for those previously screened at the routine interval, or a screen for previous non-responders. Indicators at subsequent rounds will vary according to the screening interval.

Only the first organised screening round will consist entirely of subjects invited and attending for the first time; all additional rounds will comprise subjects falling into each of the categories described above. The cut-off point for separating 'subsequent regular' from 'subsequent irregular' screening should be established, taking into consideration that most programmes do not succeed in inviting each individual participant at the routine screening interval (e.g. a cut-off point at 30 months for a programme with a 2-year screening interval).

Data should be analysed separately for those invited/screened at:

- initial screening, i.e. the first invitation of individual people within the screening programme, regardless of the organisational screening round;
- subsequent invitation for previous never responders;
- subsequent invitation for those previously screened[6];
- screens as a result of self-referral (defined as people requesting screening before reception of an invitation or outside the invited age range); and
- screened following self-registration (those not recorded in target population).

Tables 3.2–3.5 list the key performance indicators for gFOBT, iFOBT, FS and colonoscopy respectively that have been reported from randomised controlled trials and from population-based programmes. For the majority of indicators the published values will have been influenced by the screening policy adopted in the respective trials and programmes. Other than those related to participation, the values reported here have therefore not been used to define acceptable levels.

There are a large number of possible process indicators, reflecting specific parts of the screening process. The present outline is confined to those that have epidemiological importance as identified within the trials. They measure participation, quality, efficacy, and organisation. Except for measures of participation, all other indicators are presented separately for in vitro tests (FOBT) and for endoscopic tests (FS or colonoscopy).

[6] Where possible, these should be separated into invitations at the routine screening interval defined by the screening policy, and subsequent invitations at irregular intervals, i.e. those who have been screened at least once who do not respond to an invitation to routine re-screening and are invited in a subsequent organisational screening round [or attend a subsequent screening more than a defined time frame after the previous test].

3.3.1 Programme coverage and uptake

Coverage and uptake, i.e. participation are organisational parameters that apply to CRC screening programmes using any kind of primary screening test.

Coverage by invitation

Coverage of the screening programme by invitation is the extent to which the invitations sent out by the screening programme within the defined screening interval include the eligible population. It gives information on the performance of the organisation of the programme in inviting the target population within the defined screening period.

$$\frac{\text{N people invited during the time frame*}}{\text{N eligible people in the target population during the time frame*}}$$

* equal to the defined screening interval or reporting period, e.g. 12 months in the case of yearly reporting.

The eligible population is defined in Ch. 2, Sect. 2.3.1.1 (inclusion/exclusion criteria).

Recommendation

- Invitation coverage should be high (95%) in order to maximise screening impact. **(VI - A).**[Rec 3.7]

Coverage by examination

Coverage of the screening programme by examination is the extent to which screening examinations have actually been delivered to the eligible population**.**

$$\frac{\text{N screened/tested during the time frame*}}{\text{N eligible people in the target population during the time frame*}}$$

* equal to the defined screening interval or reporting period

Screened here is defined as people tested at least once regardless of whether the result was adequate or inadequate and includes self referrals but not self registrations. The latter should be counted but reported separately. Coverage of the target age range for invitation will by definition exclude self referrals outside the age range. This is important in programmes where no comprehensive population lists are available and self referral or self registration can account for a large proportion of subjects screened.

Both of the coverage indicators (by invitation and examination) are useful at a local level to assess completeness of population lists and target population's database.

Uptake (participation) rate

The number of people who have been screened, within a defined time frame following an invitation, as a proportion of all people who are invited to attend for screening.

$$\frac{\text{N people invited and screened/tested during the time frame*}}{\text{N eligible people invited during the time frame*}}$$

* equal to the defined screening interval or reporting period

The effectiveness of the programme will depend on the participation rate. In the randomised FOBT trials, uptake at the first round was between 49.5% and 66.8% (Table 3.2); uptake at subsequent rounds varied according to the policy for reinvitation. In a US study that recruited volunteers 75%–78% of subjects invited were screened at least once (Mandel et al. 1993). Reported uptake in population-based programmes ranges from 17.2% to 90.1% at the first round; the range at subsequent rounds is smaller (22.3%–52.1%) (see Tables 3.2 and 3.3).

For flexible sigmoidoscopy, uptake rates in RCTs ranged from 32.4% to 83.5%, again with high rates being associated with recruitment of volunteers or those who had expressed interest in participation). In population-based programmes, uptake rates range from 7% to 55% (Table 3.4).

Recommendation

- A minimum uptake of at least 45% is acceptable **(III - A)**, but it is recommended to aim for a rate of at least 65% (Faivre et al. 1991; Zorzi et al. 2008) **(III - A).**[Rec 3.8]

3.3.2 Outcomes with faecal occult blood testing (FOBT) for primary screening

A table should be made to present the test results (positive, negative, or inadequate) by gender and age. Results should also be broken down by initial and subsequent screens as described above (Section 3.3). FOBT indicators will vary according to the type of test used and programme policy, and therefore these should be reported.

Inadequate FOBT rate

The rate of inadequate tests is defined as the proportion of people screened with one or more FOBT returned during the respective time frame (e.g. a 12-month period) none of which were adequate.

$$\frac{\text{N people who returned only inadequate FOBTs during the time frame*}}{\text{N people tested during the time frame*}}$$

* equal to the defined screening interval or reporting period

Rates of inadequate tests should remain low. They reflect, among other things, the understanding of the people who are using a test and therefore also the quality of the information provided to them.

In population-based programmes, inadequate gFOBT rates between 0.4% and 4.5% (Table 3.2) have been reported. No data are available yet for iFOBT.

Recommendation

- An inadequate rate of FOBT less than 3% is acceptable, less than 1% is desirable (see Ch.4, Rec 4.21, Sect. 4.3.4) **(III - A).**[Rec 3.9]

Positive FOBT rate

In the RCTs of gFOBT, the positive rate without rehydration was 1.2%–3.8%, and with rehydration 1.7%–15.4%. In average risk population-based programmes the positive rate for gFOBT in participants aged 50-69 years was 1.5% – 8.5% in the first round. Only two studies have reported rates at subsequent rounds, with positive rates of 0.8% and 1.8% (Table 3.2).

$$\frac{\text{N people with a positive FOBT result during the time frame*}}{\text{N people adequately tested during the time frame*}}$$

* equal to the defined screening interval or reporting period

For iFOBT the range of positive rates in population-based studies was 4.4%–11.1% in the first round, with one study reporting a rate in subsequent rounds of 3.9% (Zorzi et al. 2008) (Table 3.3).

Positive test rates for gFOBT will depend on the method of slide handling used, and will be higher if the slides are rehydrated. The positive rate for iFOBT will vary according to the cut-off level adopted (see Chapter 4).

Positive rates should be presented in a table by 5–year age groups and gender. Positive rates are higher in men than in women and increase with age in both genders reflecting the natural history of the disease.

Referral to follow-up colonoscopy after FOBT

The rate of referral for follow-up colonoscopy after a positive FOBT is defined as the proportion of people screened with a positive test and referred to colonoscopy among those presenting with a positive/abnormal test during the respective time frame.

$$\frac{\text{N people presenting with a positive test and referred for colonoscopy during the time frame*}}{\text{N people presenting with a positive/abnormal test during the time frame*}}$$

* equal to the defined screening interval or reporting period

Recommendation

- High rates of referral to follow-up colonoscopy should be achieved for people with a positive screening test or examination requiring follow-up (90% is acceptable, >95% is desirable) **(VI - A).**[Rec 3.10]

Follow-up colonoscopy compliance rate

In the RCTs using gFOBT, colonoscopy compliance rates range from 73% to 95%; in population programmes rates between 88% and 92% have been reported. (Table 3.2)

$$\frac{\text{N people having attended a colonoscopy examination during the time frame*}}{\text{N people presenting with a positive screening test and referred during the time frame*}}$$

* equal to the defined screening interval or reporting period

Recommendation

- High rates of compliance with follow-up colonoscopy should be achieved (85% is acceptable, >90% is desirable) **(III - A).**[Rec 3.14]

Follow-up colonoscopy outcome, detection rates

A table should be made to present colonoscopy results by gender and age:

- Negative, (defined as no identified lesions, adenomas or cancers);
- Presence of adenomas of any size;
- Presence of non-advanced adenomas;
- Presence of advanced adenomas; and
- Presence of advanced cancers.

The above colonoscopy indicators are essential programme indicators of efficacy.

Completion of follow-up colonoscopy after FOBT

The proportion of incomplete colonoscopies should be recorded (see Chapter 5 for definition). One RCT of FOB testing reported a completion rate at follow-up colonoscopy of 89% (Kronborg et al. 1996).

Recommendation

- A completion rate of follow-up colonoscopy of >90% is acceptable, >95% is desirable (see also Ch. 5, Rec. 5.41) **(III - A).**[Rec 3.11]

If more than one lesion is found, the lesion with the worst prognosis should be used for evaluation purposes as the result of follow-up colonoscopy.

In the event of more than one detected lesion in a person where it is not possible to determine difference in prognosis, then the lesion requiring the most invasive procedure should be recorded, (see Ch. 1 and Ch. 7).

Detection rates of FOBT screening programme

- **Lesion detection rate**

The lesion detection rate is reported in % and is defined as the proportion of participants with at least one detected lesion among those adequately tested during the respective time frame.

$$\frac{\text{N people with at least one detected lesion during the time frame*}}{\text{N people adequately tested during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **Adenoma detection rate**

The adenoma detection rate is reported per 1 000 (‰) and is defined as the proportion of participants with at least one detected adenoma among those adequately tested during the respective time frame.

$$\frac{\text{N people with at least one detected adenoma during the time frame *}}{\text{N people adequately tested during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **Advanced adenoma detection rate**

The advanced adenoma detection rate is reported per 1 000 (‰) and is defined as the proportion of participants with at least one detected advanced adenoma among those adequately tested during the respective time frame.

$$\frac{\text{N people with at least one detected advanced adenoma during the time frame *}}{\text{N people adequately tested during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **Cancer detection rate**

Detection rates for cancers and adenomas observed in population-based programmes using FOBT are summarised in Table 3.2 and 3.3. Cancer detection rates range from 1.2‰ to 9.5‰ at the first round, with lower rates at subsequent rounds. Detection rates of all adenomas range from 5.2‰ to 22.3‰ at the first round, with lower rates at subsequent rounds. (However some studies report only advanced or high-risk adenomas.)

$$\frac{\text{N people with at least one detected cancer during the time frame *}}{\text{N people adequately tested during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **Stage of screen-detected cancers**

The stage distribution of screen-detected cancers should be reported by screening round, age and gender. In the RCTs using only gFOBT, the proportion of screen-detected cancers that were Dukes Stage A ranged from 26% to 36% (Table 3.2).

The staging of colon cancer should use firstly the international TNM classification and secondly the Dukes classification (see Chapter 7).

Recommendation

- A favourable stage distribution in screen-detected cancers compared to clinically diagnosed cancers should be observed. In absence of this condition a screening programme could not be effective **(I - A).**[Rec 3.12]

Positive predictive values for FOBT screening programmes

Since lesions can only be detected if follow-up colonoscopy is performed, the definitions below take into account whether or not follow-up CS was actually performed. Other positive predictive values can be calculated, such as the PPV of the positive test without any further adjustment. In this case, the denominator would be the number of people presenting with a positive test result leading to referral for colonoscopy.

- **PPV for detection of lesions**

The positive predictive value (PPV) for detection of a lesion through an FOBT screening programme is defined as the percentage of people with detection of at least one lesion at follow-up CS among those with positive FOBT tests who have attended follow-up CS.

$$\frac{\text{N people with at least one detected lesion during the time frame *}}{\text{N people positive to FOBT having attended a colonoscopy during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **PPV for detection of adenoma**

The positive predictive value for detection of an adenoma through an FOBT screening programme is defined as the percentage of people with detection of at least one adenoma at follow-up CS among those with positive FOBT tests who have attended follow-up CS.

$$\frac{\text{N people with at least one detected adenoma during time frame*}}{\text{N people positive to FOBT having attended a colonoscopy during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **PPV for detection of advanced adenoma**

The positive predictive value for detection of an advanced adenoma through an FOBT screening programme is defined as the percentage of people with detection of at least one advanced adenoma at follow-up CS among those with positive FOBT tests who have attended follow-up CS.

$$\frac{\text{N people with at least one detected advanced adenoma advanced adenoma during time frame*}}{\text{N people positive to FOBT having attended a colonoscopy during the time frame*}}$$

* equal to the defined screening interval or reporting period

Values varied between 14.6% and 54.5% in the RCTs using only gFOBT without rehydration and from 6.0% to 11.0% with rehydration.

- **PPV for detection of cancer**

The positive predictive value for detection of a cancer through an FOBT screening programme is defined as the percentage of people with detection of at least one cancer at follow-up CS among those with positive FOBT tests who have attended follow-up CS. Values varied between 5.2% and 18.7% in the RCTs without rehydration and from 4.5% to 8.6% in the initial round of population-based programmes (5.3% to 10.6% in subsequent screening) (Tables 3.2 and 3.3).

$$\frac{\text{N people with at least one detected cancer during time frame*}}{\text{N people positive to FOBT having attended a colonoscopy during the time frame*}}$$

* equal to the defined screening interval or reporting period

Table 3.2: Evidence on performance indicators for guaiac based FOB testing.

	Range from RCTs[1]	Range from population-based programmes[2]
Uptake rate 1st round	49.5%–66.8%	17.2%–70.8%
Subsequent round	60%–94%	22.3%–52.1%
Inadequate rate	-	0.4%–4.5%
Positive rate for FOBT	1.2%–3.8% (1.7%–15.4%) (with rehydration)	1st screen 1.5%–8.5% Subsequent screen 0.8%–1.8%
Colonoscopy compliance rate	73%[3]–95%	87.8%–91.7%
Colonoscopy completion rate	89%–100%	72%–95%
Adenoma detection rate 1st screen	5–14.5 ‰	5.2–10.5 ‰
Subsequent screen	3.8 ‰	3.3–4.7 ‰
Cancer detection rate 1st screen	1–2.5 ‰	1.2–2.3 ‰
Subsequent screen	1.1–1.4 ‰	0.9–0.94 ‰
Proportion of screen detected cancers that are stage A	26%–36%	-
PPV for adenoma as the most severe lesion	14.6%–54.8% (6.0%–11.0%) (with rehydration)	30.3% 26.8%
PPV for cancer	5.2%–18.7% (0.9%–6.1%) (with rehydration)	1st screen 6.2%–8.5% Subsequent screen 5.3%–10.6%
Adverse effects (perforation, serious haemorrhage)	0.5%–1.6% of subjects undergoing colonoscopy	-

[1] Minnesota (Mandel et al. 1993) age range 50-80 annual and biennial, Hemoccult, 82.5% rehydrated.
Goteborg (Kewenter et al. 1994) age range 60-64 2 screens at 16-24 month interval, Hemoccult II, majority hydrated.
Funen (Kronborg et al. 1996) age range 45-75 biennial, Hemoccult II not rehydrated.
Nottingham (Hardcastle et al. 1996) age range 45-74 biennial, Hemoccult not rehydrated.
Netherlands (Hol et al. 2010) age range 50-74

[2] Greece (Chrissidis et al. 2004) age range 50+
France (Denis et al. 2007) age range 50-74
Italy (Federici et al. 2006) age range 50-74
UK (Hart et al. 2003) age range 41-65
Spain (Peris et al. 2007) age range 50-69
UK (Weller et al. 2007) age range 50-69
Finland (Malila et al. 2008) age range 60-69

[3] Others had an alternative such as barium enema

Table 3.3: Evidence on performance indicators for iFOB testing

		Data from RCT[1]	Range from population-based programmes[2]
Uptake (participation) rate		61.5%	17%–90.1%
Inadequate rate		-	-
Positive rate	Round 1	4.8%	4.4%–11.1%
	Any round		7.1%
	Round 2		3.9%
Colonoscopy compliance rate		96%	60%–93.1%
Colonoscopy completion rate		98%	-
Adenoma detection rate	1st screen	27.6 ‰	13.3–22.3 ‰
Cancer detection rate	1st screen	4.7 ‰	1.8–9.5 ‰
	2nd screen		1.3 ‰
PPV adenoma	1st screen	59.8%	19.6%–40.3%
PPV cancer	1st screen	10.2%	4.5%–8.6%
	2nd screen		4.0%

[1] Netherlands (Hol et al. 2010) age range 50-74

[2] Italy (Crotta et al. 2004) age range 50-74
Italy (Grazzini et al. 2004) age range 50-70
Uruguay (Fenocchi et al. 2006) age range 50+
Japan (Saito 2006) age range 40+

Endoscopic complications in FOBT screening programme

In addition to death within 30 days, other serious complications that may be attributable to the endoscopic examination are described in Sect. 3.2.3.2. However, many different endoscopic complications can occur in FOBT screening programmes, all complications should be recorded as well as the respective cause, if ascertainable.

For any complication the rate is defined as the proportion of participants presenting with a complication among those having attended a colonoscopy during the respective time frame. The rate should be calculated in total and separately for screening and follow-up colonoscopy if applicable.

$$\frac{\text{N people presenting with complication during the time frame*}}{\text{N people having attended a colonoscopy during the time frame *}}$$

* equal to the defined screening interval or reporting period

Recommendation

- The rate of serious adverse effects should be monitored carefully **(VI - A).**[Rec 3.13]

The RCTs in Nottingham and Minnesota showed that approximately 16 major complications due to follow-up CS occurred per 1 million persons screened with FOBT. This corresponds approximately to the risk of major complications from follow-up colonoscopy in a well-organised high-quality flexible sigmoidoscopy screening programme (see Ch. 1, Sect. 1.2.1.4 and 1.3.1.4).

3.3.3 Outcomes with flexible sigmoidoscopy (FS) or colonoscopy (CS) as primary screening tests

A table should be made to present the test results (positive, negative, or inadequate) by gender and age. Results should also be broken down by initial and subsequent screens as described above (Sect. 3.3).

Inadequate FS or CS rates

An inadequate FS or CS occurs when the examination cannot be performed because of inadequate-preparation.

In two RCTs inadequate FS rates ranged from 11% to 12.7% (Table 3.4) (Weissfeld et al. 2005; Segnan et al. 2007).

$$\frac{\text{N people with an inadequate FS or CS, respectively, during the time frame*}}{\text{N people screened with FS or CS, respectively, during the time frame*}}$$

* equal to the defined screening interval or reporting period

Complete FS or CS rates

FS and CS examinations are considered complete when conducted under adequate bowel preparation and with visualisation of the colon beyond the sigmoid-descending-colon-junction (FS), or the caecum (CS).

$$\frac{\text{N people with complete FS or CS, respectively*}}{\text{N people screened with FS or CS, respectively, under adequate bowel preparation}}$$

* equal to the defined screening interval or reporting period

One RCT has reported a rate of incomplete CS examination of 7.5% (Segnan et al. 2007). Other authors reported rates of 1.3% and 8.9% for CS (Schoenfeld et al. 2005; Regula et al. 2006). The recommended standard (unadjusted caecal intubation rate, see Ch. 5, Sect 5.4.5.1) is >90%.

Endoscopy outcome tables

A table should be made to present the screening endoscopy results by gender and age:

- Negative, (defined as no identified lesions, adenomas or cancers);
- Presence of adenomas of any size;
- Presence of non-advanced adenomas;
- Presence of advanced adenomas; and
- Presence of cancers.

A similar table should be made to present the endoscopic results of follow-up colonoscopy in participants with positive FS or CS screening exams who are referred to follow-up colonoscopy (see below).

To calculate the following detection rates, the data of the two tables should be combined. Separate analysis of screening and follow-up endoscopy is also recommended for quality assurance purposes (see below: “Follow-up colonoscopy outcome tables”).

Positive FS or CS rate

The positive FS rate reported in different studies depends on the definition used (for example whether removed lesions not requiring further surveillance are recorded as a positive result or a negative result). The reported rates varied from 17.6% to 27.7% in 4 RCTs (Table 3.4). Positive CS rates ranging from 20.4% to 53.8% have been reported from population studies (Lieberman et al. 2000; Shoenfeld et al. 2005; Regula et al. 2006). The latter rate was reported in a study with a high percentage of participants with a family history of CRC.

$$\frac{\text{N people with a positive FS or CS result, respectively, during the time frame *}}{\text{N people screened with FS or CS, respectively, during the time frame *}}$$

* equal to the defined screening interval or reporting period

Detection rates of FS or CS screening programmes

- **Lesion detection rate**

The lesion detection rate is reported in % and is defined as the proportion of participants with at least one detected lesion among those adequately tested during the respective time frame.

Detection rates should be presented in a table by 5-year age groups and gender.

$$\frac{\text{N people with at least one detected lesion during the time frame*}}{\text{N people adequately tested with FS or CS, respectively, during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **Adenoma detection rate**

The adenoma detection rate is reported in % and is defined as the proportion of participants with at least one detected adenoma among those adequately tested during the respective time period.

In the RCTs of flexible sigmoidoscopy, adenoma detection rates ranged from 8.7% to 12.1% (Table 3.4).

$$\frac{\text{N people with at least one detected adenoma during the time frame*}}{\text{N people adequately tested with FS or CS, respectively, during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **Advanced adenoma detection rate**

The advanced adenoma detection rate is reported in % and is defined as the proportion of participants with at least one detected advanced adenoma among those adequately tested during the respective time period.

Advanced adenoma detection rates of 4.9% to 8.6% have been reported in population studies of colonoscopy (Lieberman et al. 2000; Shoenfeld et al. 2005; Regula et al 2006) (Table 3.5).

$$\frac{\text{N people with at least one detected advanced adenoma during the time frame*}}{\text{N people adequately tested with FS or CS, respectively, during the time frame*}}$$

* equal to the defined screening interval or reporting period

- **Cancer detection rate**

The cancer detection rate is determined as the proportion of FS or CS screening participants, respectively, with at least one detected colorectal cancer among those adequately examined during the respective time period. In the RCTs of flexible sigmoidoscopy, detection rates ranged from 2.9‰ to 5.4‰ (Table 3.4). Somewhat higher rates can be expected for screening CS due to inspection of the entire colon.

$$\frac{\text{N people with at least one detected cancer during the time frame*}}{\text{N people adequately tested with FS or CS, respectively, during the time frame*}}$$

* equal to the defined screening interval or reporting period

Referral to follow-up colonoscopy after FS or CS

The respective rate of referral for follow-up colonoscopy after a positive screening FS or CS is defined as the proportion of people with a positive screening examination and referred to colonoscopy among those presenting with a positive/abnormal screening exam during the respective time frame and requiring follow-up CS according to the programme policy. In the RCTs of flexible sigmoidoscopy, referral rates ranged from 8.3% to 19.5% of all participants with a positive FS (Table 3.4).

$$\frac{\text{N people presenting with a positive FS or CS, respectively, and referred for follow-up CS during time frame*}}{\text{N people presenting with a positive/abnormal FS or CS, respectively, and requiring follow-up during the time frame*}}$$

* equal to the defined screening interval or reporting period

As a percentage of all people with a positive test result, referral rates for follow-up colonoscopy will be much higher in FOBT-based screening programmes, than in FS screening programmes, depending on the programme policy for referral after a positive screening FS. Referral for follow-up CS after screening CS will be much less common than after screening FS because most lesions found at screening can be removed during screening CS. However, as a proportion of all people referred to follow-up according to the programme policy, compliance should be high irrespective of type of primary screening test.

Recommendation

- High rates of referral to follow-up colonoscopy should be achieved for people with a positive screening FS or CS requiring follow-up (90% is acceptable, >95% is desirable) **(VI - A).**[Rec 3.10]

Follow-up colonoscopy compliance rate after screening FS or CS

The rate of compliance with referral to follow-up colonoscopy after a positive endoscopic screening examination is defined as the proportion of people having attended a follow-up CS during the time frame among those presenting with a positive screening FS or CS, respectively, who were referred during the time frame.

$$\frac{\text{N people having attended a follow-up CS examination during the time frame*}}{\text{N people presenting with a positive screening FS or CS, respectively, and referred during the time frame*}}$$

* equal to the defined screening interval or reporting period

Recommendation

- High rates of compliance with follow-up colonoscopy should be achieved (85% is acceptable, >90% is desirable) **(VI - A).**[Rec 3.14]

Follow-up colonoscopy outcome tables

A table should be made to present colonoscopy results by gender and age:

- Negative (defined as no identified lesions, adenomas or cancer);
- Presence of adenomas of any size;
- Presence of non-advanced adenomas;
- Presence of advanced adenomas; and
- Presence of cancer.

As mentioned above, a similar table should be made to present the results of primary screening endoscopic exams. To calculate the programme detection rates of lesions, adenomas and cancers, the data of the two tables should be combined.

Completion of follow-up colonoscopy after FS or CS

The proportion of follow-up colonoscopies that are incomplete (lack of visualisation of the caecum, see Ch. 5, Sect. 5.4.5.1) should be recorded.

Recommendation

- For follow-up colonoscopy after FS or screening CS, a completion rate of 90% is acceptable, >95% is desirable (see also Ch. 5, Rec. 5.41) **(III - A).**[Rec 3.11]

If more than one lesion is found during follow-up colonoscopy, then the lesion with the worst prognosis should be used for the programme evaluation.

In the event of more than one detected lesion in a person where it is not possible to determine difference in prognosis, then the lesion requiring the most invasive procedure should be used for the evaluation database (see Sect. 3.2.4; Ch. 7).

Endoscopic complications of FS or CS screening programmes

The endoscopic complications that can appear in CRC screening programmes using FS or CS are the same as those described above with respect to follow-up colonoscopy performed in an FOBT screening programme (see Sect. 3.3.2, p. 89).

The following complications are defined as serious: death within 30 days; or hospitalisation within 30 days due to serious haemorrhage involving transfusion, or due to perforation, vagal syndrome or peritonitis-like syndrome. All complications should be recorded as well as the respective cause, if discernible.

For any complication the rate is defined as the proportion of participants presenting with a complication among those having attended the respective type of endoscopic exam (FS or CS). Rates should be broken down by exams performed for primary screening and exams performed for follow-up of positive screening results.

$$\frac{\text{N people presenting with complication of FS or CS, respectively, during time frame*}}{\text{N people having attended the respective exam (FS or CS) during the time frame *}}$$

* equal to the defined screening interval or reporting period

In RCTs, rates of severe complications of FS have been reported at 0.02% to 0.03% (Weissfeld et al. 2005; Segnan et al. 2007). Three studies of colonoscopy screening have reported rates of severe complications of 0.0% to 0.3% (Lieberman et al. 2000; Schoenfeld et al. 2005; Regula et al. 2006). In a well-organised high-quality flexible sigmoidoscopy screening programme the risk of major complications is about 0.3%–0.5% for follow-up colonoscopy **(III)** (see also Ch. 1, Sect. 1.2.1.4 and 1.3.1.4).

Recommendation

- The rate of serious adverse effects should be carefully monitored **(VI - A).**[Rec 3.13]

Table 3.4: Evidence on performance indicators for flexible sigmoidoscopy

	Range from RCTs[1]	Range from population studies[2]
Uptake rate	32.4%–83.5%	7%–55%
Inadequate rate	11%–12.7%	-
Positive rate	10.2%–27.7%	1st round 5.4% 2nd round 3.9%
Referral rate for further investigation	8.3%–19.5%	-
Adenoma detection rate	8.7%–20.6%	14% 5yr recall 11%
Cancer detection rate	2.9‰–5.8‰	4‰ 5yr recall 0.0‰
Proportion of screen detected cancers Dukes stage A	54%–62%	69% (Stage I)
Severe complications Perforations Severe haemorrhage	0.02%–0.03% Near to 0%	-

[1] SCORE (Segnan et al. 2002) age range 55-64
UKFS (UK Flexible Sigmoidoscopy Screening Trial Investigators 2002) age range 55-64
NORCCAP (Gondal et al. 2003) age range 55-64
PLCO (Weissfeld et al. 2005) age range 55-74
SCORE2 (Segnan et al. 2005) age range 55-64
SCORE3 (Segnan et al. 2007) age range 55-64
Netherlands (Hol et al. 2010) age range 50-74

[2] Italy (Federici et al. 2006) age range 50-74
UK (Brotherstone et al. 2007) age range 60-64
Australia (Viiala & Olynyk 2007) age range 55-64
Italy (Zorzi et al. 2008) age range 50-69

Table 3.5: Evidence on performance indicators for screening colonoscopy

	Population studies[1]
Positive rate	20.4%–53.8%[2]
Any adenoma or cancer detection rate	14.9%–37.5%[2]
Advanced neoplasia detection rate	4.9%–10.5%
Advanced adenoma detection rate	4.9%–8.6%
Complication rate	0.0%–0.3%

[1] US (Schoenfeld et al. 2005) women age range 50-79
US (Lieberman et al. 2000) men age range 50-75
Poland (Regula et al. 2006) age range 50-66

[2] High percentage of participants with family history of CRC

3.3.4 Screening organisation

A number of indicators can be used to monitor the organisational performance of a screening programme.

Time interval between completion of test and receipt of results

The time interval between performing a test and receipt of results will affect patient outcomes in terms of anxiety and potentially screening outcomes in terms of stage of diagnosis of disease.

Recommendation

- The time interval between completion of test and receipt of results by the subject should be as short as possible, (acceptable standard: >90% within 15 days) **(VI - A).**[Rec 3.15]

Time interval between positive test and follow-up colonoscopy

A timely procedure is not critical in the context of primary screening but it is very important when endoscopy is performed following a previous positive screening test. A delayed procedure may not be critical biologically, but it can cause unnecessary anxiety for the screenee.

To ensure that patient anxiety is not unnecessarily increased, it is recommended that follow-up colonoscopy after positive screening be performed as soon as reasonably possible but no later than within 31 days of referral.

Recommendation

- Follow-up colonoscopy after positive screening (any modality) should be scheduled within 31 days of referral (an acceptable standard is >90%, >95% is desirable). (See Ch. 5, Rec. 5.19, Sect. 5.3.5). **(VI - B).**[Rec 3.16]

Time interval between positive endoscopy (CS or FS) and start of definitive management

The interval between the diagnosis of screen-detected disease and the start of definitive management is a time of anxiety for the patient and affords the opportunity, if prolonged, for disease progression. For these reasons, standards aimed at minimising delay have set the maximum interval at 31 days (NHS 2007) (see Ch. 8, Rec. 8.2, Sect. 8.2).

Recommendation

- The time interval between the diagnosis of screen-detected disease and the start of definitive management should be minimised. Acceptable standard: >90%, desirable >95% within 31 days (see Ch. 8, Rec. 8.2) **(VI - B).** [Rec 3.17]

Time interval between consecutive primary screening tests

The time interval between two consecutive primary screening tests will affect the coverage of the programme by invitation/screening.

The interval between two consecutive primary screening tests should be monitored to remain within an acceptable level (depending on the screening interval). People should be re-invited according to the date of their last test and not that of their last invitation.

If possible data pertaining to endoscopic surveillance should be monitored.
Proportion of people referred for endoscopic surveillance and proportion of people complying to endoscopic surveillance.

3.4 Long-term impact indicators

The primary objective of screening for CRC is to achieve a reduction in disease-specific mortality; in the case of FS or colonoscopy screening this will be achieved largely by a reduction in the incidence of CRC. However such a reduction in either mortality or incidence will not be discernible until many years after the introduction of the screening programme. (In some areas, opportunistic screening by colonoscopy may be widespread before the start of the programme, therefore diluting the effect of a programme). Methods for studying mortality reduction are discussed later in this chapter. In the meantime other indicators of the impact of screening on disease incidence and mortality should be monitored. These include rates of interval cancers, and surrogate outcome measures that can be used to predict the impact of screening on CRC mortality (or on the incidence of invasive disease) such as rates of overall (age-specific) incidence, stage-specific incidence rates (Denis et al. 2007).

Costs associated with all aspects of the programme should be recorded. Estimates of cost effectiveness will vary according to the health care system in the area. Costs should be monitored carefully, but comparisons between countries will be complex. (Aspects of cost-effectiveness are discussed in Chapter 1).

Finding the appropriate networking level for evaluation of incidence and mortality depends on the organisational structure of the programme. In some programmes (e.g. UK) this will be at a national level, whereas for others it will be at a regional level.

Recommendation

- Evaluation of surrogate outcome measures requires rigorous data collection of bowel cancer registrations and stage of disease in the target population. It is also preferable that such data are collected for the time period leading directly up to the introduction of a screening programme to allow trends to be analysed **(VI - A).**[Rec 3.18]

3.4.1 Interval cancers

Interval cancers are those that occur following a negative screening episode, in the interval before the next invitation to screening is due. For faecal occult blood testing interval cancers may occur following a negative FOBT, or following a positive test result with negative further assessment (colonoscopy). Rates of interval cancers reflect both the sensitivity of the screening test (false negatives), and the incidence of newly-arising cases not present at the time of screening. With increasing time since negative test, the rate and proportion of the latter will increase. In the absence of repeat screening, incidence rates would eventually reach the background level again. Rates of interval cancers should therefore be presented by time period (years) since previous screen.

For endoscopy screening and for colonoscopy follow-up of FOBT, interval cancers reflect the quality of screening as well as the sensitivity of the screening test.

Recommendation

- Data on interval cancers should be collected and reported **(VI - A).**[Rec 3.19]

Recommendation

- Evaluation of interval cancer rates requires careful linkage of cancer registrations with screening history to allow cancers to be classified (i.e. as screen detected, interval, non-responders, other). The requisite linkage must be established with the cancer registry **(VI - A).**[Rec 3.20]

Rates of interval cancers will depend on the underlying incidence in the population. They will also depend on the extent of selection bias, whereby rates in those not participating in screening differ from the general population rates. For this reason it is important that (age- and gender-specific) incidence rates in non-responders are also monitored, to allow for the underlying incidence in responders to be estimated.

Background incidence rates can be estimated from rates prior to the introduction of screening (although time trends need to be considered) or from areas not covered by the screening programme (when geographic differences need to be considered).

The interval cancer rate can therefore be expressed as a proportion of the background incidence rate, standardised for age and gender, by dividing the number of interval cancers in the specific age/gender group (I) by the ones expected based on the background incidence for that age/gender group (C), or as a proportion of the background incidence rate adjusted for non-participants (C*). The adjusted rate can be calculated as:

$$C^* = (C - (1 - P)\,N) / P$$

P: participation rate
N: rate in non-responders

The comparisons can be adjusted for differences in age and gender.

The rate of interval cancers in the period after a negative screening provides information on the sensitivity of the programme. The sensitivity of gFOBT-based program for detection of cancer has been estimated as 55%–57% using this method. In the Nottingham trial the estimate was based on overall

rates of interval cancers of 0.64 per 1000 person-years in the two year period after screening (Moss et al. 1999). Using the same method, the sensitivity of iFOBT-based programme has been reported as 82% (Zappa et al. 2001).

No data are available yet on the sensitivity of FS or colonoscopy-based programmes.

3.4.2 CRC incidence rates

Immediately following the introduction of a screening programme, incidence rates in the target age range should increase due to the detection of prevalent disease by screening. At re-screening, rates should return to background level apart from the advancement of the age of diagnosis by screening.

Age- and gender-specific incidence rates should therefore be reported over time. FS screening should eventually lead to a reduction in incidence rates due to detection and removal of adenomas of the distal colon, but as discussed above this is a long-term effect. Screening FOBT may also have an eventual impact in reducing incidence rates, but the effect will be less due to lower detection rates of adenomas.

Cumulative incidence rates or proxies should be used to monitor potential over-diagnosis of cancer that is cancer that would not otherwise appear during the lifetime of the individual.

3.4.3 Rates of advanced-stage disease

Screening (both FOBT and FS) should result in a reduction in the overall population incidence of late stage disease (DUKES C & D) prior to any reduction in mortality and can therefore be used as an early indicator of effectiveness. Because screening will result in the detection of a large number of early stage cases, and hence a reduction in the proportion of late stage disease, it is preferable to monitor rates of late stage disease. The ability to do this will depend on the completeness of stage information that ideally should be available for a sufficiently lengthy period immediately prior to the introduction of the screening programme, to allow trends to be studied.

Projected mortality based on stage-adjusted cancer incidence.

Models have been developed to use prognostic information provided by Dukes stage and age at diagnosis to predict cancer mortality.

3.4.4 CRC mortality rates

As discussed above, it will be several years before the impact of population screening on CRC mortality becomes observable, and many more years before the full effect is achieved. The timing of a reduction depends on the natural history of the disease, and the ‘lead time’ due to screening (i.e. the time by which screening advances the date of diagnosis) as well as on the time taken to cover the target population. It will also depend on the quality of screening.

Methods to evaluate the impact of screening on CRC mortality include analyses of population trends, cohort studies (aggregated or individual-based) and case-control studies.

Population trends

Mortality from CRC has been decreasing in many European countries since the mid 1990's, (Karim-Kos et al. 2008). Analyses of the routinely produced age-gender specific population rates over time will be subject to limitations due to the dilution of the effect of screening from deaths occurring in cases diagnosed prior to the introduction of screening, and/or at an age below which invitations begin. This can be overcome by use of refined CRC mortality rates in which such deaths are excluded. However, the rates will also be confounded by other factors such as cohort effects on underlying incidence, and by the effects of improvements in treatment and/or the stage of diagnosis of symptomatic disease on survival and mortality. Thus whilst a lack of any reduction in population mortality rates several years after the introduction of a screening programme should be a cause for concern, it is difficult to use such trends to quantify the effect, and attempts to do so should take account of the factors discussed above.

Cohort studies

In some settings, the introduction of population screening will have been phased in such a way as to facilitate comparisons of populations invited at different time points. Such a model has been used in Finland (see Ch. 2, Sect. 2.6.4). In the absence of such a system, comparisons can be made between geographical areas (regions invited/not invited to screening) or between the same population in different time periods before and after the introduction of screening. Both types of comparison are liable to possible bias due to underlying differences in the risk in the populations/time-periods. This may – under certain circumstances – be compensated for by including also a comparison group from geographic areas where no invitational program existed from before the introduction of screening. Cohort studies using aggregated data need estimates of incidence in order to avoid dilution effect discussed above.

These biases can be avoided by individual-based cohort studies in which deaths and cancer registrations are linked to screening histories.

Case-control studies

Case control studies that compare 'exposure' (i.e. 'screening') between cases (deaths from CRC) and controls are an attractive alternative to cohort studies in terms of cost and effort. However, careful consideration of the design issues is necessary to avoid a number of potential biases, (Hosek, Flanders & Sasco 1996). The major problem with such studies is that of selection bias, due to different levels of underlying risk in participants and non-participants with screening. Methods to adjust for this are required both to estimate the mortality benefit in those actually screened, and the 'impact' on the population invited for screening.

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4

Faecal Occult Blood Testing

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Recommendations[1]

Guaiac-based faecal occult blood tests

4.1 Guaiac-based faecal occult blood tests have proven characteristics that make them suitable for population screening. They lack the analytical specificity and sensitivity of immunochemical tests, their analysis cannot be automated and the concentration at which they turn from negative to positive cannot be adjusted by the user. For these reasons guaiac-based tests are not the preferred test for a modern population screening programme, although depending on local labour costs, the mechanism of kit distribution and collection and reduced sample stability in immunochemical testing, they might prove more practicable and affordable than immunochemical testing **(I - B).**[Sect 4.2.4; 4.2.7; 4.3; 4.4.2]

Immunochemical faecal occult blood tests

4.2 Immunochemical tests have improved test characteristics compared to conventional guaiac-based tests. They are analytically and clinically more sensitive and specific, their measurement can be automated and the user can adjust the concentration at which a positive result is reported. Immunochemical tests are currently the test of choice for population screening; however, individual device characteristics including, ease of use by the participant and laboratory, suitability for transport, sampling reproducibility and sample stability are all important when selecting the iFOBT most appropriate for an individual screening programme **(II - A).**[Sect 4.2.5; 4.2.7; 4.3; 4.4.2]

DNA and other related new markers

4.3 Only tests for blood in faeces have been demonstrated to have the necessary characteristics to be suitable for population screening. DNA and other related new markers are currently unsuitable for screening, either singly or as members of a panel of tests **(III - D).**[Sect 4.2.6; 4.2.7]

Sample stability between collection and analysis

4.4 Whilst a maximum period of 14 days between collection and analysis is quoted for many guaiac faecal occult blood tests, that quoted for immunochemical tests is significantly shorter. Until more stability data are published, screening programmes should adopt the conditions and period of storage described in manufacturer's Instructions for Use having determined that they are appropriate for local conditions which might expose samples to high temperatures for long periods of time **(III - A).**[Sect 4.3.3.2; 4.3.4]

Screening algorithm:

- **Sample and test numbers**

4.5 Few studies have examined the number of stool specimens necessary to optimise the diagnostic performance of FOBT. Consideration should be given to using more than one specimen together with criteria for assigning positivity which together provide a referral rate that is clinically, logistically and financially appropriate to the screening programme. The clinical sensitivity and specificity of testing can be modified depending on how the test data are used. Guaiac-based tests typically use 3 stools, but an algorithm using additional tests can be used to adjust clinical sensitivity and specificity **(III - C).**[Sect 4.4.3.2; 4.4.3.1; 4.4.4]

[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.

- **Determining test positivity**

4.6 The choice of a cut-off concentration to be used in an immunochemical test to discriminate between a positive and negative result will depend on the test device chosen, the number of samples used and the algorithm adopted to integrate the individual test results. Whilst an increasing number of studies are reporting the experience of different algorithms, local conditions, including the effect on sample stability of transport conditions, preclude a simple prescribed algorithm at this time. Adoption of a test device and the selection of a cut-off concentration should follow a local pilot study to ensure that the chosen test, test algorithm and transport arrangements work together to provide a positivity rate that is clinically, logistically and financially acceptable **(VI - A).**[Sect 4.4.3.1; 4.4.3.2; 4.4.4]

Test interference:

- **Dietary restriction**

4.7 Dietary constituents present potential interference in guaiac faecal occult blood tests. Dietary restriction has not been demonstrated to significantly increase screening specificity, and risks reducing participation rate. The potential for dietary interference is significantly less for immunochemical tests. With the qualification that a diet peculiar to a particular country or culture may not have been tested or reported, dietary restriction is not indicated for programmes using either guaiac-based or immunochemical tests **(II - D).**[Sect 4.3.2.1; 4.3.2.3; 4.3.4]

- **Drug restriction**

4.8 Interference from bleeding associated with drugs such as aspirin, nonsteroidal anti-inflammatory drugs and anticoagulants (e.g. warfarin) present potential interference in both guaiac and immunochemical faecal occult blood tests. Although the literature carries some contradicting reports of the effect of anticoagulants on screening outcome, drug restriction is not recommended for population screening programmes using either guaiac-based or immunochemical tests **(III - D).**[Sect 4.3.2.2; 4.3.2.3; 4.3.4]

Faecal sampling/collection system

4.9 Many factors influence the uptake and reliability of sample collection. Inappropriate implementation can result in grossly misleading results. No single collection methodology is supported by the literature; however, the following factors should be considered when selecting a device for taking samples in population screening:

- The distribution process should be reliable and reach all selected subjects.
- The laboratory should be able to unambiguously identify the subject ID on the test device perhaps using a suitable barcode.
- The laboratory should be able to check the manufacturer's device expiry date on each returned device.
- The instructions for using the device must be simple and clear.
- The device should to be simple and easy to use by the target population.
- The device should leave minimal opportunity for collection error.
- The device should facilitate consistency in the volume of sample collected.
- The device/instructions should discourage inappropriate repeat sampling into/onto the sample device.
- Misuse of the device by participants should not cause loss of sample buffer.
- The system should not be susceptible to interference from toilet bowl disinfectants, etc.
- The screening participant should be able to record the date of sample collection to ensure the laboratory can verify receipt within an acceptable sample stability period.

- The process used by the subject for returning the device should be simple, reliable, safe and, when appropriate, should meet EU postal regulations.

A local pilot study should be undertaken to ensure that the chosen device and associated distribution, sampling and labelling procedures are acceptable **(VI - A).**[Sect 4.2.3; 4.2.4; 4.3.2.1; 4.3.3.4; 4.3.4]

Laboratory organisation:

- **Number of laboratory sites**

4.10 Population screening necessitates the receipt, measurement and recording of thousands of tests each day. The samples should be analysed without delay to avoid further sample denaturation and avoid an increase in false negative results. Inter-laboratory analytical imprecision is well described and can be observed through established external quality assurance schemes. Improved consistency is achieved by adopting common analytical platforms, analytical and quality standards and shared staff training. The analysis needs to be reproducible across a screening population and therefore the number of analytical centres should be minimised with automated analytical systems utilised wherever possible and agreed common testing procedures adopted by each centre **(VI - B).**[Sect 4.3.3.4; 4.3.4]

- **Laboratory staff**

4.11 All laboratories providing population screening should be led by a qualified clinical chemist who is trained and experienced in the techniques used for analysis and with clinical quality assurance procedures **(VI - B).**[Sect 4.3.3.4; 4.3.4]

- **Laboratory accreditation and quality monitoring**

4.12 All laboratories providing screening services should be associated with a laboratory accredited to ISO 15189:2007 *Medical laboratories - Particular requirements for quality and competence*. The laboratories should perform Internal Quality Control (IQC) procedures and participate in an appropriate External Quality Assessment Scheme (EQAS) **(VI - B).**[Sect 4.3.3.4]

- **Distribution of FOBT kits by mail**

4.13 Distribution and receipt of FOBT kits using local postal services can be an effective means of reaching the designated population (Ch. 2, Rec. 2.14) **(II - B).** [Sect 2.5.1.1; 4.2.1; 4.3.3.4]

Maximisation of uptake – Influencing factors associated with the test kit

4.14 The choice of the test kit must be influenced by factors that enhance accessibility and uptake (see below and Ch. 2, Rec. 2.14) **(II - A):**[Sect 4.2.3; 4.2.4; 4.4.4]

- **Dietary restrictions**

  In order to enhance participation in screening, test kits should not require dietary restrictions (Ch. 2, Rec. 2.17) **(II - A)**.[Sect 4.3.2.1; 4.3.2.3; 4.4.4; 2.5.1.2]

- **Kit design**

  The design of a test kit should make it acceptable to the target population (see Ch. 2, Rec. 2.14) **(II - A)**.[Sect 4.2.3; 4.2.4; 4.4.4; 2.5.1.1]

- **Simple and clear instructions**

  A clear and simple instruction sheet should be provided with the test kit (Ch. 2, Rec. 2.16) **(V - A).**[Sect 4.2.3; 4.2.4; 4.4.4; 2.5.1.1]

Identification of participants and test results

4.15 Automated check protocols should be implemented to ensure correct identification of the screened population and complete and accurate recording of individual screening participation and test results (see Ch. 2, Rec. 2.18) **(VI - A).**[Sect 4.3.4; 2.5.1.3]

Classification of test results

4.16 Protocols should be implemented to ensure standardised and reliable classification of the test results (Ch. 2, Rec 2.19) **(VI - A).**[Sect 4.3.4; 2.5.1.3]

Quality Assurance:

- **Quality assurance of gFOBT testing**

4.17 Whilst an immunochemical test is recommended, programmes that adopt a traditional guaiac test need to apply additional laboratory quality procedures. To minimise variability and error associated with visual test reading, including manual results input, the following procedures should be considered **(VI - B):**[Sect 4.3.3.4; 4.3.4]

- o Use of appropriate temperature for artificial lighting and neutral-coloured walls in the reading laboratory;
- o Use of a national laboratory training programme to prosper consistency of interpretation;
- o A blinded internal QC check each day for each analyst prior to commencing testing;
- o Adoption of a monitoring programme to identify operator related analytical performance (e.g. positivity variability and bias); and
- o Double entry of test results

- **Quality assurance of iFOBT testing**

4.18 Consistency in analytical performance must be assured by the adoption and application of rigorous quality assurance procedures. Manufacturer's Instructions for Use must be followed. Laboratories should perform daily checks of analytical accuracy and precision across the measurement range with particular emphasis at the selected cut-off limit. Rigorous procedures need to be agreed and adopted on how internal quality control data is interpreted and how the laboratory responds to unsatisfactory results. Performance data, both internal quality control and external quality assessment data, should be shared and reviewed by a Quality Assurance team working across the programme. Sufficient instrumentation should be available to avoid delays in analysis due to instrument failure or maintenance procedures **(VI - B).**[Sect 4.3.3.4; 4.3.4]

- **External quality assessment**

4.19 A European external quality assessment scheme should be developed to facilitate Europe-wide quality assurance of occult blood testing and enhance the reproducibility of testing within and between countries providing population screening **(III - B).**[Sect 4.3.3.4; 4.3.4]

- **Outcome monitoring**

4.20 All aspects of laboratory performance in respect of the screening test should be part of a rigorous quality assurance system. Uptake, undelivered mail, time from collection to analysis, analytical performance (internal QC and external QA), positivity rates, lost & spoilt kits and technical failure rate, technician performance variability and bias should each be subject to rigorous monitoring **(VI - A).**[Sect 4.3.3.4; 4.3.4]

- **Quality of information**

4.21 The proportion of unacceptable tests received for measurement is influenced by the ease of use of the test kit and the quality of the instructions for use. This proportion should not exceed 3% of all kits received; less than 1% is desirable (see Ch. 3, Rec. 3.9) **(III - A).**[Sect 4.3.4; 3.3.2]

4.1 Introduction

The ideal biochemical test for population-screening of colorectal cancer would use a biomarker, specific and sensitive for both cancer and pre-cancer, on an easily collected sample, which could be safely and cheaply transported to a centralised laboratory for accurate, reproducible, and cheap automated analysis. None of the currently available tests fully meet all of those criteria.

That colorectal cancers and adenomatous polyps bleed, be it to varying degrees and perhaps intermittently, has provided faecal blood haemoglobin as the biomarker of choice for current screening programmes. The presence of blood in faeces can be due to pathological conditions other than neoplasia, from physiological blood loss of between 0.5 and 1.0 mL/d (Moore, Derry & McQuay 2008), from vigorous brushing of gums and from dietary constituents such as meat and meat products (Fludger et al. 2002).

The cheapest but least specific means of detecting haemoglobin uses guaiac gum, is often referred to as the guaiac Faecal Occult Blood Test or gFOBT, and its efficacy as a colorectal cancer screening test has been demonstrated in three randomised controlled trials (Mandel et al. 1993; Hardcastle et al. 1996; Kronborg et al. 1996). The test detects the haem component of haemoglobin, which is identical across human and animal species and is chemically robust and only partially degraded during its passage through the gastrointestinal tract. gFOBTs provide little specificity for lesions of the distal intestinal tract and cannot distinguish between human blood and blood residues from the diet.

The analytical sensitivity of gFOBTs to haemoglobin can be increased by hydrating the sample prior to analysis; however this brings little benefit because increased clinical sensitivity is accompanied by decreased clinical specificity. More subtle adjustment to the analytical sensitivity of gFOBTs is not technically possible, and screening programmes must configure their programme algorithm (the required number of stool samples and the required number of positive test spots) and secondary investigations, usually colonoscopy, to meet the gFOBT positivity rate.

A significant technical enhancement to the simple guaiac test for blood is achieved by using an antibody (immunoglobulin) specific to human globin, the protein component of haemoglobin. These immunochemical techniques use specific antibodies and are well-established and ubiquitous in clinical laboratories. At the point-of-care, immunochemical tests have been widely adopted, notably in fertility, pregnancy and drug tests.

Whilst the haem component of blood is common to all species, globin is conveniently species specific, so immunochemical Faecal Occult Blood tests, frequently referred to as iFOBT or FIT should not be subject to interference from dietary blood. Detection of globin also confers the advantage of making the test more specific to bleeding from the distal gastrointestinal tract, since protease enzymes gradually digest blood from the proximal tract during its passage through the intestine, rendering it less likely to be recognised by the antibodies used in an iFOBT.

Immunochemical technology enables detection of blood at lower concentrations than gFOBTs and therefore increases clinical sensitivity by detecting smaller blood losses from small or intermittently bleeding lesions. Whilst improved analytical specificity reduces false positive tests from dietary blood, their increased analytical sensitivity means that small losses from inflammatory diseases or physiological sources will bring new false positives with a higher positivity rate and decreased specificity. Several newer iFOBTs have the ability to adjust and set the cut-off concentration above which the device will report a positive result. These adjustments are made on an instrument reader, and such instruments can provide the additional and important opportunity of automating the process. Examples of products with these characteristics are the OC-Sensor Diana, *Eiken Chemical Co., Tokyo, Japan*, and the SENTiFOB, *Sentinel Diagnostics SpA, Milan, Italy*.

Population screening for colorectal cancer can now benefit from tests that have an adjustable detection limit and have the efficiencies and analytical reproducibility facilitated through automated analysis; currently only iFOBT provides this opportunity.

4.2 Biochemical tests for colorectal cancer

4.2.1 Characteristics of a test for population-screening of colorectal cancer

The list below summarises the analytical and clinical aspects of biomarker testing that make it suitable for population screening and identifies characteristics that are important for effective and efficient implementation.

Testing Process

a. Sample
    i. Reliable sample collection, reproducible sample size
    ii. Sample collection process is simple requiring minimal contact with the stool
    iii. Safe and acceptable for the chosen method of transport, meets EU mail regulations

b. Biomarker (analyte)
    i. Sufficiently stable, at ambient temperature, between sample collection and testing
    ii. Analytical sensitivity and specificity
        1. Adequate analytical sensitivity and specificity
        2. Adequate discrimination between neoplastic colorectal pathology and other pathologies or physiological sources of the biomarker
        3. Minimal analytical or biological interference (e.g. diet and drugs)
    iii. Ability to adjust sensitivity (and specificity) to be clinically and practically acceptable

c. Analysis
    i. Easy and reliable to measure
    ii. Amenable to automation
    iii. Acceptably reproducible
    iv. Amenable to quality control and assessment monitoring

d. Availability of test
    i. Reliable commercial source, long-term quality provider
    ii. Acceptable inter and intra-batch reproducibility
    iii. Affordable

Clinical Outcome

a. Acceptable clinical performance
    i. Sensitivity
    ii. Specificity
    iii. Positive predictive value

The outcome of a screening test must be the identification of an acceptable proportion of the population who have early-stage colorectal cancer or adenoma and are amenable to successful treatment (Wilson & Jungner 1968). The screening test must also show adequate discrimination between those who have the disease and those who do not. Critically, the clinical sensitivity and specificity of the test and the way it is implemented must only identify that number of participants which is logistically and financially acceptable for referral to colonoscopy clinics.

When interpreting the clinical sensitivity and specificity of tests described in the literature, it is important to do so in the specific context of the study, the method of implementation, the nature of the population served and other local health and social welfare issues.

4.2.2 Faecal blood loss

An abnormal increase in blood loss into the intestine is necessary for the success of gFOBTs and iFOBTs. Faecal haem, haem-derived porphyrin and 51-chromium-labelled red cells have all been used to determine physiological blood loss. A recent systematic review by Moore, Derry & McQuay (2008) of the effect of non-steroidal anti-inflammatory drugs (NSAIDs) on blood loss showed a normal daily loss in 1000 participants of less than 1 mL/d. Blood losses greater than 1 mL/d may be seen following vigorous brushing of teeth and gums, and in irritation and inflammation of the intestinal tract. Most NSAIDs, and aspirin in low doses, produce an increased blood loss of 1 to 2 mL/d which increases to 5 mL/d in 5% and 10 mL/d or more in 1% of those taking larger doses. Large daily aspirin doses of 1800 mg or more, cause daily blood losses of between 5 mL/d and 10 mL/d. Other chronic inflammatory conditions of the gastrointestinal tract including inflammatory bowel disease, colitis, Crohns' disease and perianal lesions also increase blood loss.

Macrae & St John (1982) showed the close relationship between adenoma size and blood loss using 51-chromium-labelled red cells. Levi et al. (2007) used the iFOBT OC-Sensor to show increasing faecal haemoglobin from normal and hyperplastic polyps through non-advanced and advanced polyps to cancer, with a wide spread of concentrations within each category. Fraser et al. (2008) demonstrated a clear relationship between increasing faecal blood concentration, measured with the FOB Gold iFOBT, and pathological change in 375 fresh samples from participants of the Scottish population. Ciatto et al. (2007) used the iFOBT OC-Sensor and a population that included 191 cancers and 890 adenomas detected at colonoscopy to show increasing faecal haemoglobin concentration with increasing lesion severity and size. It remains a matter of conjecture whether all early-stage cancers bleed and whether they bleed intermittently, dependant perhaps upon on the mechanics of the gastrointestinal tract and the passage of digested foodstuffs. Intermittent or variable blood loss partially explains why the less-sensitive guaiac tests do not show consistently positive tests results in patients who are later diagnosed with colorectal cancer and why, even with highly sensitive tests, 100% clinical sensitivity is not achieved.

4.2.3 Sample collection for Faecal Occult Blood Test devices

Effective sample collection is critical to the success of a screening programme. The process of collection needs to be as simple as possible. Participants will always find the process inconvenient and unpleasant. Clear, simple and practical instructions are very important both to encourage participation and to the collection of a satisfactory specimen. The easier it is to present the stool for sampling and to transfer it to the test device, the greater the likely uptake to a screening programme. Current test kits use cardboard and wooden spatulas, plastic probes with serrated ends and brushes. Whilst most kits require the sample to remain away from the water in the toilet bowl prior to sampling, other devices sample the water that surrounds the stool. Many systems accept samples taken from toilet tissue paper. One RCT (Cole et al. 2003) showed that different sampling techniques can change FOBT screening compliance and two cross-sectional studies (Greenwald 2006; Ellis et al. 2007) reported information on preference among different type of stool sampling methods. Practical experience has shown that in the age group commonly screened, physical and mental disabilities present a further reason for non-participation. Difficult sampling procedures with complex instructions greatly aggravate the inherent difficulties in collecting faecal samples.

Effective sampling is also important to the reliability of the test. Whilst the composition of faecal samples is affected by intestinal transit time, stool consistency (Rosenfield et al. 1979), undigested foodstuffs, variable sample volume will also add to poor test performance. A technique which enables the sample to reflect blood throughout the stool is preferable and so a probe which can be inserted into various parts of the stool or a spatula or brush which enables collection of material across a large surface area must be better than single point sampling (Cole et al. 2003; Young et al. 2003; Smith et al. 2006). A well-designed RCT conducted in Australia on 1818 urban residents, aged 50-69 years, compared the participation rate of three screening cohorts (Cole et al. 2003). The invited population used a wooden spatula (Hemoccult SENSA *Beckman Coulter Inc. Fullerton, CA, USA*), a spatula (FlexSure OBT *Beckman Coulter Inc. Fullerton, CA, USA*, three samples), and a brush (InSure *Enterix Inc., Edison, New Jersey, USA*, two samples) for sample collection. The overall participation rate was significantly higher in the InSure group (Hemoccult SENSA: 23.4%, FlexSure: 30.5%, InSure: 39.6% $\chi 2=37.1$, $p<0.00001$). In a UK cross-sectional study (Ellis et al. 2007) 1318 (50%) of the eligible population (n = 2639) registered with two general practices were randomly selected and sent a three page questionnaire to determine the acceptability of three methods of FOBT sampling, a sterile long stick transport swab, a conventional smear card with short wooden applicator and a scoop with collection pot. The swab was found most preferable and the smear-card the least preferred method of collection. A small cross-sectional study (Greenwald 2006) compared toilet tissue and the short wooden applicator with the Hemoccult test but failed to show a statistical difference ($p=0.05$).

When applying a sample to the test device, consistent application of the required volume is important. Doubling the sample volume can double the analytical sensitivity and halving it will halve analytical sensitivity. The thickness of the card surrounding the sample collection window on a guaiac test kit is important since it will influence the volume of sample transferred onto the window. A probe that, after collection, has to pass through a small hole to wipe off sample excess is an elegant system that is used in the Hem-SP, OC-Sensor and FOB Gold iFOBT, the latter two having devices which make use of a serrated probe. This collection method is only used for immunochemical devices and the probe surface, the number and depth of the groves in the serrated probe and the size of the hole through which the probe is inserted will affect the sample volume added to the buffer in the collection tube. Stool consistency will alter the volume of sample which adheres to the groves in the probe. Poor manufacturing tolerance will also contribute to a reduction in reproducibility of the sampling system.

4.2.4 Guaiac Faecal Occult Blood Test - gFOBT

The guaiac-based FOBT is still a commonly used method for detecting blood in faeces. The method exploits the pseudoperoxidase properties of the haem moiety in haemoglobin and liberates oxygen from 3–5% dilutions of hydrogen peroxide in ethanol or methanol. The released nascent oxygen then reacts with alpha guaiaconic acid, the phenolic compound (2,5-di-(4-hydroxy-3-methoxyphenyl)-3,4-dimethylfuran) present in guaiac, a resin extracted from a hardwood tree guaiacum officinale (lignum vitae). The reaction produces a compound with a quinine structure that rearranges by two-fold electron transfer to produce an unstable blue bis-methylene quinone dye.

Guaiac is still manufactured by extraction from tree resin and is therefore susceptible to batch variation. Batch variation is potentially a significant problem for population screening programmes for which a small change in analytical sensitivity could markedly change the referral rate for colonoscopy.

Guaiacum officinale is a tree native to South America and the Caribbean and is subject to Appendix 2 of the Convention on International Trade in Endangered Species (CITES) (Keong 2009). This is an international agreement regulating trade in endangered species in order to protect them from exploitation and extinction. Under CITES, export of specimens is subject to a government-issued permit certifying that they are legally obtained and that export will not be detrimental to the survival of the species.

In all current guaiac-based devices, the guaiac is absorbed into filter paper contained within a cardboard support. Faeces is applied by the participant to one side of the filter paper and, on receipt of the card, the laboratory applies an alcoholic solution of hydrogen peroxide to the other side of the paper. The volume of hydrogen peroxide added is not critical but the quantity of faeces applied is. The mass of the faecal sample will be influenced by the size of the application window and the thickness of the cardboard surrounding it. The hydrogen peroxide is usually applied from a dropper bottle and the laboratory staff look for the development of a blue colour within a time window prescribed by the kit manufacturer, typically 30–60 seconds. The blue dye is unstable and late reading will result in false negative results.

The test kit should have a means of checking performance; many kits will have a test positive and test negative quality control strip that develops alongside the participant's results and can highlight gross product or user errors. This QC strip should extend across the area used for clinical testing to enable identification of incomplete application of guaiac to the filter paper during product manufacture.

Good kit design can greatly facilitate proper use. The identity of the card and participant should be easily and uniquely identified by the laboratory, usually by way of a barcode. Instructions and directions must be clear so that the sample is applied to the correct window. The design of the sample applicator needs to facilitate easy sample transfer and be suitable for the particular design of the kit. The size of the test window and the applicator must match to minimise marked under- or over-application of the sample. The device should carry the date the sample was applied so that the laboratory can disregard specimens that are too old to give reliable results.

Guaiac tests typically have an analytical sensitivity (limit of detection) of between 0.3 and 1 mg Hb/g of faeces, but this will be affected by the sample loading levels and the time between collection and testing. The guaiac test can be made more sensitive (0.15 mg Hb/g) by hydrating the sample on the test kit prior to adding hydrogen peroxide; that is the principal use in the Hemoccult Sensa, *Beckman Coulter Inc. Fullerton, CA, USA*.

4.2.5 Immunochemical tests - iFOBTs

Unlike gFOBT, the utility of immunochemical faecal occult blood tests (iFOBTs) has only been demonstrated in one randomised controlled trial (van Rossum et al. 2008); however the analytical superiority of immunochemical tests mean that they have recently become the test of choice for colorectal cancer screening programmes. iFOBTs have been used for population screening in Japan since 1992 (Saito 2007), and the OC-Sensor was approved for use in the U.S. by the Food and Drugs Administration (FDA) in 2001. Immunochemical tests can use monoclonal or polyclonal antibodies raised against human globin, the protein component of haemoglobin. The antibodies are attached to a latex particle, dye or an enzyme that in the presence of human globin forms a complex that can be detected by turbidity, aggregation (latex agglutination, haem-agglutination and colloidal gold agglutination) or coloured dye produced by an enzyme. Since the protein structure of human globin is unique to humans, the immunochemical test should not be subject to interference from animal blood in the diet. Unlike haem, proteolytic enzymes gradually degrade globin as it moves through the intestine, and this confers on it more specificity for pathology in the distal intestinal tract than does haem. A variation of the immunochemical test marketed by *Chemicon Europe Ltd,* MonoHaem, uses antibodies against human globin to specifically immobilise haemoglobin and then the guaiac reaction to detect the haem.

iFOBTs are typically 10-fold more expensive than gFOBTs (Fraser 2008). Increased iFOBT test kit cost can be offset by the use of automated analysers and thus reduced staff costs and, where multiple gFOBT test cards are in use, by using a single iFOBT because adequate clinical sensitivity and specificity can be obtained using a single iFOBT.

Immunochemical tests confer increased analytical specificity for human haemoglobin, and by using sensitive detection systems, they increase test sensitivity to low blood concentrations. iFOBT's typically have limits of detection of less than 0.2 mg/g stool and can detect as little as 0.3 mL of blood added to a stool sample (Saito 1996).

Immunochemical FOBTs provide opportunities for improved population screening. Hem-SP, OC-Sensor and FOB Gold all use spectrophotometric measurement systems, sometimes with charged coupled devices (CCD), to measure the degree of agglutination, turbidity or the colour generated by the test. Automating instrument measurement increases test throughput and measurement precision, and eliminates user bias (Fraser et al. 2008). Instrumentation also provides an opportunity to manually adjust the cut-off limit below which the test is reported as negative and not referred for prospective colonoscopy.

Whilst the measurements performed on the buffered faecal sample using automated analysers can be quantitative, the impossibility of providing a reproducible sample means that these systems must not be considered capable of providing reliable quantitative test results. The gFOBT and iFOBT must both be considered at semi-quantitative although the immunochemical test is analytically superior.

4.2.6 Other tests

o-Toluidine and benzidine have both been used as alternatives to guaiac but have been discontinued because they have been shown to be to be carcinogenic (IARC 2010). Imipramine and desipramine have also been described as alternative reagents to guaiac and have reports of less interference from vegetable peroxidases, iron and vitamin C, but they have not gained a place in the market (Syed, Khatoon & Silwadi 2001). Alpha guaiaconic acid, the active component of guaiac gum, has been synthesised but proved unstable and unsuitable as an alternative to the tree extract, which may contain contaminants with stabilising properties.

The measurement of porphyrins produced by the action of intestinal bacteria on haemoglobin provides an alternative method for measuring blood in faeces (Schwartz 1983; Ahlquist et al. 1984; Ahlquist et al. 1985) and recently mass spectrophotometric methods have been described, but they are unlikely to be adopted for population screening.

The literature describes many alternative biomarkers for the presence of colorectal cancer. These markers includes albumin, haptoglobin, transferrin, pyruvate kinase isoenzyme type M2, calprotectin, Ca3 anaphylotoxin, colon-specific antigen (CCSA-3 and CCSA-4) and a variety of DNA-related markers.

PK isoenzyme type M2 has shown poor sensitivity and specificity when used alongside two immunochemical devices (Mulder et al. 2007). Calprotectin has a role in identifying patients with inflammatory bowel disease, but a meta-analysis of the literature in 2006 concluded that it was unsuitable for screening for colorectal cancer (von Roon et al. 2007).

The use of molecular biology techniques to identify cancer-related DNA or protein biomarkers, used singly or as a panel, shows promise but is in its infancy. The use of DNA microarrays to detect the present of mutations in genes such as TP53, K-ras, APC, BAT-26 and BRAF might bring us closer to earlier detection. A study of 5486 asymptomatic patients by Imperiale in 2004 showed increased sensitivity and specificity for invasive cancer and advanced neoplasia using faecal DNA relative to gFOBT, but failed to detect over 50% in each group (Imperiale et al. 2004). A recent paper by Wang & Tang (2008) showed the hypermethylated SFRP2 gene in faecal DNA to be a candidate colorectal biomarker, but none of these DNA related markers have been demonstrated to have the necessary characteristics to qualify them for use in population screening. In Young's review of new screening tests he remarks that the epigenetic marker for the methylated vimentin gene has improved sensitivity

for cancer but that its overall performance relative to existing gFOBT and iFOBT remains unclear (Chen et al. 2005; Young & Cole 2007). In a 2008 review of the cost-effectiveness of faecal DNA, immunochemical and guaiac-based tests using the Markov model, the authors conclude that blood markers remain the preferred option in high-adherence populations (Parekh, Fendrick & Ladabaum 2008). A MEDLINE review of new stool-based tests by Haug concluded that "while promising performance characteristics have been reported for some tests, more persuasive evidence from larger, prospectively designed studies… was needed" (Haug & Brenner 2005). Currently the new markers are both expensive and show very poor sensitivity to cancer and adenomas.

In the short term, marker tests based on gene or epigenetic mutations may show merit for use in screening selected high-risk populations or for monitoring disease progression or recurrence, but in the long term we may see them as the preferred markers for general population screening.

4.2.7 Recommendations

Guaiac-based faecal occult blood tests

Guaiac-based faecal occult blood tests have proven characteristics that make them suitable for population screening. They lack the analytical specificity and sensitivity of immunochemical tests, their analysis cannot be automated and the concentration at which they turn from negative to positive cannot be adjusted by the user. For these reasons guaiac-based tests are not the preferred test for a modern population screening programme, although depending on local labour costs, the mechanism of kit distribution and collection, and reduced sample stability in immunochemical testing, they might prove more practicable and affordable than immunochemical testing (Sect. 4.2.4, 4.3 and 4.4.2) **(I - B).**[Rec 4.1]

Immunochemical faecal occult blood tests

Immunochemical tests have improved test characteristics compared to conventional guaiac-based tests. They are analytically and clinically more sensitive and specific, their measurement can be automated and the user can adjust the concentration at which a positive result is reported. Immunochemical tests are currently the test of choice for population screening; however, individual device characteristics including, ease of use by the participant and laboratory, suitability for transport, sampling reproducibility and sample stability are all important when selecting the iFOBT most appropriate for an individual screening programme (Sect. 4.2.5, 4.3 and 4.4.2) **(II - A).**[Rec 4.2]

DNA and other related new markers

Only tests for blood in faeces have been demonstrated to have the necessary characteristics to be suitable for population screening. DNA and other related new markers are currently unsuitable for screening, either singly or as members of a panel of tests (Sect. 4.2.6) **(III - D).**[Rec 4.3]

4.3 Analytical characteristics and performance

4.3.1 Analytical sensitivity

Analytical sensitivity or limit of detection describes the lowest concentration that an analytical system can detect with confidence. The detection system used by iFOBTs makes the test inherently more sensitive than guaiac-based systems. The concentration units quoted for analytical sensitivity depend on the method used for determination, for example mL of blood/g or mL of faeces, or mg (or µg) of haemoglobin/g or mL of faeces. Most manufacturers and scientific papers quote mg Hb/g faeces. The haemoglobin content should be determined with knowledge of the haemoglobin concentration in the blood used, and faeces should be measured as the wet weight of a formed stool sample. Some manufactures and studies also quote the concentration of haemoglobin not in faeces but in the buffer solution used for analysis, and this is different for different devices, making simple comparison of device sensitivity difficult e.g. the Hem-SP devices carry 0.3 mg faeces/mL buffer and OC-Sensor 10 mg faeces/mL buffer.

Given the variable consistency of faecal samples and the dependence upon diet and intestinal transit time, the relationship between patient samples and test samples prepared in the laboratory is often a poor one. Manufacturers may quote sensitivity on blood solutions rather than spiked faecal samples and if quoted for faecal samples, the time period between in-vitro addition of blood to faeces and analysis is unlikely to be typical of that between participant sampling and analysis in a screening programme. The unstable nature of samples used in FOBTs is discussed later in this chapter.

4.3.1.1 Analytical sensitivity and cut-off limits

Until recently it has not been possible to adjust the analytical sensitivity of FOBTs and so adjust the proportion of positive tests. This facility to adjust sensitivity is still not available for gFOBTs, with the exception of the simple process of hydrating the specimen prior to testing. With Hemoccult SENSA this process increases test sensitivity but at the expense of specificity, thereby increasing the false positive rate (Mandel et al. 1993; Ransohoff & Sandler 2002).

Point-of-care iFOBTs typically use an immunochromatographic technique that produces a coloured line where the antibodies and haemoglobin are immobilised. The presence of the line is detected by eye, and the limit of detection is dependent upon the configuration of the device, the characteristics of the antibodies and chromogens and the visual acuity of the reader. These iFOBT devices are suitable for small-volume point-of-care testing but are unsuitable for population screening and do not provide numeric results.

The heterogeneous nature of faeces and the inherent inconsistency in sample collection makes reliable quantitative measurement of blood in faeces impracticable. However, many of the automated immunochemical test devices that are suitable for population screening provide a numeric analytical result for the sample presented for analysis. These systems determine the turbidity or colour density of a reaction between haemoglobin and the antibody/chromogen system. Measurement is usually performed in a cuvette containing an aliquot of sample in buffer and added reagents (OC-Sensor, FOB Gold).

Whilst the results provided by these systems must not be considered quantitative measures of faecal haemoglobin, the numeric results provide an opportunity to select a cut-off limit above which a test can be defined as positive. This feature enables the user to adjust the positivity rate and thereby the clinical sensitivity and specificity of the test. Such a system enables colonoscopy referral rates to meet

the available colonoscopy resource. The clinical implications of manipulating the cut-off limit and/or the number of samples used for analysis is described later in this chapter.

Table 4.1 gives the analytical sensitivities quoted by manufacturers for a range of FOBT devices. Differences in quoted analytical sensitivity may reflect the use of different methods of assessment as well as product characteristics.

Table 4.1: Analytical sensitivities

Product name	Manufacturer/Supplier	Analytical Sensitivity
Guaiac-based test		
Coloscreen	Helena Laboratories, Texas, USA	0.9 mg Hb/g
Hema-screen	Immunostics Inc. 3505 Sunset Avenue, Ocean, New Jersey, 07712, USA	0.6 mg Hb/g
Hemoccult	Beckman Coulter Inc. Fullerton, CA 92835, USA	30% positivity at 0.3 mg Hb/g
Hemoccult SENSA	Beckman Coulter Inc. Fullerton, CA 92835, USA	75% positivity at 0.3 mg Hb/g
MonoHaem	Chemicon Europe Ltd	1.05 mg Hb/g
Hema-Check	Siemens PLC	6 mg Hb/g
HemaWipe	Medtek Diagnostics LLC, supplier; BioGnosis Ltd	2 mg Hb/g
Automated Immunochemical Test/*Analyser*		
OC-Sensor/OC-Sensor Diana & OC-Sensor Micro	Eiken Chemical Co., Tokyo, Japan	40 µg Hb/g
Hem-SP/MagStream HT	Fujirebio Inc. Japan	10 ng Hb/mL
FOB Gold/SENTiFOB analyser	Medinostics Products Supplier; Sentinel Diagnostics SpA, Milan, Italy	14 ng Hb/mL

4.3.2 Analytical specificity and interference

In the context of gFOBT and iFOBT, *analytical* specificity is the ability of the test to detect human blood accurately without interference from other endogenous or exogenous components of the faeces. It does not include interference from blood produced from pathological or physiological sources, which is termed *biological* interference since the interference is not as a result of a weakness in the analytical system.

4.3.2.1 Analytical interference

gFOBTs use a non-specific reaction for detecting blood and whilst cheap and simple to use, they are inherently susceptible to positive interference from oxidising agents and compounds with oxidase or

peroxidase properties. gFOBTs are also subject to negative interference from compounds with reducing properties such as vitamin C. In its 2007 guidance to industry, the US FDA Centre for Device and Radiological Health illustrated the range of dietary substances known to interfere with gFOBTs: broccoli, cantaloupe, cauliflower, horseradish, parsnip, red radish, turnip, iron and vitamin C supplements, and haemoglobin from beef, chicken, fish, horse, goat, pig, rabbit and sheep.

Evidence suggests that although the gFOBT test is open to interference from normal diets, this is not substantial and is reported to be negated by a time delay of at least 48 h between sample collection and analysis (Sinatra, St John & Young 1999). A diet including 750 g of raw peroxidase rich fruit and vegetables daily is reported to cause false positive results however 750 g is an unusually large daily consumption. A systematic review of the effect of diet on gFOBT showed that dietary restriction was not necessary (Pignone et al. 2001). The five randomised trials included in the review all used gFOBT Hemoccult tests. None of the studies showed a statistically significant difference between the group in which peroxidise-containing food (red meat, no red meat, poultry, fish, or certain raw vegetables and fruits), nonsteroidal anti-inflammatory drugs (NSAIDs, including aspirin), and vitamin C were prohibited compared with a control group without dietary restrictions (meta-analysis: absolute difference in positivity rate 0%; 95% CI, –1% to 1%). A cohort study conducted in Israel by Rozen, Knaani & Samuel (1999) on 944 asymptomatic subjects attending colorectal cancer screening (mean age 60.2±11.1) reported an overall gFOBT positive rate of 7.5%, while neoplasia was found in 16 (22.5%) subjects with positive gFOBT. Among subjects with and without dietary restriction, the positivity rates were 7.2% and 5.5% respectively (p = 0.26). These positivity rates are markedly higher than those observed in the UK screening pilots (1.6% in England and 2.1% in Scotland with an average of 1.9%) and are now observed in the fully rolled-out screening programme which does not advocate dietary restriction (UK Colorectal Cancer Screening Pilot Group 2004).

iFOBT brings a significant improvement in analytical specificity. The use of a specific antibody against human globin makes cross reactivity with dietary haemoglobin very unlikely, and the method used for detecting the antibody reaction can also be made largely free from interference from other dietary interference. Studies have not been published that demonstrate whether the reagents used in iFOBTs will detect haemoglobin variants. Polyclonal assays are unlikely to show cross-reactivity problems, but manufacturers should provide evidence that their analytical systems react similarly with all known haemoglobin variants. A recent evaluation has shown that with HbA1c, HbS, HbC, HbD, HbE and HbF using the Hem-SP/MagStream HT, OC-Sensor/Diana and FOB Gold Sentinal Systems, only HbF showed poor recovery and might give false negative negative results (Lamph et al. 2009).

Instant-View is an iFOBT that was used by the Australian health service, and since it requires sampling from the toilet bowl it is subject to other potential analytical interferences. In their US FDA 510(k) submission, the US supplier of Instant-View, Alfa Scientific Designs, disclosed decreased analytical sensitivity in the presence of toilet bowl deodorizers, fresheners and cleaner, and required that toilet bowl deodorizers/fresheners or cleaners be removed from the toilet bowl prior to collecting samples and that the toilet be freshly flushed.

Table 4.2 lists known gFOBT interferences. A good account is included in the MHRA Report of 2000 and summarized by Starkey (2002).

4.3.2.2 Biological interference

Any physiological process or non-colorectal cancer related pathological lesion that increases the loss of blood into the intestine is a source of biological interference. Although aspirin and NSAIDs pose potential interference, studies have shown either no effect or an increased sensitivity to the detection of cancer and adenomas among those who are taking aspirin.

Table 4.2: gFOBT Analytical interference

Positive interference	Comment	Reference
Non-human blood (beef, pork, chicken, pheasant, salmon, sardines, black pudding, German blutwurst, French boudin noir, Spanish morcilla and liver)	Reduced by cooking. Avoid red meat for 3 days prior to sampling. Meta-analysis suggests dietary restriction not necessary	(Illingworth 1965; Fludger et al. 2002)
Myoglobin		(Lifton & Kreiser 1982; Achord 1983; Welch & Young 1983; Scriven & Tapley 1989; Anderson, Yuellig & Krone Jr. 1990)
Iron	Mixed reports about whether iron supplements interfere	
Providone-iodine antiseptic	Use on perianal area or in urinary catheters should be avoided since iodine will oxidise guaiaconic acid.	(Said 1979)
Contact with toilet sanitizers in toilet water	Potential for negative and positive interference. gFOBT less than iFOBT. Reported in chlorine-releasing agents	(Imafuku, Nagai & Yoshida 1996)
Raw fruits & turnips, broccoli, horseradish, cauliflower, cantaloupe, parsnip and red radish	Large daily consumption only, causes interference. Caused by peroxidases that act like haemoglobin and give false positives. Cooking for 20 mins at 100°C destroys peroxidases and a delay of 2 days between collection and analysis is also effective as long as a non-hydrated gFOBT is used	(Illingworth 1965; Sinatra, St John & Young 1999)
Negative interference	**Comment**	**Reference**
Vitamin C (Ascorbic acid)	Reducing agents counters oxidising effect on guaiaconic acid. Vitamin C intake should be <250 m/d. Normal diet unlikely to interfere but high dose supplements might do so	(Jaffe et al. 1975; Garrick, Close & McMurray 1977; Jaffe & Zierdt 1979)
Degradation of haem	Haem degrades slowly a process that is accelerated if the faecal sample remains moist and warm	CEP Report 2006 (Bennitt, Burtonwood & Halloran 2006)
Contact with toilet sanitizers in toilet water	Potential for negative and positive interference. gFOBT less than iFOBT	(Imafuku, Nagai & Yoshida 1996)

Aspirin and NSAIDs

One double-blind RCT and one cohort study investigated whether the use of regular aspirin or NSAIDs is a risk factor for a false-positive FOBT result. A double-blind RCT (Greenberg, Cello & Rockey 1999) was conducted on healthy volunteers aged 29.8 ± 0.6 years who were randomised to placebo and those receiving doses of 30 mg, 81 mg, and 325 mg of aspirin. Short-term (30 days) use of low-dose aspirin did not induce sufficient intestinal injury to cause positive FOBTs (number of GI erosions aspirin group: 6/30 (20%); placebo: 1/10 (10%) p = 0.66). A cohort study (Kahi & Imperiale 2004) showed no difference in the prevalence of colonoscopic findings that would potentially explain a positive FOBT result between regular aspirin or NSAID users and non-users, even after adjusting for factors that affect the risk of a lesion that would account for a positive result (absolute difference 2% (95% CI -10–14), p=0.7). The study also found no relationship between the dose of aspirin and the likelihood of colonoscopic findings (chi-squared test for trend p=0.6). Overall, advice to patients to

restrict their diet and avoid NSAIDs and vitamin C does not appear to change positivity rates. This finding was consistent across all studies, regardless of the intensity of the restriction. A recent report by Levi et al. (2009) showed an increase in sensitivity but no loss of specificity of iFOBT (OC-Sensor) for detection of cancer and advanced adenomas in those using asprin/NSAIDs or anticoagulants.

Anticoagulants

Anticoagulants present a further source of biological interference. The effect of anticoagulants on the false-positive rate in a population-based FOBT screening programme was evaluated in two studies (Bini, Rajapaksa & Weinshel 2005; Clarke et al. 2006). The cohort study conducted within the Scottish arm of the national colorectal cancer screening pilot on 846 subjects aged 50–69 years old showed that taking anticoagulant medication (aspirin, COX-2 inhibitors, other NSAIDs and warfarin) at the time of testing is associated with a statistically significant 6.4% increased rate of negative colonoscopy. Diagnosis of colorectal neoplasia was higher in the no-anticoagulant group compared with the anticoagulant medication cohort (56.5% vs. 47.5%; absolute difference 9%, p=0.012). A study in an American healthcare system programme looked at all patients taking warfarin who were referred for the evaluation of a positive FOBT (Bini, Rajapaksa & Weinshel 2005). For each patient taking warfarin, an age- and gender-matched control was enrolled. The positive predictive value of FOBT for gastrointestinal lesions consistent with occult blood loss in patients taking warfarin was similar to that in the age- and gender-matched control group of subjects with a positive FOBT who were not taking oral anticoagulants (59.0%, 95% CI, 52.3–65.8%; 53.8%, 95% CI, 47.0–60.6%; p=0.27).

Table 4.3 summarises sources and mechanisms of biological interference which will reduce the specificity of either gFOBT or iFOBT analysis.

Table 4.3: Biological interferences

Physiological	**Comment**	**Reference**
Loss from the gums after vigorous teeth brushing		
Menstrual bleeding	-	-
Pathological		
Inflammatory bowel disease (Crohns disease, colitis)		(Rockey et al. 1998)
Gastritis from alcohol or chemotherapeutic drugs	-	
Gastric Cancer		(Zhou, Yu & Zheng 1999; Zappa et al. 2007)
Anti-inflammatory drugs (ibuprofen, naproxen, corticosteroids, phenybutazone)	Increased blood loss of 1-2 mL/d. 5% of those on high dose NSAIDs lost 5mL/d	(Moore, Derry & McQuay 2008) (Levi et al. 2009)
Aspirin	No iFOBT interference reported in low dose aspirin. High-dose blood loss 5 mL/d	(Ahlquist et al. 1985), (Moore, Derry & McQuay 2008) (Levi et al. 2009)
Proximal intestinal tract inflammation (gastritis, oesophagitis and gastric and duodenal ulceration)		(Rockey et al. 1998)
Anticoagulation therapy	2005 study showed no effect from warfarin	(Bini, Rajapaksa & Weinshel 2005)
Perianal bleeding	-	-

4.3.2.3 Dietary and drug restrictions

Potential interference of diet and drug intake on test performance has been pointed out above (Sect. 4.3.2.1 and 4.3.2.2) and the organisational aspects of drug and dietary restriction are discussed in Ch. 2 (Section 2.5.1.2). Whilst most gFOBT manufacturers recommend dietary advice, the potential

detrimental impact on participation rates makes it unattractive. One study used an immunochemical test and compared the participation rates of two groups, one with and one without dietary restriction (Cole & Young 2001). Two further studies (Cole et al. 2003; Federici et al. 2005) compared participation rate in a guaiac test with dietary restriction and in an immunochemical test without dietary restriction. Predictably, all three studies found greater participation when the diet was unrestricted. However, these studies and their data are not sufficient to exclude the possibility of other factors contributing to the outcomes.

4.3.3 Other factors influencing analytical performance

4.3.3.1 Prozone effect

Immunochemical analysis is prone to giving falsely low results when the analyte being tested is at markedly elevated concentrations. This well described interference is called the prozone or “hook” effect. The concentration of haemoglobin at which an iFOBT exhibits this effect needs to be very high and should be disclosed by the manufacturer. If an analytical method exhibits a prozone effect, then the measurement system should be able to detect erroneous results and warn the analyst. This is a requirement of U.S. FDA 510(k) submissions.

4.3.3.2 Sample quality

The quality of the sample is very important; it must be reproducible and representative of the stool, to be of the required volume and be adequately preserved. Many of the issues that impinge on sample quality have been discussed earlier. The stability of haemoglobin in faeces is an important consideration when selecting the preferred test, developing arrangements for sample transport to the laboratory and determining the urgency of analysis on the arrival of samples in the laboratory.

The haem moiety used in gFOBTs is more stable than the globin moiety used in iFOBTs. Transport of a dried sample, which is used for most guaiac test kits, provides greater stability than that in wet buffer which is usually used for immunochemical tests. The acceptable time period between sampling and testing is defined by the product manufacturers in their Instructions For Use (IFU). For gFOBTs the maximum time period is usually between 14 and 21 days; for iFOBT it is much less.

Haem in haemoglobin is degraded slowly after collection; if samples are collected onto filter paper, the design of the test device and envelope should maximise the speed of drying and so help preserve the sample. Young et al. demonstrated the deterioration of wet samples in a study using gFOBT in 1996 (Young, Sinatra & St John 1996). The UK NHS MHRA report of 2000 illustrated the influence of excessive sample loading, high temperature storage, and exposure to sunlight on 12 occult blood kits (Pearson, Bennitt & Halloran 2000). The UK NHS CEP report of 2006 reported the effect of sample storage time upon positivity for four gFOBT kits, the change from positive to negative test result being most marked with those test kits that have the lowest limit of detection (Bennitt, Burtonwood & Halloran 2006). For gFOBT, a regression study by Faure et al. investigated the influence of temperature and moisture on gFOBT sensitivity. In this study it was observed that the positivity rate of Hemoccult II in a 10-year screening programme showed a significant change between 1.61% in summer to 2.80% during the winter (Faure et al. 2003). No significant effect of temperature alone was observed: the positive rate decreased from 74.0% at 4°C in the presence of silica gel to 68.0% at 30°C in the presence of water ($p=0.52$). In this study the decrease in positive rate due to the presence of moisture was statistically significant (84.0% at 4°C and 100% humidity, 58.0% at 25°C with silica gel; $p=0.007$).

Globin in haemoglobin is an easily degraded protein moiety and more susceptible to denaturation than haem. Proteolysis of globin should be minimised between sample collection and analysis. Whilst appropriate constituents in collection buffer solutions might reduce degradation, the stability of globin in the wet collection systems used by most iFOBTs is poor compared with haem used in gFOBTs. The concentration of haemoglobin in the buffer solutions after sampling can be very low, typically 20ng/mL with the collection device used by the MagStream HT. At these low concentrations the haemoglobin molecule is susceptible to decomposition and may be adsorbed onto the surface of the collection vessel and measurement cuvette. Buffers that are rich in proteins such as bovine serum albumin (BSA) and haptoglobin can minimise adsorption and help stabilise the haemoglobin. Unpublished data from the manufacturers of the immunochemical devices Hem-SP and OC-Sensor show good stability at refrigerator temperatures (4°C) but marked deterioration with rising temperature. Vilkin et al. (2005) and Rozen et al. (2006) showed, over 21 days, no significant change at 4ºC or 20ºC but a daily fall of 3.7% ± 1.8 at 28°C with the iFOBT OC-Micro system (*Eiken Chemical Co., Tokyo, Japan*). Rozen used storage in a refrigerator and supplied an opaque double zip-lock bag for such storage. Fraser et al. (2007) reported the successful use of dried samples for iFOBTs using two Immunostics products (*Immunostics Inc. Sunset Avenue, Ocean, New Jersey, USA*). Hema-screen Devel-A-Tab was used to collect the sample and Hema-screen Specific as the immunochemical assay system. The low concentrations of haemoglobin detectable in iFOBT devices increases susceptibility to stability problems. Whilst sample stability has not presented a major difficulty for programmes using gFOBTs, it is likely to do so for those adopting wet sample collection with iFOBTs. The acceptable time between collection and analysis is markedly influenced by ambient temperature during storage and transport, and this will depend on transport and weather conditions.

Between December 2008 and May 2009, the Australian Screening Programme encountered stability problems with the Haem-ST/MagStream HT system (Australian Government 2009). Positivity levels fell markedly during the 6-month period, and participants will require retesting. Very high summer temperatures and the introduction of a new buffer with a lower protein concentration may have contributed to haemoglobin instability in this programme and a consequent reduction in positivity rates. A recent report describes retrospective analysis of measured haemoglobin over several years by the screening programme in Northern Italy (Grazzini et al. 2010). The study reveals significant seasonal variation in the positivity rates of in the OC-Sensor iFOBT that may be attributed to by high summer temperatures. Manufacturers of iFOBT devices specify stringent storage and transit conditions to minimise the sample deterioration. These conditions present a practical challenge to the organisation of iFOBT-based screening programmes.

4.3.3.3 Device consistency

The ability of iFOBT and gFOBT kits to maintain consistent performance across reagent batch changes and product redesigns is important for population screening since minor changes in product sensitivity and specificity can greatly change the number of patients referred to colonoscopy. Companies need to be able to demonstrate good quality manufacturing practice and quality assurance procedures that minimise batch-to-batch variation. Guaiac gum is a natural product and is therefore more susceptible to product inconsistency than manufactured monoclonal antibody reagents that can be used by iFOBTs. Polyclonal antibodies, which are used for each of the current automated iFOBTs, are susceptible to batch-to-batch variation, and therefore an understanding of the batch size of all reagent components is important. In a market with many small manufacturers, the long-term viability of the product and company should also be considered.

4.3.3.4 Analytical quality assurance – Internal Quality Control (IQC) and External Quality Assessment Schemes (EQAS)

Rigorous analytical quality assurance procedures must be adopted by laboratories providing gFOBT and iFOBT analysis for population screening. To minimise analytical and procedural variability, the

number of laboratories used for population screening should be small. In the English programme, laboratories typically serve a population of 10–15 million, approximately 10–16 % of which will be within the screening age group. All laboratories providing screening services should be associated with a laboratory accredited to ISO 15189:2007, *Medical laboratories - Particular requirements for quality and competence (http://www.iso.org/iso/iso_catalogue.htm)* The laboratory should be led by a qualified clinical chemist who is trained and experienced in the techniques used for analysis and in clinical quality assurance procedures. The laboratory staff should be appropriately trained and competent in the use of the analytical device/ instrumentation, quality control and assessment procedures and associated information technology.

For those laboratories using visually read gFOBTs, the design of the test kit will influence the reliability of analysis. Reproducibility in detecting the blue gFOBT colour in the presence of dark faecal pigments depends on good staff training and experience but can be improved by other factors. The visual acuity and colour perception of the reader should be professionally checked and monitored. The colour of the test card surrounding the sample, the colour of surrounding walls and the colour temperature and brightness of artificial lighting all should be considered. The opportunity for errors due to operator fatigue should be minimised by enforcing periodic work breaks. The competence of staff to perform visual tests should be checked before they commence each batch of analysis, typically using preloaded test kits with known positivity that is hidden from the operator. A rigorous monitoring system should be adopted to identify staff who have spot positivity rates which are markedly different to the mean or who exhibit marked variability.

Most gFOBTs and point-of-care iFOBT devices have a means of checking the integrity of the device and reagents by way of a quality control check integral to the device. For gFOBT, this control can check whether guaiac has been applied across the whole of the test area and whether the hydrogen peroxide reagents are working correctly. Point-of-care iFOBT devices provide a similar check of reagent integrity but are unsuitable for population screening.

The case for automation in population screening programmes is a strong one, and should significantly influence the choice of an acceptable occult blood testing system. Automated iFOBT analysis will require internal quality control procedures appropriate to the chosen technique and instrument. As a minimum, laboratories should adopt the manufacturers' instructions for use, and give consideration to what additional internal quality control measures can be used to check instrument accuracy and imprecision throughout the period of analysis. Good analytical performance is particularly important at the selected cut-off concentration, and quality control measures should reflect that requirement.

Participation in an external quality assessment scheme (EQAS) is seen as mandatory for tests performed in a clinical laboratory. Participation in an EQAS enables assessment of bias between participating laboratories, and is particularly important for a national screening programme utilising several laboratories. The availability of an EU-wide EQAS is desirable. National population screening programmes should have quality assurance procedures that enable oversight of the analytical performance of all screening laboratories. Satisfactory performance in an EQAS provides an objective criterion of competence.

A summary of the three iFOBT systems that have some of the characteristics suitable for population screening is provided in Table 4.4.

Table 4.4: Comparative table of automated iFOBT

Hem-SP / MagStream HT

Alternative name(s): Developed from Immudia-Hem-SP (Marketed as HaemSelect in the US)

Manufactured by: Fujirebio Inc. Japan

Sold by: Fujirebio Europe B.V. (http://www.fujirebio.co.jp/english/index.html)

Principle of measurement system: MagStream Hem-Sp® is based on magnetic particle agglutination. The faecal specimens are incubated with magnetic gelatine particles which are ferrite and gum Arabic coated with rabbit anti-human haemoglobin antibodies. The solid particles are collected in the centre of microplate wells by magnetic attraction and inclined to about 60 degrees and examined for change in particle aggregates. In the presence of human haemoglobin, the particles remain aggregated in a spot with minimal change (positive result). In the absence of human haemoglobin, particles flow down the slope (negative result). The appearance of particle aggregates is interpreted by MagStream HT using CCD image capture and computer determination of the length of the line of magnetic particles. The company recommends that 1 of 2 samples need to be positive and state that the measurement system has not been designed for quantitative measurement. This system has been developed to give a sharp cut-off at a concentration of 20 ng/mL and not to provide quantitative measurements for user-defined cut-off concentrations, and is not CE marked for this purpose.

Recommended number of separate samples used for assessment: 2 samples

Method of sample collection: Stick in buffer held within the device

Means of reading: MagStream HT, an automated instrument which holds 400 samples and has a memory capacity of 2 million test results

Speed of analysis: 960 tests per hour (MagStream HT)

Quantity collected by sampling device: 0.3 mg of faeces

Volume of buffer in collection device: 1 mL

Analyser sample volume: 25 µL

Quality control: Standard laboratory QC procedures

Mailing acceptable to EU: It is being used in both France and Slovenia.

Cut-off level: Not designed or CE marked for an adjustable cut-off

Limit of detection: 10 ng/mL

Use in population screening: Japan, France and Slovenia

Recent pertinent scientific papers: (Launoy et al. 2005; Morikawa et al. 2005; Morikawa et al. 2007)

Website URL: Fujirebio

Fujirebio Inc Japan

http://www.fujirebio.co.jp/english/product/immunological.html

OC-Sensor

Alternative name(s): OC-Hemodia, OC light (not available in EU)

Manufactured by: Eiken Chemical Co., Tokyo, Japan

Sold by: Mast (UK), Alfa Wassermann (Italy), Pharmatrade (Israel)

Principle of system: Latex agglutination using polystyrene latex particles coated with polyclonal anti haemoglobin Ao antibodies. The assay uses a 6-point standard curve, and measurement is made at 600 nm with an algorithm which uses a kinetic endpoint.

Recommended number of separate samples used for assessment: 1 sample

Method of sample collection: Serrated stick in buffer held within the device

Means of reading: OC-Sensor Diana & OC-Sensor Micro (successor to OC-Sensor Neo) are both automated instruments and are both CE marked. The Diana has a memory capacity for 100 000 test results

Speed of analysis: 280 samples per hour (OC-Sensor Diana)

Quantity collected by sampling device: 10 mg of faeces

Volume of buffer in collection device: 2 mL

Analyser sample volume: 35 µL

Quality control: Standard laboratory QC procedures

Mailing acceptable to EU: Reported to have been agreed by the UK post office

Cut-off level: CE marked for a user defined cut-off. Default setting 100 ng/mL

Limit of detection: 20 ng/mL in buffer

Use in population screening: The Netherlands (van Rossum et al. 2008; van Rossum et al. 2009), Northern Italy (Castiglione et al. 2000), US, Uruguay (Fenocchi et al. 2006) and France

Website URL: http://www.eiken.co.jp/en/company/index.html

URL: http://www.eiken.co.jp/en/product/index.html#anc03

FOB Gold

Manufactured by: Sentinel Diagnostics SpA, Milan, Italy

Principle of system: The FOB Gold reagents use an antigen-antibody agglutination reaction between human haemoglobin and polyclonal anti-human haemoglobin antibodies coated on polystyrene particles. Agglutination is measured as an increase in absorbance at 570 nm and is proportional to the concentration of human haemoglobin contained in the sample. The calibrator is a lyophilized material containing human haemoglobin, and this is used to generate a six-point calibration curve using serial dilutions of the reconstituted material. The manufacturer provides lyophilized quality control preparations at two haemoglobin concentrations. The total reading time is 8 minutes.

Means of reading: The FOB Gold reagents can be used on any suitable immunoassay automated analyser although the manufacturer provides the SENTiFOB analyser

Speed of analysis: 75 tests/hr (SentiFOB)

Quantity collected by sampling device: 10 mg of faeces

Volume of buffer in collection device: 1.7 mL

Analyser sample volume: 10 µL

Quality control: Standard laboratory QC procedures

Mailing acceptable to EU: Not known

Cut-off level: CE Marked for a user defined cut-off

Limit of detection: 14 ng/mL buffer

Range Measuring range: 15-1000 ng/mL.

Use in population screening: Italy (Rubeca et al. 2006) & France

Recent pertinent scientific papers: (Fraser et al. 2008)

Website URL: http://www.sentinel.it/uk/

4.3.4 Recommendations

Sample stability between collection and analysis

Whilst a maximum period of 14 days between collection and analysis is frequently quoted for many guaiac faecal occult blood tests, that quoted for immunochemical tests is significantly shorter. Until more stability data are published, screening programmes should adopt the conditions and period of storage described in manufacturer's Instructions for Use having determined that they are appropriate for local conditions which might expose samples to high temperatures for long periods of time (Sect. 4.3.3.2) **(III - A).**[Rec 4.4]

Test interference - drug and diet restriction

Dietary constituents present potential interference in guaiac faecal occult blood tests. Dietary restrictiton has not been demonstrated to significantly increase screening specificity, and risks reducing participation rate. The potential for dietary interference is significantly less for immunochemical tests. With the qualification that a diet peculiar to a particular country or culture may not have been tested or reported dietary restriction is not indicated for programmes using either guaiac-based or immunochemical tests (Sect. 4.3.2.1, 4.3.2.3) **(II - D).**[Rec 4.7]

Interference from bleeding associated with drugs such as aspirin, nonsteroidal anti-inflammatory drugs and anticoagulants (e.g. warfarin) present potential interference in both guaiac and immunochemical faecal occult blood tests. Although the literature carries some contradicting reports of the effect of anticoagulants on screening outcome, drug restriction is not recommended for population screening programmes using either guaiac-based or immunochemical tests (Sect. 4.3.2.2, 4.3.2.3) **(III - D).**[Rec 4.8]

Faecal sampling/collection system

Many factors influence the uptake and reliability of sample collection. Inappropriate implementation can result in grossly misleading results. No single collection methodology is supported by the literature; however, the following factors should be considered when selecting a device for taking samples in population screening:

- The distribution process should be reliable and reach all selected subjects.
- The laboratory should be able to unambiguously identify the subject ID on the test device perhaps using a suitable barcode.
- The laboratory should be able to check the manufacturer's device expiry date on each returned device.
- The instructions for using the device must be simple and clear.
- The device should to be simple and easy to use by the target population.
- The device should leave minimal opportunity for collection error.
- The device should facilitate consistency in the volume of sample collected.
- The device/instructions should discourage inappropriate repeat sampling into/onto the sample device.
- Misuse of the device by participants should not cause loss of sample buffer.
- The system should not be susceptible to interference from toilet bowl disinfectants, etc.
- The screening participant should be able to record the date of sample collection to ensure the laboratory can verify receipt within an acceptable sample stability period.

- The process used by the subject for returning the device should be simple, reliable, safe and, when appropriate, should meet EU postal regulations.

A local pilot study should be undertaken to ensure that the chosen device and associated distribution, sampling and labelling procedures are acceptable (Sect. 4.2.3, 4.2.4, 4.3.2.1, 4.3.3.4) **(VI - A).**[Rec 4.9]

Laboratory organisation:

- **Number of laboratory sites**

  Population screening necessitates the receipt, measurement and recording of thousands of tests each day. The samples should be analysed without delay to avoid further sample denaturation and avoid an increase in false negative results. Inter-laboratory analytical imprecision is well described and can be observed through established external quality assurance schemes. Improved consistency is achieved by adopting common analytical platforms, analytical and quality standards and shared staff training. The analysis needs to be reproducible across a screening population and therefore the number of analytical centres should be minimised with automated analytical systems utilised wherever possible and agreed common testing procedures adopted by each centre (Sect. 4.3.3.4) **(VI - B).**[Rec 4.10]

- **Laboratory staff**

  All laboratories providing population screening should be led by a qualified clinical chemist who is trained and experienced in the techniques used for analysis and with clinical quality assurance procedures (Sect. 4.3.3.4) **(VI - B).**[Rec 4.11]

- **Laboratory accreditation and quality monitoring**

  All laboratories providing screening services should be associated with a laboratory accredited to ISO 15189:2007 *Medical laboratories - Particular requirements for quality and competence*. The laboratories should perform Internal Quality Control (IQC) procedures and participate in an appropriate External Quality Assessment Scheme (EQAS, Sect. 4.3.3.4) **(VI - B).**[Rec 4.12]

- **Distribution of FOBT kits by mail**

  Distribution and receipt of FOBT kits using local postal services can be an effective means of reaching the designated population (Ch. 2, Rec. 2.15, Sect. 2.5.1.1 and Sect. 4.4.3.4) **(I - B).**[Rec 4.13]

Identification of participants and test results

Automated check protocols should be implemented to ensure correct identification of the screened population and complete and accurate recording of individual screening participation and test results (see Ch. 2, Rec. 2.18, Sect 2.5.1.3) **(VI - A).**[Rec 4.15]

Classification of test results

Protocols should be implemented to ensure standardised and reliable classification of the test results (Ch. 2, Rec 2.19, Sect. 2.5.1.3) **(VI - A).**[Rec 4.16]

Quality Assurance

- **Quality assurance of gFOBT testing**

  Whilst an immunochemical test is recommended, programmes that adopt a traditional guaiac test need to apply additional laboratory quality procedures. To minimise variability and error associated with visual test reading, including manual results input, the following procedures should be considered (Sect. 4.3.3.4) **(VI - B):**[Rec 4.17]

- Use of appropriate temperature for artificial lighting and neutral-coloured walls in the reading laboratory;
- Use of a national laboratory training programme to prosper consistency of interpretation;
- A blinded internal QC check each day for each analyst prior to commencing testing;
- Adoption of a monitoring programme to identify operator related analytical performance (e.g. positivity variability and bias); and
- Double entry of test results

- **Quality assurance of iFOBT testing**

  Consistency in analytical performance must be assured by the adoption and application of rigorous quality assurance procedures. Manufacturer's Instructions for Use must be followed. Laboratories should perform daily checks of analytical accuracy and precision across the measurement range with particular emphasis at the selected cut-off limit. Rigorous procedures need to be agreed and adopted on how internal quality control data is interpreted and how the laboratory responds to unsatisfactory results. Performance data, both internal quality control and external quality assessment data, should be shared and reviewed by a Quality Assurance team working across the programme. Sufficient instrumentation should be available to avoid delays in analysis due to instrument failure or maintenance procedures (Sect. 4.3.3.4) **(VI - B).**[Rec 4.18]

- **External quality assessment**

  A European external quality assessment scheme should be developed to facilitate Europe-wide quality assurance of occult blood testing and enhance the reproducibility of testing within and between countries providing population screening (Sect. 4.3.3.4) **(III - B).**[Rec 4.19]

- **Outcome monitoring**

  All aspects of laboratory performance in respect of the screening test should be part of a rigorous quality assurance system. Uptake, undelivered mail, time from collection to analysis, analytical performance (internal QC and external QA), positivity rates, lost & spoilt kits and technical failure rate, technician performance variability and bias should each be subject to rigorous monitoring (Sect. 4.3.3.4) **(VI - A).**[Rec 4.20]

- **Quality of information**

  The proportion of unacceptable tests received for measurement is influenced by the ease of use of the test kit and the quality of the instructions for use. This proportion should not exceed 3% of all kits received; less than 1% is desirable (see Ch. 3, Rec. 3.9, Sect. 3.3.2) **(III - A).**[Rec 4.21]

4.4 Clinical performance

4.4.1 Description of terms used to describe test effectiveness

gFOBT screening has been proven to be effective in reducing colorectal cancer mortality (Hewitson et al. 2007). In randomised trials the reduction in cause-specific mortality ranged from 15% (Hardcastle et al. 1996) to 33% (Mandel et al. 1993). Such a large variance in mortality can be explained by test differences, different numbers of faecal samples, different intervals between invitation cycles (one-

year or two-year) and different responses to invitation associated with the characteristics and composition of the population screened. The sensitivity and specificity quoted for a test will therefore be influenced both by the test's analytical characteristics and the context in which the test is used and evaluated.

gFOBTs come in two forms, the conventional form with normal sensitivity and the more sensitive variety, Hemoccult SENSA, in which the sample is hydrated before analysis. Hemoccult SENSA performs quite differently from the gFOBTs used in European trials (Hardcastle et al. 1996; Kronborg et al. 1996) and is both more sensitive and less specific. Comparison of the clinical performance of gFOBT and iFOBT is complex because iFOBTs can have different levels of specificity and sensitivity indeed they may have variable positive cut-off concentrations. Changes in cut-off concentrations result in different clinical performance characteristics.

Although only one population-based RCT has been described with iFOBT (van Rossum et al. 2008), the many published diagnostic accuracy studies provide information on the comparative ability of current tests to distinguish subjects with or without colorectal cancer and adenoma and can be considered an acceptable indication of the satisfactory performance of iFOBT in population screening (Burch et al. 2007).

Diagnostic accuracy studies have compared:

a) subjects performing one or both tests (gFOBT and iFOBT) and performing a total colonoscopy (or sigmoidoscopy) independently from the result of the test (cohort studies);

b) subjects performing one or both tests and undergoing colonoscopy if one or both tests are positive (cohort studies);

c) Diagnosis determined beforehand and the test performed subsequently (case-control studies); and

d) Different subjects performing different tests.

Colorectal cancer, large adenomas (≥ 10 mm), high-risk adenomas (high-grade dysplasia, villous change, serrated histology or ≥ 3 polyps), all adenomas (including small adenomas), alone or combined have been used as reference standards in the various studies.

The comparative clinical performance of the different tests has usually been based on the following indicators: Sensitivity, specificity, Positive Predictive Value (PPV), false positive rate, likelihood ratio for a positive or a negative test which is derived from sensitivity and specificity (sensitivity/(1-specificity)) for + LR; (1-sensitivity)/specificity for –LR.

All of these parameters derive from the well-described 2*2 table

		Disease Present	**Disease Absent**	
		+	-	Total
Positive Test	+	a	b	a+b
Negative Test	-	c	d	c+d
	Total	a+c	b+d	

Where, *a* are true positive, *b* are false positive, *c* are false negative and *d* are true negative

Sensitivity = a/(a+c)
Specificity = d/(b+d)
PPV = a/(a+b)

"True" in true positive, is an abstract concept because in practice a reference standard must be adopted. For colorectal cancer screening, true is usually defined by the outcome of total colonoscopy, the best practical diagnostic procedure we have though it does not have a sensitivity of 100%. In a clinical setting it is not always possible to perform a total colonoscopy on all subjects who have negative screening tests, so it is difficult to estimate the number of false negatives (c) and true negatives (d). The difficulty of estimating false negative has a great impact on sensitivity but much less so on specificity. In fact (c) is a number much lower than (d), so that the sum c+d (i.e. the number of negatives to the test) is a small overestimate of d.

For sensitivity, (c) is a significant proportion of (a+c), so that it is necessary to have a direct estimate of the number of false negatives. Very often this estimate is obtained by measurement of the interval cancers (i.e. the number of colorectal cancers that are diagnosed in subjects negative to the test during defined interval of time). Clearly the reliability of the estimated number of false negatives will depend on the time interval, and that will increase as time elapses. It is therefore important when comparing estimates of sensitivity obtained in this way to verify that the time interval used is the same.

The ideal theoretical approach to estimating cancer-screening performance would be to obtain the disease status using a "gold-standard" method that is independent of the screening method. For colorectal cancer, the disease status is usually determined from a histological examination of biopsy specimens of those with positive test results, because it is not ethically acceptable to collect biopsies from all individuals undertaking a screening test. The sensitivity and specificity of screening test are therefore usually estimated using interval cancers. As initially described by Day (1985) interval cancers will not include slow-growing cancers missed by the test and not evident between two screening events (therefore clinical sensitivity will be overestimated). Conversely, interval cancers will include fast-growing cancers not present at the time of the screening test, but developing during the interval period (thus underestimating clinical sensitivity). This limitation is common to all screening procedure evaluations.

Programme sensitivity is an estimate of sensitivity (i.e. the number of CRC detected/the number of cancers detected plus the number of interval cancers occurring in a certain interval of time) and is biased toward overdiagnosis of CRC (i.e. it estimates diagnosis of CRC that would never occur clinically). For this reason it is sometime preferable to give an estimate of sensitivity based on the ratio between interval cancers (in a defined time period) and the number of cancers expected in the same period (more precisely, 1- (interval cancers occurred in x years/expected cancers in x years)). This estimate gives an idea of cancers anticipated by screening, and it is not affected by overdiagnosis.

It is also worth noting that from a practical point of view, the choice of the test (or combination of tests) is not based on clinical sensitivity and specificity but on the determination of detection rate (for cancer or adenomas) and its correlation with positivity being first correlated to sensitivity and latter to specificity.

4.4.2 Comparative clinical performance - gFOBT and iFOBT

Many studies comparing iFOBT and gFOBT have been performed in the last 8 years, and several systematic reviews of the literature have been undertaken more recently.

In 2007 Kerr published a systematic review by the Health Technology Assessment (NZHTA) of New Zealand which had the aim of identifying the international evidence for the clinical and cost effectiveness of screening tests for colorectal cancer (Kerr et al. 2007). This review included all primary research published as full original reports and secondary research, systematic reviews and meta-

analyses published since November 2004. It also included seven eligible primary research papers (Rozen, Knaani & Samuel 1997; Rozen, Knaani & Samuel 2000; Saito et al. 2000; Zappa et al. 2001; Cheng et al. 2002; Cole et al. 2003; Ko, Dominitz & Nguyen 2003) and five eligible secondary research papers; Australian Health Technology Advisory Committee (AHTAC) (1997), Conseil d'Évaluation des Technologies de la Santé du Quebec (2000), Canada, Craven UK (Craven 2001), Young World Health Organization and World Organization for Digestive Endoscopy (Young et al. 2002), Piper Blue Cross Blue Shield Association Technology Evaluation Center US (Piper 2004).

The review concluded that "there is limited definitive evidence regarding superior immunochemical FOBT performance over the guaiac tests. However, evidence from cross-sectional studies suggests that the immunochemical test HemeSelect, *Beckman Coulter Inc. Fullerton, CA, USA*... is comparable, or superior, to guaiac testing... The conclusions on this topic should be revisited if further reliable evidence on the comparative performance of screening FOBTs becomes available".

A similar conclusion was reached in a systematic review commissioned by the UK NHS and undertaken by the Centre for Reviews and Dissemination of the University of York in 2007 (Burch et al. 2007) which examined the literature until 2004. The review included 59 studies 39 evaluated gFOBTs, 35 evaluated iFOBTs and one evaluated sequential FOBTs. It concluded that there was no clear evidence from direct or indirect comparisons to suggest that guaiac or immunochemical FOBTs performed better. However amongst iFOBTs, Immudia-HemSP (now Hem-SP) appeared to be the most sensitive and specific.

In the four years since 2004, six studies comparing the performance of gFOBT and iFOBT have been published (Levi et al. 2006; Smith et al. 2006; Allison et al. 2007; Guittet et al. 2007; Dancourt et al. 2008; van Rossum et al. 2008). Some further studies have investigated the accuracy of iFOBTs which, although without a direct comparison with gFOBTs, confirmed the performance of iFOBTs which was reported in the following studies (Morikawa et al. 2005; Castiglione et al. 2007; Levi et al. 2007).

In Australia, Smith et al. (2006) performed a paired comparison of an iFOBT (InSure) with a sensitive gFOBT (Hemoccult SENSA); 2351 asymptomatic and 161 symptomatic subjects were requested to perform both FOBTs. iFOBT returned a true-positive result significantly more often in cancer (n = 24; 87.5% vs. 54.2%) and in significant adenomas (n = 61; 42.6% vs. 23.0%) while the false-positive rate for any neoplasia was marginally higher with the iFOBT than the gFOBT (3.4% vs. 2.5%; 95% CI of difference, 0–1.8%): the PPV for cancer and significant adenomas was slightly better for iFOBT (41.9% vs 40.4%).

In Israel, Levi et al. (2006) compared, a gFOBT with an iFOBT (OC-MICRO, now OC-Sensor) in a small number (151) of patients referred for colonoscopy either because of a positive gFOBT or because they were above average risk of colorectal cancer. Sensitivity, specificity, and positive predictive value for significant colorectal neoplasia were 75%, 34% and 12%, respectively, for gFOBT, and were 75%, 94% and 60% for iFOBT. For a positive gFOBT, 4 times more colonoscopies were needed to identify a significant neoplasm compared with iFOBT, and at more than 4 times greater cost.

In France, Guittet et al. (2007) compared the performance of gFOBT and iFOBT (Immudia-HemSP (now Hem-SP)) among 10 673 average-risk persons aged 50–74 years. Colonoscopy was offered only if either FOBT was positive. The threshold for a positive iFOBT was varied between 20 ng/mL and 75 ng/mL. Overall, the results depended on the adopted iFOBT threshold. At the lower threshold (20 ng/mL), iFOBT detected 1.5 times as many cancers and nearly 2.6 times as many high-risk adenomas as gFOBT; however, it also increased the relative false-positive rates (2.17 times more frequent for each relevant lesion detected in iFOBT as compared to gFOBT). It is worth noting that at a threshold of 75 ng/mL, iFOBT detected 90% more advanced neoplasms with a significant 33% decrease in the false-positive risk. A further publication from this study (Guittet et al. 2009a) reported that the gain in sensitivity from using iFOBT vis gFOBT was proportional to the degree of blood loss from the lesion and its location. The benefits for cancer detection were restricted to lesion of the rectum.

In the USA, Allison et al. (2007) prospectively compared two types of FOBTs, a sensitive gFOBT (Hemoccult SENSA) and a manual iFOBT (Flexsure). A large number of patients (7394 subjects were eligible for the study) were requested to perform both tests. All patients positive for either FOBTs were invited to have a total colonoscopy, whereas all patients negative to FOBT were advised to have a sigmoidoscopy. All cancers occurring during the two years following the test were identified, so that it was possible to estimate the absolute sensitivity and specificity for detecting advanced neoplasms in the left colon within two years after the FOBT screening for the two tests administered separately and in combination. The sensitivity for detecting cancer was 81.8% (95% CI = 47.8% to 96.8%) for the iFOBT and 64.3% (95% CI = 35.6% to 86.0%) for the gFOBT. The sensitivity for detecting distal advanced adenomas was higher for gFOBT than for iFOBT 41.3% (95% CI = 32.7% to 50.4%) vs 29.5% (95% CI = 21.4% to 38.9%). PPV was much higher for iFOBT than for gFOBT for distal cancer (5.2% and 1.5% for iFOBT and gFOBT respectively) and for advanced adenomas (19.1 and 8.9% for iFOBT and gFOBT respectively). The authors concluded that iFOBT has high sensitivity and specificity for detecting left-sided colorectal cancer and that it may be a useful replacement for the gFOBT.

The study by Dancourt et al. (2008) compared the performance of a 3-day gFOBT and 2-day iFOBT in 17 215 subjects. For 1205 subjects who participated and had colonoscopy, the PPV for the guaiac and immunochemical test was respectively 5.9% v 5.2% for cancer and 27.2% and 17.5% for adenoma.

The study by van Rossum et al. (2008) represents a milestone in the comparison of gFOBT with iFOBT, being the first randomised trial in a population based screening setting. A large number of people (20 623) aged 50–75 years were randomised to either gFOBT (Hemoccult II, *Beckman Coulter Inc. Fullerton, CA, USA*) or iFOBT (OC-Sensor). For iFOBT, the standard cut-off of 100 ng/mL was used. iFOBTs showed higher compliance than did gFOBTs (56.9% vs 46.9% respectively $p<.01$). The positivity rate was significantly higher in iFOBTs compared to gFOBTs (5.0% vs. 2.4% respectively, $p<0.01$). Cancer or advanced adenomas were found, respectively, in 11 and 46 of gFOBTs and in 24 and 121 of iFOBTs. The detection rate per 1000 examinations for cancer was 71% higher in iFOBT compared to gFOBT; the detection rate per 1000 examinations for advanced adenomas was 106% higher in iFOBT as compared to gFOBT. The number-to-scope to find 1 cancer or 1 adenoma was comparable between the tests, with the PPV not statistically different. In conclusion, iFOBT compared to gFOBT demonstrated a higher detection rate with a similar PPV.

The results of these five studies are consistent with data from the first European screening programmes. The UK Pilot study adopted Hema-screen, a conventional non-rehydrating gFOBT, using duplicate samples on 3 consecutive stools extended to 2 further sets of 3 stools if indicated. This UK pilot study gave a positivity rate during the first round of 1.9%. The Detection Rates (DR) for cancer and neoplasia (cancer and advanced or non-advanced adenoma) were 1.62 in 1000 and 6.91 in 1000 respectively. The PPV for neoplasia was 46.9% in England and 47.3% in Scotland (UK Colorectal Cancer Screening Pilot Group 2004).

In Italy, a 1-day single sample iFOBT biennial test with positivity cut-off at 100 ng/mL is used in the regional colorectal cancer programmes. The paper by Zorzi that described Italian screening programmes showed a quite different outcome to the UK Pilot study (Zorzi et al. 2008). The positivity rate was relatively high, 5.3% during the first round, the DR for cancer was 3.1 in 1000 (almost two times the UK figure) and the DR for adenoma was 24.7 in 1000 (more than three times the UK result). The PPV for neoplasia was slightly higher than that observed in UK pilot study (54% vs 46.9%) (UK Colorectal Cancer Screening Pilot Group 2004). The Italian programme had adopted a more sensitive (but less specific) strategy compared to the UK.

Hol et al. (2009) recently reported a randomised comparison of gFOBT (Hemoccult II) and iFOBT (OC-Sensor) in a population-based trial in the southwest Netherlands (age 50–74 years). For gFOBT, any 1 of 6 windows collected from 3 stools was designated positive and for iFOBT a single result above a cut-off concentration of 50 ng/mL was designated positive. Test kits were all distributed and returned by mail. Participants with positive results received colonoscopy. gFOBT positivity was 2.8%, and iFOBT positivity was 8.1% at a cut-off of 50 ng/mL, 5.7% at 75 ng/mL, 4.8% at 100 ng/mL and 4.0% at 150

ng/mL. At an iFOBT cut-off concentration of 75 ng/mL, the detection rate for advanced neoplasia was 2x higher than that by gFOBT and was considered to be the optimum cut-off and balance between detection rate and positivity.

4.4.3 Optimising clinical performance using test cut-off limits & algorithms

4.4.3.1 Cut-off limits

Until recently it has not been possible to adjust the analytical sensitivity of FOBT tests. This is still not possible for existing gFOBTs, with the exception of the simple adjunct of hydrating the specimen prior to testing with Hemoccult SENSA. With Hemoccult SENSA, hydration increases test sensitivity at the expense of specificity, thereby increasing the false positive rate (Mandel et al. 1993; Ransohoff & Sandler 2002). Hemoccult and Hemoccult SENSA have been compared in two large studies (Mandel et al. 1993). As a result of rehydration, the rate of positive results increased more than fourfold, from 2.4 to 9.8%. Sensitivity increased from 80.8% to 92.2% while both specificity and PPV decreased (specificity: 90.4% rehydrated and 97.7% non-rehydrated. PPV: 2.2 rehydrated and 5.6 non-rehydrated). In the study by Levin, Hess & Johnson (1997) the positivity rates were 5% and 14.6% and PPV 14% and 7% respectively for the non-rehydrated and the rehydrated. Rehydration using Hemoccult SENSA increases clinical sensitivity and decreases specificity and positive predictive value. The high positivity rate of this approach renders it unsuitable for population screening.

With iFOBTs that provide a numeric result, it is possible to adjust the cut-off limit to obtain an acceptable compromise between clinical sensitivity and specificity. This manipulation can provide an adequate detection rate from an acceptable cohort of subjects invited for colonoscopy. Several recent papers have addressed the issue of modifying the faecal haemoglobin cut-off limit of iFOBTs including the following studies (Sieg et al. 1999; Castiglione et al. 2000; Nakama, Zhang & Zhang 2001; Castiglione et al. 2002; Launoy et al. 2005; Vilkin et al. 2005; Rozen et al. 2006; Chen et al. 2007; van Rossum et al. 2009). The data are summarised in Table 4.5. By increasing the positive cut-off limit, the test sensitivity and positivity rate decreases and specificity and positive predictive values for colorectal cancer detection increase. It must be appreciated that these studies used different commercial products with different analytical characteristics, and therefore simple comparisons can be misleading.

Chen found an analytical cut-off limit range of 100–150 ng/mL faecal haemoglobin in an iFOBT to provide an acceptable balance between sensitivity and specificity (Nakama, Zhang & Zhang 2001; Chen et al. 2007). Increasing the cut-off limit to 300 ng/mL brought an increase in specificity that was small for the corresponding decrease in sensitivity and detection of cancers. A recent study by Rossum of 6157 50–75 year old Dutch participants and using a single OC-Sensor collection and OC-Micro analyser concluded that dropping from the standard 100 ng/mL cut-off to 75 ng/mL brought 'optimal' results and may be recommended for population screening in the Netherlands (van Rossum et al. 2009). This study also concluded that where colonoscopy capacity is insufficient, a cut-off up to 200 ng/mL would result in minimal false negatives for cancer although more for advanced adenoma. Policy makers are faced with an arbitrary decision based on the balance between missed cancers/advanced adenomas and the cost of colonoscopy

4.4.3.2 Number of stool specimens

Several studies have now examined the influence of the number of samples used for testing on clinical sensitivity and specificity. Allison takes any positive result from 3 stool samples measured using FlexSure OBT as an indication for referral and shows higher sensitivity for cancer than studies using

single stool samples (Allison et al. 2007). Unsurprisingly other studies show agreement with that conclusion (St John et al. 1993; Allison et al. 1996; Knaani & Samuel 1997; Nakama et al. 1999; Greenberg et al. 2000; Nakama, Zhang & Fattah 2000; Rozen, Wong et al. 2003). Nakama et al. using Monohaem, showed sensitivities of 89% for cancer with 3 stools compared with 56% for a single stool (Nakama et al. 1999).

Using Hem-SP, Morikawa showed low sensitivity for cancer using a single-day sample (Morikawa et al. 2005). Rozen et al. (2006) used 3 stools for the OC-Sensor which contrasts with 2-day samples used in Japan (Nakama, Zhang & Fattah 2000) and 1-day biennial testing performed in Italy (Castiglione et al. 2002). The relative insensitivity in the Italian study to lesions in the proximal bowel (16.3 vs 30.7%) raises further doubts about the use of a single-day sample. In a study using OC-Sensor in an at-risk population, Levi et al. (2007) took numeric measurements from three samples and used the highest concentration of the three as the discriminating factor. Recent studies have taken the average concentration from 2 stool measurements as the discriminating parameter, an approach that reduces the positivity rate.

The use of different cut-off limits and different numbers of stool samples illustrates how programme algorithms can manipulate clinical sensitivities and specificities for the lesions of interest. Chen describes the use of a cost-effectiveness model as a method of determining the optimal cut-off concentration for an iFOBT (Chen et al. 2007). In the study by Levi et al. (2007) using an iFOBT OC-Micro, a scatter plot of 2 consecutive samples showed that of those with cancer or adenomas, 21 of 91 had elevated or markedly elevated faecal blood in one sample but were normal in the other. This is further evidence of intermittent or variable bleeding, sample heterogeneity or poor sample technique that will reduce clinical sensitivity. Imperiale (2007) commenting on the paper by Levi in his editorial in *Annals of Internal Medicine* (Levi et al. 2007), speculated that concentration-related clinical sensitivity and specificity could be used to determine post-test risk. If risk was related to subject age or sex, this would provide more sophisticated criteria for colonoscopy referral than is currently used.

Guittet et al. (2009b), using a cut-off concentration of 20 ng/mL, reviewed the relative effectiveness of using one sample, one positive from two samples, two positives from two samples or a mean positive from two samples all measured using the Magstream iFOBT. The study concluded that for any sensitivity the mean of two results provided the highest specificity, and at any positivity it provided the highest sensitivity and specificity. It also concluded that one positive from a single specimen was better than one from two specimens and the cut-off should be adjusted to provide an acceptable positivity rate.

A recent paper by Grazzini et al. (2009) looks at the clinical outcome of biennial population screening in 20 596 residents of Northern and Central Italy aged 50–69 years. The study uses OC-Sensor and compares outcomes from strategies using different cut-off limits (80, 100 and 120 ng/mL), one or two samples and referral criteria based on either one positive or two positive results. No strategy is singled out as preferable, although some show limited benefit. Generally, those strategies resulting in more colonoscopy referrals increase the detection rate, particularly for adenomas, decrease the positive predictive value and cost more. At the annual Digestive Diseases Week conference in 2010 van Roon et al. (2010) illustrated the relationship between positivity rate, detection rate, cut-off limits, the number of samples measured and the use of different algorithms for combining the results. For positivity rates between 4% and 9% the user can obtain similar clinical outcomes by changing the cut-off with either one or two samples. The dilemma for a population-screening programme is where to draw the line between detection rates, cost and the inconvenience and morbidity associated with colonoscopy. The study showed no significant reduction in uptake for the two-sample strategy, but it did require the samples to be stored in a refrigerator. The choice is likely to be influenced greatly by both financial and logistical considerations.

Table 4.5: Comparison of clinical performance at different cut-off concentrations

Study		Nakama, Zhang & Fattah (2000) Japan	Castiglione et al. (2000) Italy (OC-Hemodia)	Castiglione et al. (2002) Italy (Latex agglutination)	Launoy & Berchi (2005) France	Li et al. (2007) Taiwan	Vilkin et al. (2005) Rozen et al. (2006) Israel	Sieg et al. (1999) Germany
	Faecal Hb cut-off (ng/mL)							
Test Positivity (%)	20	-	-	-	5.8	-	-	-
	50	6.5	-	-	3.1	-	-	-
	75	-	-	-	2.0	-	-	-
	100	-	3.5	4.2	-	5.5	-	-
	150	4.1	2.5	3.0	-	-	-	-
	200		2.0	2.3	-	-	-	-
	300	3.3	-	-	-	-	-	-
Test Sensitivity (%)	20	-	-		85.0	-	-	-
	50	89	-		68.0-83.0	81.5	79.4	-
	75	-	-		61.0-81.0	-	76.5	-
	100	-	84.0		-	81.5	76.5	-
	150	81	78.9		-	69.2	70.6	87
	200	-	73.4		-	64.6	64.7	83
	300	56	-		-	-	-	78
Test Specificity (%)	20	-	-		94.0		-	-
	50	94	-		97.0		89.7	-
	75	-	-		98.0		93.3	-
	100	-	97.2		-		95.3	-
	150	96	97.2		-		95.9	-
	200	-	97.2		-		96.3	-
	300	97	-		-		-	-
PPV for CRC (%)	20	-	-	-	6.0		-	-
	50	8.6	-	-	9.0		36.0	-
	75	-	-	-	13.0		45.6	-
	100	-	8.8	9.0	-		54.2	-
	150	12.6	11.5	11.6	-		54.5	-
	200	-	13.9	13.4	-		56.4	-
	300	10.8	-	-	-		-	-

4.4.3.3 Sequential testing

Two consecutive diagnostic accuracy studies conducted in Scotland as part of the UK pilot screening study investigated whether testing individuals with positive gFOBT tests using an iFOBT could be more effective in selecting those who should receive colonoscopy (Fraser et al. 2006; Fraser et al. 2007) In both studies the two-tier approach gave very high sensitivities of 95–96% with a negative carrying a less than 1% chance of invasive cancer. The odds ratio for iFOBT positive subjects of having cancer was 7.75 (95% CI 1.84–31.4).

A Chinese study (Li et al. 2006) of 324 subjects who had colonoscopy (mean age 53.5±15.3) showed that an iFOBT following a positive gFOBT had a better specificity for colon cancer detection than gFOBT (94.2% vs. 75.5%), and with similar sensitivity (93.8% and 95.9% vs. 95.9%, p>0.05).

In a multicentre comparison using different FOBT tests on 554 patients referred for colonoscopy (mean age 59.8±11.7), a combination test with a highly sensitive gFOBT (Hemoccult SENSA) and an iFOBT (FlexSure-FS or Hemeselect-HS, *Beckman Coulter Inc. Fullerton, CA, USA*) showed slightly reduced sensitivity but significantly fewer false-positive tests than any single test (Greenberg et al. 2000). The specificity of SENSA/FS (95.7%, p=0.03) and SENSA/HS (95.2%, p=0.07) for the detection of colorectal cancer were each greater than that of any individual test.

4.4.3.4 Participation rate and choice of test

Factors that influence participation rate (uptake) are addressed in Chapter 2 (Sect. 2.4, 2.5.1.1 and 2.5.1.2). Whilst many studies have reported the effect on compliance of different test devices and sampling permutations, some of these are contradictory and many reflect local circumstances. Whilst the analytical methodology, gFOBT vs. iFOBT, will not directly influence compliance, the influence of test methodology on the method of sampling, the number of samples required, a requirement for dietary restriction and the improved clinical outcome will all have a bearing on uptake. The magnitude of the influence will depend on local circumstances. Well-conducted randomised trials have clearly demonstrated that better compliance can be achieved using current iFOBTs than with gFOBTs, but the major influencing factor(s) remain a matter of speculation. In his recent paper Grazzini makes the important observation that, in a biennial screening programme looking for a slow growing adenoma, greater compliance over the long term might be more important than a higher detection rate on a single screen (Grazzini et al. 2009).

4.4.4 Recommendations

Screening algorithm:

- **Sample and test numbers**

  Few studies have examined the number of stool specimens necessary to optimise the diagnostic performance of FOBT. Consideration should be given to using more than one specimen together with criteria for assigning positivity which together provide a referral rate that is clinically, logistically and financially appropriate to the screening programme. The clinical sensitivity and specificity of testing can be modified depending on how the test data are used. Guaiac-based tests typically use 3 stools, but an algorithm using additional tests can be used to adjust clinical sensitivity and specificity (Sect. 4.4.3.2, 4.4.3.1) **(III - C).**[Rec 4.5]

- **Determining test positivity**

  The choice of a cut-off concentration to be used in an immunochemical test to discriminate between a positive and negative result will depend on the test device chosen, the number of samples used and the algorithm adopted to integrate the individual test results. Whilst an increasing number of studies are reporting the experience of different algorithms, local conditions, including the effect on sample stability of transport conditions, preclude a simple prescribed algorithm at this time. Adoption of a test device and the selection of a cut-off concentration should follow a local pilot study to ensure that the chosen test, test algorithm and transport arrangements work together to provide a positivity rate that is clinically, logistically and financially acceptable (Sect. 4.4.3.1, 4.4.3.2) **(VI - A).**[Rec 4.6]

Maximisation of uptake - Influencing factors associated with the test kit

The choice of the test kit must be influenced by factors that enhance accessibility and uptake (see below and Sect. 4.2.3 and 4.2.4; see also Ch. 2, Rec. 2.14, Sect. 2.5.1.1) **(II - A):**[Rec 4.14]

- **Dietary restrictions**

  In order to enhance participation in screening, test kits should not require dietary restrictions (Ch. 2, Rec. 2.17, Sect. 2.5.1.1; 4.3.2.1 and 4.3.2.3) **(II - A).**

- **Kit design**

  The design of a test kit should make it acceptable to the target population (see Ch. 2, Rec. 2.14, Sect. 2.5.1.1, 4.2.3 and 4.2.4) **(II - A).**

- **Simple and clear instructions**

  A clear and simple instruction sheet should be provided with the test kit (Ch. 2, Rec. 2.16, Sect. 2.5.1.1; Sect. 4.2.3 and 4.2.4) **(V - A).**

4.5 Conclusions

Although it is difficult to draw simple conclusions from the variety of different tests and study settings, we can conclude that iFOBT, in comparison with gFOBT:

- Has no need for dietary restriction;
- Has a major problem with sample instability, and collected samples should *preferably* be kept cool and returned immediately for analysis;
- Provides a greater participation rate than gFOBT;
- Needs a smaller number of stool samples than gFOBT;
- Shows a greater relative sensitivity than gFOBT;
- Shows a greater sensitivity for the detection of advanced adenomas than gFOBT;
- Has a higher recall rate than most gFOBTs;
- Has a PPV similar to those obtained with most gFOBTs;
- Provides an opportunity of using a numeric threshold to find the most appropriate balance between sensitivity and specificity (i.e. between detection rate and positivity to the test); and
- Allows the opportunity to balance recall and detection rates providing each country with the tools to implement a colorectal cancer screening programme that will meet local healthcare expectations within available resources.

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Quality assurance in endoscopy in colorectal cancer screening and diagnosis

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Guiding principles for a colorectal screening endoscopy service

1. People undergoing endoscopy, whether for primary screening, for assessment of abnormalities detected in screening, for assessment of symptoms, or for surveillance, should have as good an experience as possible, permitting them to encourage screening, assessment and surveillance of appropriate quality to their friends, family and colleagues.
2. The provision of the service must take into account the perspectives of endoscopists and public health to ensure that the experience is high-quality, safe, efficient as well as person-oriented.
3. Provision of screening should take account of historic development within different local and cultural contexts.
4. The provision of primary screening endoscopy is less complex than follow-up endoscopy (of screen-positives) primarily because of the lower frequency of high-risk lesions in primary screening endoscopy.
5. The introduction of screening must not compromise endoscopy services for symptomatic patients.
6. Screening and symptomatic (diagnostic) services should achieve the same minimum levels of quality and safety.
7. Wherever possible the quality assurance required for screening should have an enhancing effect on the quality of endoscopy performed for symptomatic patients and for other reasons.
8. Screening and diagnosis of appropriate quality requires a multidisciplinary approach to diagnosis and management of lesions detected during endoscopy.

Recommendations[1]

Planning and location of endoscopy services

5.1 When implementing high-volume primary screening endoscopy consideration should be given to locating services in convenient locations for participants **(VI - B).**[Sect 5.1.4]

5.2 Screening services should be provided in proximity to clinical services **(VI - C).**[Sect 5.1.2]

5.3 The planning of screening services should take account of the frequency of high-risk lesions in the screening population and the competencies and equipment required to remove these lesions safely and completely **(III - B).**[Sect 5.1.2]

5.4 The referral rate for excision of high-risk lesions should be audited **(VI - B).**[Sect 5.1.2]

5.5 The clinical lead of the screening service should be satisfied that staff have the necessary competencies, that the equipment is sufficient to perform the necessary procedures and that adverse events can be dealt with effectively **(VI - A).**[Sect 5.1.2]

5.6 Equipment and training needs should be assessed before screening begins **(VI - A).**[Sect 5.1.2]

5.7 The impact of demand from screening on waiting times for symptomatic patients should be assessed to ensure that there is sufficient planned new capacity to avoid inappropriately long waiting times for symptomatic patients **(VI - A).**[Sect 5.1.5]

5.8 Any screening service, regardless of setting, should make an assessment of the risk of adverse events and develop the capability to respond to emergencies **(VI - A).**[Sect 5.1.8]

Infrastructure and equipment

5.9 The infrastructure of an endoscopy unit must include facilities for pre-procedure assessment and recovery, and be designed to allow good patient flow in order to maximise efficiency **(VI - B).**[Sect 5.1.6]

5.10 The environment must have sufficient privacy to maintain the dignity of patients **(VI - B).**[Sect 5.1.6; 5.3.6]

5.11 The volume of equipment should match the demand put upon it to maximise efficiency and avoid patient delays **(VI - B).**[Sect 5.4.3]

5.12 Video endoscopes with the facility for focal application of dye are required for the detection and assessment of high-risk colorectal lesions **(III – B).**[Sect 5.4.3]

5.13 There should be an adequate supply of accessories suited to the endoscopic interventions undertaken within the unit **(VI - B).**[Sect 5.4.3]

5.14 National policies on the use of re-usable accessories should be adopted **(VI - B).**[Sect 5.4.3]

5.15 There should be properly maintained resuscitation equipment in the endoscopy room and recovery area **(VI - B).**[Sect 5.4.3; 5.5.2]

5.16 Maintenance of equipment should be undertaken by competent staff **(V - A).**[Sect 5.4.3]

5.17 There should be regular review of the functioning and cleansing of all endoscopes, according to national or pan-European guidelines containing accepted, published recommendations and standards **(VI - B).**[Sect 5.4.3]

5.18 The results of the review should be available at all times in the endoscopic unit **(VI - A).**[Sect 5.4.3]

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[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.

Preparation of the patient and aftercare

5.19 Follow-up colonoscopy after positive screening (any modality) should be scheduled within 31 days of referral (acceptable >90%, desirable >95%). (See also Ch. 3, Rec. 3.16) **(VI - B).**[Sect 5.3.5; 3.3.4]

5.20 Each endoscopy service must have a policy for pre-assessment that includes a minimum data set relevant to the procedure. There should be documentation and processes in place to support and monitor the policy (see also Ch. 10, Rec. 10.28) **(III - B).**[Sect 5.3.2; 10.4.3]

5.21 Bowel preparation for screening flexible sigmoidoscopy should involve a single procedure, either enema or oral preparation **(II)**. A single self-administered enema seems to be the preferred option, but cultural factors should be taken into account, and patient preferences should be assessed (see also Ch. 2, Rec. 2.20) **(II - B).**[Sect. 5.3.3]

5.22 To date no single bowel preparation for colonoscopy has emerged as consistently superior over another **(I)** although sodium phosphate may be better tolerated and it has been shown that better results are obtained when the bowel preparation is administered in two steps (the evening before and on the morning of the procedure) **(II)**. It is therefore recommended that there should be colonic cleansing protocols in place and the effectiveness of these should be monitored continuously **(VI - A).**[Sect 5.3.3]

5.23 Several providers of bowel preparation close to the target population should be available when a patient is required to reach health or community facilities to obtain the preparation. Clear and simple instruction sheets should be provided with the preparation. For flexible sigmoidoscopy screening, organisational options should include the possibility of having the enema administered at the endoscopy unit. (See Ch. 2, Rec. 2.21) **(VI - B).**[Sect 5.3.3]

5.24 Cleansing solution containing mannitol or other malabsorbed carbohydrates (e.g. sorbitol) must be avoided in the preparation of the colon because of the risk of explosion with electrocautery **(III - A).**[Sect 5.4.4]

5.25 The endoscopy service must have policies that guide the consent process, including a policy on withdrawal of consent before or during the endoscopic procedure (see also Ch. 10, Rec. 10.29) **(VI - B).**[Sect 5.3.1; 10.4.3]

5.26 Before leaving the endoscopy unit, patients should be given a verbal explanation of the results of their procedure; they should also be given written information to support the verbal explanation (see also Ch. 10, Rec. 10.30) **(VI - A).**[Sect 5.5.3; 10.4.3]

5.27 The outcome of screening examinations should be communicated to the primary care doctor (or equivalent) so that it becomes part of the core patient record (see also Ch. 10, Rec. 10.31) **(VI - B).**[Sect 5.5.5; 10.4.3]

5.28 There should be pre-defined clinical pathways for individuals found to require further intervention for cancer, including pT1 cancers, incompletely-removed lesions and difficult-to-remove lesions; as well as for incomplete examinations; and for individuals requiring further surveillance. (See Sect. 5.4.4 and Ch. 8, Sect. 8.3.6 and Ch. 9). In addition, failsafe mechanisms must be in place to ensure that these interventions occur **(I - B).**[Sect 5.5.5]

Endoscopic technique

5.29 There should be local policies and processes in place to optimise sedation and patient support in order to maximise tolerance and minimise risk of complications **(I - B).**[Sect 5.4.4]

5.30 Because there is no clear benefit from a particular approach **(I)**, and for practical reasons it is recommended that policies on the use of sedation should be adopted according to protocols based on national or pan-European guidelines, and must take into account historical context, the impact on the patient experience and costs **(I - B).**[Sect 5.1.3]

5.31 Carbon dioxide insufflation is recommended for colonic endoscopic procedures **(I - A).**[Sect 5.4.4]

5.32 Carbon dioxide insufflation should be avoided in patients with COPD, known $C0_2$ retention or reduced pulmonary function **(VI - A).**[Sect 5.4.4]

5.33 The utilisation of magnetic endoscope imaging (MEI) technology may be considered for patients requiring colonoscopy, particularly when little or no sedation is used **(II - B).**[Sect 5.4.2]

5.34 The use of variable stiffness colonoscopes is recommended for screening colonoscopy **(I - B).**[Sect 5.4.2]

5.35 To achieve a high-quality colonoscopic examination it is necessary to perform a complete intubation of the colon and to carefully inspect the mucosa during withdrawal **(I - A).**[Sect 5.4.5.1]

5.36 If the endoscopist doubts whether he/she is able to remove a high-risk lesion, the lesion must be appropriately documented and, if necessary, its position marked with a tattoo. The patient should then be referred elsewhere to have the lesion removed endoscopically or surgically **(VI - A).**[Sect 5.1.2]

Performance of endoscopists and quality improvement

5.37 It is recommended that the annual number of procedures performed by an endoscopist is recorded to ensure that the sample size for key performance indicators is sufficient **(III - A).**[Sect 5.4.5.1]

5.38 Each endoscopist participating in a colorectal cancer screening programme should undertake to perform at least 300 procedures per year to ensure there is a sufficient sample size to assess competence. A higher volume of procedures is desirable **(III - B).**[Sect 5.4.5.1]

5.39 Services should be planned such that individual endoscopists achieve a desirable volume of procedures (>300/year) **(III - B).**[Sect 5.1.2; 5.4.5.1]

5.40 There should be auditable photo documentation of completion, preferably a panoramic image of the ileo-caecal valve and caecum, or a video clip with a respective snapshot **(VI - A).** [Sect 5.4.5.1]

5.41 The unadjusted caecal intubation rate should be a prime indicator of quality of colonoscopy. The acceptable standard is >90%; >95% is desirable (see also Ch.3, rec. 3.11) **(III - A).**[Sect 5.4.5.1; 3.3.2; 3.3.3]

5.42 There should be documentation and review of reasons for failed completion **(III - B).**[Sect 5.4.5.1]

5.43 Screening programmes should adopt a minimum set of outcomes to determine the quality of inspection of the colonic mucosa **(VI - A).**[Sect 5.4.5.1]

5.44 It is recommended that unplanned hospital admission on the same day as the endoscopic procedure be a key adverse outcome. Reasons for admission should be documented **(III - A).**[Sect 5.4.5.2]

5.45 Endoscopic services must have processes in place to identify and record adverse outcomes occurring after the patient leaves the endoscopy unit **(VI - B).**[Sect 5.4.5.2]

5.46 All screening programmes should have processes in place for monitoring, auditing, reviewing and acting upon key auditable outcomes and quality indicators **(III - A).**[Sect 5.2]

5.47 All endoscopists and centres performing endoscopy should participate in a continuous quality improvement programme, including tracking of quality and safety indicators for individual endoscopists. This should include action plans, for both endoscopists and staff, for addressing suboptimal performance **(VI - A).**[Sect 5.1.7]

Policies and processes

5.48 Decontamination policies and procedures should be compliant with national or pan-European guidelines containing accepted, published recommendations and standards. The policies should be available in the endoscopy department and updated regularly **(VI - A).**[Sect 5.4.1]

5.49 Decontamination processes should be audited against defined indicators **(VI - A).**[Sect 5.4.1]

5.50 The endoscopy unit should create and regularly review clinical guidelines, policies and processes, taking into account relevant national or pan-European guidelines **(VI - B).**[Sect 5.6]

5.1 Effect of screening modality on the provision of endoscopic services for screening

5.1.1 Clinical setting

Colonoscopy is the recommended test for follow-up investigation for individuals who have tested positive with other CRC screening tools (FOBT, Flexible sigmoidoscopy (FS), and also in experimental studies assessing potential screening tools, e.g. DNA faecal markers and CT colonography). High-quality endoscopy (colonoscopy and flexible sigmoidoscopy (FS)) is also used in some Member States as a screening tool for colorectal cancer. The frequency of endoscopy when used as a primary screening tool will be much higher than endoscopy used as a follow-up investigation of another screening test. Thus the phrase 'high-volume screening endoscopy' will be used to refer to endoscopy used as a primary screening tool and 'low-volume screening endoscopy' will be used to refer to follow-up endoscopy. However, it is recognised that if the test positivity rate in a FOBT screening programme is high a large volume of colonoscopies will be generated. The key practical difference of these high- and low-volume populations requiring endoscopy in a screening context is the probability of identifying and nature of high-risk lesions (see below).

The setting in which the endoscopic procedure will be performed will be determined by:

- quality and safety determinants;
- the need for sedation;
- patient-oriented factors;
- possible impact on symptomatic services;
- infrastructure and efficiency;
- staff competencies and equipment; and
- availability of support services.

5.1.2 Quality and safety

Diagnostic procedures, both flexible sigmoidoscopy and colonoscopy, can be performed safely in diverse clinical settings. When providing services for a colorectal cancer screening programme, the key consideration is what facilities and level of competence are required to remove high-risk lesions. Removing large high-risk lesions safely requires a considerable level of competence and appropriate support close at hand when a complication occurs. For example, it would be inappropriate to remove large or difficult high-risk lesions if the colonoscopist is only rarely faced with such a lesion (as in high-volume, low-risk population screening) or if the procedure is being done in a remote setting.

The setting in which screening (or follow-up colonoscopy) is established will be determined by the ability to perform high-quality endoscopy (defined later) and by the probability of finding a high-risk lesion that is difficult to remove completely and safely. If there is concern about removing the lesion it is entirely appropriate for the colonoscopist to leave it (and perhaps tattoo it) and refer the patient on for either endoscopic, or in some instances, surgical excision.

The colonoscopist needs to judge whether he/she is competent to remove a lesion and whether it is safe to remove the lesion in this setting. On the basis of good practice it is recommended that if there is doubt, the lesion must be appropriately documented and the patient referred elsewhere to have the lesion removed **(VI - A).**[Rec 5.36]

Thus, when considering where endoscopic screening services are to be located, the commissioner should be aware of how often a patient may need to be referred elsewhere. If it is expected that referral somewhere else will be a frequent occurrence (perhaps >1% of patients) then it is better to consider locating the service elsewhere, i.e. where the competence of the available endoscopists would permit less referral.

To help in the planning of location of endoscopic services for screening, the following five levels of competency are proposed.

- **Level 0:** The operator does not remove any lesions, referring on all patients with any detected lesions. The operator will be able to biopsy lesions, and pathological material may inform the decision to refer. Basic level of competency for diagnostic FS but not recommended for screening FS.
- **Level 1:** Removing lesions <10 mm in diameter at FS. Rationale: larger lesions will indicate a need for colonoscopy and can be removed when the colonoscopy is performed. Tissue is required from smaller lesions to decide whether colonoscopy is necessary. Thus any person performing FS screening should have this level of competency.
- **Level 2:** Removing polypoid and sessile lesions <25 mm providing there is good access. All colonoscopists should have this level of competency.
- **Level 3:** Removing smaller flat lesions (<20 mm) that are suitable for endoscopic therapy, larger sessile and polypoid lesions, and smaller lesions with more difficult access. Some flat lesions <20 mm with poor access might be unsuitable for this level. Any person doing colonoscopy for positive FOBT in a screening programme should have this level of competency.
- **Level 4:** Removing large flat lesions or other challenging polypoid lesions that might also be treated with surgery. This is the type of lesion that would not be removed at the first colonoscopy because of time constraints, if applicable, or because the surgical option needs to be discussed with the patient. If the patient chooses to have endoscopic therapy, then he/she should be referred to a level 4 competent endoscopist. This level of competency would be expected of only a small number of regionally based colonoscopists.

In the context of colorectal screening and diagnosis in Europe, units only providing Level 0 competencies are not recommended, because unnecessary endoscopic procedures would be required to remove small lesions which could have been removed during the initial FS. Furthermore, unnecessary colonoscopies may be encouraged in the absence of histopathological evaluation of small lesions left in place during the initial FS.

The level of competency to perform high-quality endoscopy and to remove high-risk lesions is also dependent on the competency of the support team and the available equipment: a highly competent endoscopist requires equally competent support staff and the right equipment and supplies to perform the procedure and deal with any problems that might arise (such as clips for uncontrolled bleeding).

It is recognised that the methodology does not currently exist to reliably recognise who has achieved the proposed levels of competence. Thus, until a competency–based assessment process is available the clinical lead of the service should be satisfied that:

- the professionals have the necessary competence;
- the unit has the necessary equipment; and
- in the event of a serious adverse event, it will be possible to manage the patient locally or transfer the patient safely to another institution with the expertise and facilities to care for the patient.

A review of capabilities may identify shortcomings that can be addressed with further training or investment (cross reference to Chapter 6). This training and investment should occur before screening begins.

It is recommended that:

- Screening services be provided in proximity to clinical services **(VI - C).**[Rec 5.2]
- The planning of screening services should take account of the frequency of high risk lesions in the screening population and the competencies and equipment required to remove these lesions safely and expertly **(III - B).**[Rec 5.3]
- Services should be planned such that individual endoscopists achieve a desirable volume of procedures to maintain high competence (>300/year, see section 5.4.5.1) **(III - B).**[Rec 5.39]
- The clinical lead of the screening service should be satisfied that staff have the necessary competencies, that the equipment is sufficient to perform the screening procedures, and that serious adverse events can be dealt with effectively **(VI - A).**[Rec 5.5]
- A review of equipment and training needs should be performed before screening begins **(VI - A).**[Rec 5.6]
- Referral rate for excision of high-risk lesions is an auditable outcome **(VI - B).**[Rec 5.4]

5.1.3 The need for sedation

The use of sedation for lower gastrointestinal endoscopic procedures varies between European countries. Three main patterns are readily discernible:

- infrequent use of sedation;
- frequent use of conscious sedation with opiates and benzodiazepines; and
- almost exclusive use of deep sedation with propofol or general anaesthesia.

This variation suggests there is no perfect approach, and emphasises the need to take into account historic cultural differences when implementing screening endoscopy. A review of the benefits and risks of sedation showed no clear advantage for a particular approach: conscious sedation provides a high level of physician and patient satisfaction and a low risk of serious adverse events with all currently available agents (McQuaid & Laine 2008).

The risk of an adverse cardio-respiratory event is lower if the patient does not have sedation (Eckardt et al. 1999; Rex, Imperiale & Portish 1999; Lieberman et al. 2000; Rex 2000b). Thus, there is less need for monitoring equipment and recovery facilities if sedation is not used. Therefore sedationless endoscopy can occur in more remote settings, and it requires lower set-up costs. However, if no sedation is offered, the patient must accept a higher chance of unacceptable discomfort and the endoscopist a lower chance of completing the procedure because of patient discomfort. These downsides might affect the uptake and impact of screening: potential screenees are worried about comfort, and incomplete procedures may miss important pathology.

In most circumstances it is possible for the endoscopist to administer conscious sedation, but in some European countries propofol administration requires an attending anaesthetist. Thus the costs of providing sedation, particularly if an anaesthetist is required to administer propofol, will vary between countries. The relative quality and safety of different approaches are reviewed later in this chapter.

Because there is no clear benefit from a particular approach **(I)**, and for practical reasons it is recommended that policies on the use of sedation must be adopted according to protocols based on na-

tional or pan-European guidelines, and take into account historical context, the impact on the patient experience and costs **(I - B).**[Rec 5.30]

5.1.4 Patient considerations

Patients generally prefer services that are close to home and easily accessible. Thus high-volume screening endoscopy is probably best situated closer to the population to be screened. In contrast, level 3 and 4 expertise for removing high-risk lesions is likely to be provided at district and regional levels respectively. The priority here is the facility and expertise, not proximity.

When implementing high-volume screening endoscopy consideration should be given to locating services in convenient locations for patients to maximise engagement in screening **(VI - B).**[Rec 5.1]

5.1.5 Possible destabilising effect on symptomatic services

Unplanned introduction of screening endoscopy (at whatever level) creates additional demand and may lead to destabilisation of the symptomatic service. Thus, if endoscopy for screening is introduced alongside symptomatic services, care must be taken to ensue there is sufficient new capacity.

An assessment of the impact of demand from screening on waiting times for symptomatic patients should be made to ensure that there is sufficient planned new capacity such that screening does not lengthen waits for symptomatic patients **(VI - A).**[Rec 5.7]

5.1.6 Infrastructure and efficiency

The infrastructure requirements for high-volume screening endoscopy need to cater to large numbers of presumptively healthy people. High-volume screening endoscopy requires efficient booking, assessment and recovery processes to function effectively without compromising the patient experience. Thus, it may be advantageous for high-volume screening activities to be separated from routine clinical endoscopy and follow-up endoscopy of screen-positives.

It is self-evident that the infrastructure must be adequate. It must include facilities for pre-procedure assessment and recovery, and must also be designed to allow good patient flow in order to maximise efficiency **(VI - B).**[Rec 5.9] In addition, a suitable environment will maintain the privacy and dignity of patients **(VI - B).**[Rec 5.10]

5.1.7 Endoscopist and support staff competencies

Endoscopists and supporting staff providing endoscopy screening must be competent to deliver high quality FS or colonoscopy in order to achieve high patient satisfaction and all the required performance standards relating to quality and safety (see Sect. 5.4.5 and Ch. 6).

It is a fundamental requirement of quality assurance that all endoscopists and centres performing endoscopy should participate in a continuous quality improvement programme, including individual

tracking of quality and safety indicators. This should include management plans, for both endoscopists and staff, for addressing suboptimal quality **(VI - A).**[Rec 5.47]

5.1.8 Support services

Only rarely will a person undergoing a primary screening procedure require admission to hospital for further care. Thus it is not necessary to have medical support facilities close at hand. However, services performing endoscopy in more remote settings must have robust guidelines and processes in place to enable patients to be resuscitated effectively and be transferred rapidly and safely to a hospital where surgical services are available. On this basis it is recommended that any screening service, regardless of setting, should make an assessment of risks and develop the ability to respond to emergencies **(VI - A).**[Rec 5.8]

5.1.9 Conclusion

While there are no absolutes, a case can be made for delivering high-volume screening endoscopy outside traditional hospital settings to improve the patient experience and to reduce healthcare and societal costs. In contrast, risk assessments will indicate that colonoscopy following a positive FOBT or a positive FS is a more complex procedure that is associated with higher risks and should, therefore, be performed in acute hospital settings.

5.2 Audit and quality improvement

This section proposes that endoscopy services monitor key outcomes to ensure that a high-quality and safe service is being provided and to identify areas in need of improvement. Two terms are used for such outcomes: auditable outcomes and quality indicators. An auditable outcome refers to an outcome that should be measured, but for which there is not an evidence base to recommend a standard, such as the comfort of the procedure. A quality indicator is an outcome for which there is a sufficient evidence base to recommend a standard, such as caecal intubation rate.

It is expected that some auditable outcomes will become quality indicators as the evidence base improves, and that the standards of quality indicators will rise as standards improve.

On the basis of this, it is recommended that all screening programmes should have processes in place for monitoring, auditing, reviewing and acting upon key auditable outcomes and quality indicators in the following areas (see also Annex 5.1 and 5.2 and Chapter 3) **(III - A):**[Rec 5.46]

- Quality;
- Safety; and
- Patient feedback

5.3 Before the procedure

Beginning the patient journey

Section 5.3 and subsequent sections follow the patient journey from invitation to discharge from the endoscopy service.

5.3.1 Patient information and consent

Information in this context includes information related to the endoscopic procedure and should include why the procedure is being done, what it involves, preparation for the procedure, and the risks. The patient should be told what he/she might expect to happen after the procedure (including contact details in case of emergency) and the plan of aftercare. The patient should be informed about the options for sedation and how this might affect their perception of the procedure and the associated restrictions on travelling home. There are subtle differences in the approach to consent between a primary screening test and one done following a positive screening test such as FS and FOBT, explained in more detail in Chapter 10.

The consent process involves an explanation of the procedure, the potential benefits, the risks and possible consequences. Consent for endoscopic procedures begins with a recommendation to have the examination, and ends when the procedure is complete. The individual must have the opportunity to withdraw consent at any stage during this process.

It is good clinical practice for an endoscopy service to have policies that guide the consent process, including a policy on withdrawal of consent immediately before or during the endoscopic procedure. **(VI - B).**[Rec 5.25]

The key elements of patient information for endoscopy include:

- considerations related to current medications including anticoagulants and antiplatelet agents;
- considerations related to previous medical illnesses;
- the benefits of the test;
- how to prepare for the procedure (including bowel cleansing);
- the nature of the procedure and what it involves;
- possible adverse events including discomfort and complications;
- what support the patient may need after the procedure, particularly if they are sedated; and
- the importance of not driving or making important decisions after sedation.

Auditable outcomes: patient feedback on information and consent processes. These assessments should ideally be both qualitative and quantitative and make an assessment of the patient experience judged by the gap between the expectation and actual experience (see Chapter 3). Withdrawal of consent should be registered as an adverse clinical incident.

5.3.2 Pre-assessment

The purpose of pre-assessment is to identify factors that might influence the outcome of the procedure, such as anticoagulation and general health status. Pre-assessment also provides an excellent opportunity to ensure the patient understands the bowel cleansing process and to answer any questions the patient may have.

The nature of the pre-assessment will depend on whether there has been prior contact with an endoscopy service health professional. If there has been no prior contact with the service, it is advised to pre-assess the patient several days before the procedure, at least before starting bowel cleansing. This will enable the procedure to be rescheduled if there are concerns about safety, or for medication such as warfarin to be withdrawn in sufficient time to allow its anticoagulant effect to wear off.

Available evidence (Bini et al. 2003; Hui et al. 2004; Bernstein et al. 2005; Harris et al. 2007a; Lee et al. 2008; Tsai et al. 2008) suggests that the following patient-related variables should be identified and taken into account prior to FS or colonoscopy because they can be associated with more adverse events, longer duration, and incomplete examination: **(III)**

- Use of anticoagulants e.g. warfarin;
- Anatomy (female sex);
- Age of patient;
- Prior abdominal surgery;
- BMI;
- Diverticular disease;
- ASA PS (American Society of Anesthesiology classification of Patient Status)[2] and information that may influence type and level of sedation (for those procedures where sedation may be used); and
- Presence of risk factors for endocarditis

On the day of the procedure there should be a brief review of the previously collected information and measurement of basic cardio-respiratory function

It is recommended that each endoscopy service have a policy for pre-assessment that includes a minimum data set relevant to the procedure. There should be paperwork and processes in place to support the policy **(III - B).**[Rec 5.20]

Auditable outcomes: Recording and review of adverse clinical events related to inadequate pre-assessment (e.g. anticoagulants not stopped or risk factors for endocarditis not identified)

5.3.3 Colonic cleansing

Inspection of the colon requires careful preparation removing colonic contents to optimise the safety and quality of the procedure. Ideally there should be no residual stool or liquid in the lumen that could mask any suspicious area.

[2] The American Society of Anesthesiology classification of Patient Status (ASA PS) groups patients into 6 categories based on an assessment of their physical condition prior to an invasive procedure: (http://www.asahq.org/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System.aspx)

Flexible sigmoidoscopy

The ongoing European sigmoidoscopy trials adopted a bowel preparation based on a single enema, self-administered at home within two hours from the appointment, or, in one case, at the screening centre.

No studies were found assessing the effect of having the enema performed directly at the screening centre, although this represents an option that might enhance participation by reducing patient's concerns and enhancing engagement. Available evidence from one controlled trial did not indicate that using two enemas (the first the night before the test and the second two hours before the scheduled time for the exam) affects participation compared to using a single enema (Senore et al. 1996). Oral preparation was associated with a reduced participation in a large screening trial, compared to enema (Atkin et al. 2000). Adding oral preparation to the enema resulted in reduced participation (Bini et al. 2000).

No difference in the proportion of inadequate exams was observed when comparing a single enema regimen to a preparation using two enemas or to oral preparation.

Bowel preparation for screening sigmoidoscopy should involve a single procedure, either enema or oral preparation **(II)**. A single self-administered enema seems to be the preferred option, but cultural factors should be taken into account, and patient preferences should be assessed (see also Ch. 2, Rec. 2.20) **(II - B).**[Rec. 5.21]

Colonoscopy

Data on the impact of different preparation regimens in the context of population screening with colonoscopy are lacking. A recent systematic review concluded that no single bowel preparation emerged as consistently superior. Sodium phosphate was better tolerated (Belsey, Epstein & Heresbach 2007), but safety alerts on its use have recently been issued by the US FDA and Health Canada. The authors identified a general need for rigorous study design to enable unequivocal conclusions to be drawn on the safety and efficacy of bowel preparations.

Timing of administration of the recommended dose appears important, as it has been established that split dosing (the administration of at least a portion of the laxative on the morning of the examination) is superior to dosing all the preparation the day before the test, both for sodium-phosphate and polyethylene glycol (Aoun et al. 2005; Parra-Blanco et al. 2006; Rostom et al. 2006; Cohen 2010) **(II).**

A systematic review (Belsey, Epstein & Heresbach 2007) of different bowel cleansing regimens identified no significant differences other than improved patient tolerance of sodium picosulphate preparations. Furthermore, there are no preferred methods of assessing the effectiveness of bowel cleansing. Care must be taken however with some agents (i.e. phospho prep) in certain patient groups, especially the elderly and those with renal failure, due to potential renal side effects (WHO 2009) **(I)**.

See also Chapter 2 (Sect. 2.5.2.2, 2.5.2.3) for literature review about bowel preparation for FS and colonoscopy, and for organisational aspects.

To date no single bowel preparation for colonoscopy has emerged as consistently superior over another **(I)** although sodium phosphate may be better tolerated and it has been shown that better results are obtained when the bowel preparation is administered in two steps (the evening before and on the morning of the procedure) **(II)**. It is therefore recommended that there should be colonic cleansing protocols in place and the effectiveness of these should be monitored continuously (see also Ch. 2, Rec. 2.22) **(VI - A).**[Rec 5.22]

Auditable outcome: Quality of preparation, patient satisfaction with the bowel cleansing regimen.

Accessibility

Several providers of bowel preparation close to the target population should be available when a patient is required to reach health or community facilities to obtain the preparation. Clear and simple instruction sheets should be provided with the preparation. For sigmoidoscopy screening, organisational options include the possibility of having the enema administered at the endoscopy unit. (See Ch. 2, Rec. 2.21) **(VI - B).**[Rec 5.23]

5.3.4 Scheduling and choice

Booking processes must be robust to minimise late cancellations and failures to attend. To increase the chance of attendance an invitation for a primary screening test should be sent 2–3 weeks before the procedure is due, with an option for the patient to change the appointment if it is not convenient (see section 2.4.3.1).

Auditable outcome: Patient feedback on booking processes.

5.3.5 Timelines

A timely procedure is not critical in the context of primary screening but it is very important when endoscopy is performed following a previous positive screening test. A delayed procedure may not be critical biologically, but it can cause unnecessary anxiety for the screenee.

To ensure that patient anxiety is not unnecessarily increased, it is recommended that follow-up colonoscopy after positive screening be performed as soon as reasonably possible, but no later than within 31 days of referral (acceptable >90%, desirable >95%) (see also Ch. 3, Rec. 3.16, Sect 3.3.4) **(VI - B).**[Rec 5.19]

Auditable outcome: Time taken from positive screening test to secondary endoscopic examination. If further pathological information is required before the decision to perform a colonoscopy, then the maximum and the desirable targets of four and two weeks, respectively, should be timed from the receipt of the pathology report. The pathology report should be delivered to the screening programme within two weeks.

5.3.6 Environment

The environment should be conducive to a good experience and efficient processing. It should be physically comfortable, offer privacy and there should be facility to hold private conversations with screenees and their relatives. The reception and assessment areas should be separate from recovery facilities **(VI - B).**[Rec 5.10]

Auditable outcomes: patient feedback on environment and patient turn around times.

5.4 During the procedure

There is an increasing body of evidence demonstrating unacceptable miss rates of cancer following colonoscopy. Miss rates vary between endoscopists suggesting that care with the examination and technique play a key role in ensuring cancer is not missed.

Endoscopists must have a mix of technical, knowledge and judgement competencies to identify and successfully remove high-risk lesions. Ideally they will perform a complete examination quickly, safely and with minimal discomfort, leaving time to properly inspect the colon, and safely remove and retrieve lesions. They will identify all abnormal areas, characterise them and make a judgement of what to do. They will then, if it is appropriate to do so, safely remove and retrieve all neoplastic lesions

Providing such high-quality and safe endoscopy requires a team approach with appropriate equipment immediately to hand. The nursing support team must ensure the patient is comfortable and has stable observations to allow the endoscopist to devote his attention to the procedure. The nurses also provide important technical support ensuring endoscopy equipment is serviceable and that all the necessary accessories are readily available. Finally they play an important role supporting the endoscopist during therapeutic procedures. Both endoscopist and nurse should regularly reflect on their practice together with pathology and surgical teams in order to optimise patient outcomes.

High-quality and safe endoscopy also depends on adequate maintenance of equipment, and on an adequate supply of accessories for the range of procedures undertaken in the department. This should include equipment to manage complications of excision of high-risk lesions such as bleeding and in some instances, perforation. Endoscopy equipment is expensive and is subject to frequent and occasionally heavy use. It is essential that equipment be maintained by competent staff. Maintaining and repairing old endoscopic equipment is often more expensive than replacing it.

It is not appropriate for this chapter to provide a manual of how to perform colonoscopy and detect and remove high-risk lesions. However, there have been significant advances in decontamination processes, technique and technology in recent years. Because these advances might affect service provision and patient outcomes, it is considered important to review the evidence for their effectiveness.

Technological improvements have promised easier insertion of endoscopes and better visualisation of the mucosa. However, despite the potential of advances in endoscopic technology, they cannot be recommended for routine use until they have been demonstrated to be of benefit in clinical practice. The following sections provide an overview of the current state of these technologies and best practice for safe, high-quality endoscopy.

5.4.1 Cleansing and disinfection

Patients need to be reassured that decontamination processes are up to date and effective. Guidelines on cleaning and disinfection of endoscopes and endoscopic devices have been developed by the ESGE-ESGENA[3] (Beilenhoff et al. 2007; Beilenhoff et al. 2008).

[3] ESGE-ESGENA: European Society of Gastrointestinal Endoscopy - European Society of Gastroenterology and Endoscopy Nurses and Associates.

It is recommended that decontamination policies and procedures be compliant with national or pan-European guidelines based on accepted, published recommendations and standards and should be audited against defined indicators. The policies should be available in the endoscopy department and updated regularly **(VI - A).**[Rec 5.48, 5.49]

Auditable outcomes: Defined by national or European guidance.

5.4.2 Kit - technologies for improving insertion of the colonoscope

A variety of endoscope technologies may facilitate caecal intubation and improve patient tolerance. These include variable stiffness instruments, magnetic tracking devices and wire-guided techniques.

A recent meta-analysis (Othman et al. 2009) of variable stiffness colonoscopes identified seven randomised trials involving 1923 patients: four trials comparing adult variable stiffness colonoscopes with standard adult colonoscopes in adults, and three evaluating the paediatric variable stiffness colonoscope. The caecal intubation rate was higher with the use of variable stiffness colonoscopes. The variable stiffness colonoscope was associated with lower abdominal pain scores and decreased need for sedation during colonoscopy. Intubation times were unaffected by the variable stiffness colonoscope **(I).** The use of variable stiffness colonoscopes is recommended for screening colonoscopy **(I - B).**[Rec 5.34]

The present bibliographic search did not yield any relevant publications on improvement of completeness of colonoscopy through wire-guided techniques. This new technology has been investigated in endoscopic management of obstructive tumours (Ramadori, Lindhorst & Armbrust 2007).

Two RCTs of the magnetic endoscopic imaging (MEI) device showed improved performance of endoscopists, both with variable stiffness colonoscopy and with traditional colonoscopy, in terms of patient tolerance and caecal intubation rates, in particular when little or no sedation is used (Shah et al. 2000; Shah et al. 2002) **(II)**. The utilisation of magnetic endoscope imaging (MEI) technology may be considered for patients requiring colonoscopy, particularly when little or no sedation is used **(II - B).**[Rec 5.33]

5.4.3 Kit – techniques and technologies to enhance detection, characterisation and removal of high-risk lesions

Image enhancing techniques and technology promise to improve management of high-risk lesions in three ways.

1. First, they might improve the detection of lesions. This will only add value if the lesions detected are important biologically: identifying more biologically unimportant lesions will add workload and risk.
2. Second, they might better define the margins of the lesion to help the endoscopist ensure that it is completely excised.
3. Third, they might help characterise the nature of the lesion, helping the endoscopist decide whether to remove it. This third aspect is of critical importance because it might be more appropriate not to remove the lesion because of an increased risk of malignancy. Alternatively, if an endoscopist can safely leave lesions that do not need to be removed, such as small hyperplasic polyps, considerable time could be saved and small risks of polypectomy avoided.

Essentially there are two approaches to enhanced lesion recognition and characterisation: dye-spraying or chromoendoscopy, and image manipulation techniques or image-enhancing technology.

Chromoendoscopy

Widespread application of dye to the lumen of the colon (pan-chromoendoscopy) improves the detection of diminutive lesions (Brown, Baraza & Hurlstone 2007) **(I)**. However, pan-chromoendoscopy is time consuming and the extra lesions detected may be unimportant clinically as a significant number of diminutive lesions may regress (Rother, Knopfle & Bohndorf 2007). The authors of a recent Cochrane review concluded that *selective application* of dye to suspicious areas (selective chromoendoscopy) may be more appropriate during colonoscopy **(VI)**.

This approach is consistent with the conclusions of a recent international workshop which reviewed the role of non-polypoid lesions in the aetiology of colorectal cancer. The endoscopist should be skilled in recognising subtle changes in the appearance of the mucosal surface, particularly alterations in colour, vascularisation and morphology, to identify suspicious areas requiring dye spraying and to better detect polypoid lesions. Small patches of mucus may require rinsing to expose underlying suspicious areas worthy of staining, particularly in the right colon (Kudo et al. 2008).

Selective chromoendoscopy with dye spraying on the lesion has been shown to be superior to conventional colonoscopy predicting polyp histology (Pohl et al. 2008) **(III)**. Magnification chromoendoscopy is more effective than conventional chromocolonoscopy for diagnosing neoplastic colorectal polyps (Emura et al. 2007) **(II)**.

Expert opinion **(VI)** suggests that selective chromoendoscopy facilitates:

- assessment of the lesion and its borders;
- excision of the lesion and of residual tissue;
- colonoscopy for patients with chronic inflammatory bowel disease; and
- colonoscopy for high-risk family syndromes such as HNPCC.

Thus for most polypoid and non-polypoid colorectal abnormalities, a flexible high-definition video endoscope and the facility for selective application of dye (chromoscopy) to the lesion is currently sufficient for detection and characterisation of high-risk lesions. It is recommended that all but the smallest flat or sessile lesions be 'lifted' with submucosal injection of saline or colloid to facilitate safe removal (endoscopic mucosal resection). Lesions that do not 'lift' should not be removed because they are more likely to be malignant, and removal is more likely to lead to perforation **(VI)**.

Image enhancing technology

There is conflicting evidence regarding the potential for narrow band imaging (NBI), Fuji Intelligent Chromo Endoscopy (FICE), and other techniques of image processing commonly referred to as "virtual chromoendoscopy" to improve detection and characterisation of high-risk lesions. One trial showed an increase in the detection rate of diminutive adenomas (Inoue et al. 2008). There was no difference in adenoma detection rates using NBI technique compared to white-light colonoscopy reported by other published trials (Johanson 2006; Rex 2006; Kaltenbach et al. 2008; Kaltenbach, Friedland & Soetikno 2008; Adler et al. 2009) **(II)**.

The use of autofluorescence was associated with a higher polyp detection rate compared with conventional endoscopy in one study, although the observed improvement was mainly attributable to an increased diagnostic yield of diminutive adenomas (Matsuda et al. 2008; Mayinger et al. 2008; McCallum et al. 2008) **(II)**.

Studies comparing the performance of colonoscopy with high definition versus standard colonoscopes did not show an increase in the detection rate of adenomas or hyperplastic polyps when using high-definition instruments (East et al. 2008; Pellise et al. 2008; Burke et al. 2009) **(II-III)**.

The results of diagnostic accuracy studies showed better accuracy of NBI colonoscopy compared to standard colonoscopy in differentiating between neoplastic and non-neoplastic lesions (Su et al. 2006; Katagiri et al. 2008) **(III)**. In the recent Cochrane review of chromoendoscopy, it was suggested that NBI may become the gold standard in enhanced techniques for detection of colorectal lesions, but with the advantage of reduced procedure time compared to chromoendoscopy. One trial comparing diagnostic accuracy of NBI with chromoendoscopy on 99 Patients has been retrieved (Tischendorf et al. 2007). The study did not find a significant difference in accuracy between the two technologies for the differentiation of neoplastic vs. non−neoplastic lesions. Further trials comparing NBI and chromoendoscopy are needed.

Further experience and evidence about efficacy, benefits and potential adverse effects, as well as cost-effectiveness, are required before additional technologies can be recommended for routine, pan-European use in colorectal cancer screening and diagnosis. Particularly in the screening context, improvements in detection and diagnosis may be accompanied by unacceptable decreases in specificity, and/or disproportionate, unacceptable increases in cost, measured both in human and financial resources.

After sufficient standardisation of procedures and protocols in feasibility studies, pilot studies conducted in the framework of population-based screening programmes, and based on a randomised public health policy, could provide appropriate evidence to justify future recommendations for widespread implementation of new technologies.

In view of the above it is recommended that:

- The provision and maintenance of equipment in the endoscopic unit should be carefully managed based on local guidelines that comply with relevant national and pan-European guidelines containing accepted, published recommendations and standards.
- Flexible video endoscopes and the facility for focal application of dye to the lesion should be used in colorectal cancer screening **(III – B).**[Rec 5.12]
- The volume of equipment should match the demand put upon it to maximise efficiency and avoid patient delays **(VI - B).**[Rec 5.11]
- There should be an adequate supply of accessories suited to the endoscopic interventions undertaken within the unit **(VI - B).**[Rec 5.13]
- Use of re-usable accessories should be based on national policy **(VI - B).**[Rec 5.14]
- There should be properly maintained resuscitation equipment in the endoscopy room and recovery area **(VI - B).**[Rec 5.15]
- Maintenance of equipment should be undertaken by competent staff **(V - A).**[Rec 5.16]
- There should be regular review of the functioning of all endoscopes, in accordance with manufacturer specifications and instructions and relevant national or pan-European guidelines **(VI - B).**[Rec 5.17]
- The results of the review should be available at all times in the endoscopy unit **(VI - A).**[Rec 5.18]

5.4.4 Sedation and comfort

Flexible sigmoidoscopy

Although flexible sigmoidoscopy is not currently recommended by the EU for colorectal cancer screening, previous results of ongoing trials indicate that screening is feasible and the procedure is well accepted by screenees (UK Flexible Sigmoidoscopy Screening Trial Investigators 2002; Segnan et al. 2005; Weissfeld et al. 2005; Segnan et al. 2007; Hoff et al. 2009). No sedation for FS was used in these studies **(I)**.

Colonoscopy

Colonoscopy can be an uncomfortable and distressing experience. These adverse effects can be reduced by careful patient preparation and sedation. As mentioned previously in this chapter, there are widely differing practices of sedation for endoscopy in the EU that reflect historic practice and cultural differences.

Sedation improves patient tolerance of colonoscopy, particularly sedation using propofol combined with other sedative agents such as midazolam and analgesics such as pethidine and fentanyl (McQuaid & Laine 2008) **(I)**. However, excessive sedation is considered to be an important contributor to cardio-respiratory related deaths following endoscopy in high-risk patients, particularly the elderly.

According to Rex (Rex 2000b), most of the risk of colonoscopy is related to sedation. Cardio-respiratory complications are infrequent for patients without known heart or lung disease, but monitoring of oxygenation and blood pressure should be performed for all sedated patients.

Although hypoventilation, cardio-pulmonary events and vasovagal reactions may be related to pain and distension caused by the endoscopic procedure, in most cases they are more closely associated with the use of sedatives and opioids. Reduction in risk for these reactions has been observed in a study aimed to determine the incidence of such events when sedation is given only as required. All procedures in this study were performed by senior gastroenterologists with optimal equipment and nursing staff. Patients undergoing colonoscopy without sedation had less decline in blood pressure and fewer hypoxic episodes than sedated patients (Eckardt et al. 1999) **(V)**.

Heavily sedated patients are more difficult to turn, and this may compromise caecal intubation and mucosal visualisation **(V)**.

The available evidence indicates that the quality and safety of colonoscopy in patients that receive propofol sedation is comparable to that in patients receiving light, conscious sedation (or no sedation), provided patients given sedation are assessed properly prior to their procedure (McQuaid & Laine 2008; Singh et al. 2008) **(I)**.

Propofol seems to be better than benzodiazepines or narcotics on recovery, discharge time and patient satisfaction and equivalent on procedure time, caecal intubation rate and adverse events **(I).** However, in many countries an anaesthesiologist is required for propofol administration.

It is recommended that there be local policies and processes in place to optimise sedation and patient support in order to maximise tolerance and minimise risk of complications **(I - B).**[Rec 5.29]

The following categories and data relevant to sedation should be monitored:

1. No sedation;
2. Conscious sedation and substances used;

3. Propofol sedation or general anaesthesia, and substances used; and
4. Insufflation gas: air or $C0_2$ (see below).

Auditable outcomes: Sedation levels, patient feedback on comfort, dignity and privacy, and adverse incidents related to sedation, including use of reversal agents.

Carbon dioxide insufflation

Gas insufflation is mandatory to ensure good visualisation during colonoscopy. Currently, air is commonly used for this purpose (Janssens et al. 2009). However, significant amounts of air can be retained in the GI tract (Bretthauer et al. 2003) causing pain and discomfort for the patient. Pain associated with colonoscopy has been identified as a major barrier to participation in CRC screening (Denberg et al. 2005; Condon et al. 2008; McLachlan, Clements & Austoker 2009).

Randomised trials have shown that carbon dioxide insufflation significantly reduces abdominal pain and discomfort in patients undergoing colonoscopy and flexible sigmoidoscopy (Bretthauer et al. 2002a; Bretthauer et al. 2002b; Sumanac et al. 2002; Church & Delaney 2003; Wong et al. 2008) **(I)**.

Side effects of C02 insufflation were not detected in unsedated patients in two randomised studies identified in the present literature search and involving 350 patients (Bretthauer et al. 2002b; Bretthauer et al. 2005). Slightly elevated end-tidal $C0_2$ levels were detected in sedated patients in the latter study, but only 52 sedated patients were included in the study and patients with chronic obstructive pulmonary disease, as well as patients with known $C0_2$ retention, were excluded.

Since carbon dioxide is an inert gas that cannot form a combustible mixture with hydrogen and methane, $C0_2$ insufflation will avoid the very rare risk of explosion during sigmoidoscopy or colonoscopy (see below).

Following incomplete colonoscopy, an alternative examination is frequently required. Provided adequate facilities are available, same-day CT or MRI colonography, or, in appropriate cases, double-contrast barium enema would be desirable. However, same-day radiologic examination following colonoscopy frequently yields suboptimal quality when air insufflation is used for colonoscopy, due to retained air in the colon. If CO2 insufflation has been used, same-day radiologic imaging is generally feasible with appropriate quality. This avoids the necessity of scheduling the additional radiologic examinations on another day and further colon cleansing (Phaosawasdi et al. 1986; Rodney, Randolph & Peterson 1988) **(III)**.

In light of the above evidence and considerations:

- Carbon dioxide insufflation is recommended for colonic endoscopic procedures **(I - A).**[Rec 5.31]
- Carbon dioxide insufflation should be avoided in patients with COPD, known $C0_2$ retention or otherwise reduced pulmonary function **(VI - A).**[Rec 5.32]

Risk of explosion from electrocautery during air insufflation of the colon

Oxygen in room air, insufflated during colonoscopy, has been shown to react with colonic hydrogen and methane gas to produce a combustive gas mixture (Bigard, Gaucher & Lassalle 1979). A recent review found 20 cases of colonic explosion during electrocautery published since 1952 and confirmed that colonic gas explosion is a rare, but potentially lethal complication during colonoscopy with electrocautery (Ladas, Karamanolis & Ben-Soussan 2007).

Accumulation of colonic combustible gases at potentially explosive concentrations due to inadequate colon preparation and use of air, rather than a non-inert gas such as carbon dioxide for insufflation are the principal causes of gas explosion. Fifteen of the 20 reported cases were associated with bowel preparation using malabsorbable, fermentable carbohydrates (14 cases with mannitol, which is no longer commonly used in colonoscopy, and one with sorbitol). The five other cases involved argon

plasma coagulation for post-radiation colitis. Cleansing solution containing mannitol or other malabsorbed carbohydrates (e.g. sorbitol) must be avoided in the preparation of the colon because of the risk of explosion with electrocautery **(III - A).**[Rec 5.24]

5.4.5 Endoscopist techniques and performance

There is ample evidence of varying performance of endoscopists and, as a consequence, varying outcomes for patients in endoscopy (Bressler et al. 2007; Dafnis et al. 2001; Enns 2007; Shah et al. 2007; Rabeneck et al. 2008; Singh et al. 2009) **(III)**.

High-quality and safe endoscopy is critical for the success of screening therefore it is vital to have continuous monitoring of performance. Performance can be assessed by measuring outcomes that directly affect the patient or surrogate outcomes that are linked with true patient outcomes. Examples of outcomes that directly affect the patient are discomfort, reduced probability of developing cancer, perforation and interval cancer. Examples of surrogate outcomes include caecal intubation rates, withdrawal times and adenoma detection rates.

Very often it is difficult to identify true patient outcomes and link them with individual performance such as missed cancer or reduced risk of cancer. Thus, surrogate outcomes are relied on for assessing individuals. Given limitations on the volume of procedures that a competent endoscopist can regularly perform, the frequency with which an event occurs will affect the ability of a measure to determine individual performance. If the event rate is high (such as adenoma detection), relatively small numbers suffice to assess performance. In contrast, if the event rate is low (such as perforation), very large numbers of procedures are required to assess professional performance.

If there are concerns about performance, or if there is a desire to assess competence prior to participation in a screening programme, it is possible to assess knowledge and skills-based competencies in addition to reviewing key performance indicators (Barton 2008). This approach may become particularly important for assessing skills, knowledge and judgments associated with excision of high-risk lesions once a competency framework has been created.

5.4.5.1 Quality outcomes

The quality of a colonoscopic examination is not only dependent on complete intubation of the colon. Careful and complete visualisation of the mucosa during withdrawal is equally important (Brown, Baraza & Hurlstone 2007) **(I - A).**[Rec 5.35] The following quality indicators should be monitored for each endoscopist to secure good quality of the examination:

Documentation of consent

Prior informed consent should be documented for every examination. Fail-safe mechanisms should be in place to assure that the endoscopist does not conduct a procedure for which prior consent is not documented. Any exceptional cases in which prior consent is not provided should be documented and reviewed.

Numbers of procedures

There is evidence that endoscopic proficiency increases with the number of procedures performed (Enns 2007). Furthermore, low numbers of procedures are associated with a greater risk of complications: the lowest complication rate in a population-based study of outpatient colonoscopy was associated with the highest number of procedures (more than 300 per endoscopist per year; (Rabeneck et

al. 2008; Singh et al. 2009)). However, performing a large number of procedures is not sufficient proof of competency; bad habits can persist even in very experienced endoscopists.

As already mentioned, large numbers are required to provide accurate estimates of performance, particularly if events are infrequent. The 95% confidence interval for a completion rate of 90% for 150 procedures per year is 85–95%; the interval for 300 procedures per year is 87–93%.

It is recommended that the annual number of procedures performed by each endoscopist be recorded to ensure that the sample size for other performance indicators is sufficient **(III - A).**[Rec 5.37]

Although the number of procedures performed annually is not a reliable measure of quality, achieving an adequate volume is essential to maintaining skills and effectively monitoring performance. It is therefore recommended that each endoscopist participating in a colorectal cancer screening programme should undertake to perform at least 300 procedures per year. A higher volume of procedures is desirable to maintain high quality **(III - B).**[Rec 5.38]

Services should be planned such that individual endoscopists achieve a desirable volume of procedures (>300/year) **(III - B).**[Rec 5.39]

Insertion to caecum and withdrawal time

Rapid insertion of the colonoscope is a proxy indicator of technical performance of colonoscopy, provided comfort levels are satisfactory and complication rates are not elevated. Rapid insertion leads to greater efficiency but particular caution should be observed in heavily sedated patients. Withdrawal time is a proxy for careful inspection of the mucosa (see below). If adenoma detection rates are low and withdrawal times short, endoscopists should be encouraged to withdraw more slowly.

Documentation of completion of colonoscopy

Only one study was retrieved assessing specificity and sensitivity of a pair of photographs to assess the completeness of colonoscopy, using a video-clip as the reference standard. The study found a sensitivity of 51.4% and a specificity of 89.2% which were considered too low to be used for reliably documenting colonoscopy completion (Thuraisingam, Brown & Anderson 2008). A single panoramic shot showing both the ileo-caecal valve and the caecum may improve sensitivity **(VI)**.

While ileal intubation is not required in the context of colorectal screening, a picture of ileal mucosa provides strong evidence of completion. Taking ileal biopsies to document completion is discouraged, however, because of concern about transmission of variant Creutzfeldt-Jakob Disease (CJD). Also, intubation of the ileum takes extra time and effort.

It is therefore recommended that completion be documented by auditable photo documentation: preferably a panoramic image of the ileo-caecal valve and caecum, or a video clip with a respective snapshot **(VI - A).**[Rec 5.40]

Completion rates

Caecal intubation rate is one of the key quality indicators of colonoscopy. Caecal intubation rates are affected by a number of factors including age, sex, low BMI, bowel cleansing, sedation, diverticular disease and general health status (Eloubeidi et al. 2003; Rathgaber & Wick 2006; Harris et al. 2007b; Segnan et al. 2007; Radaelli et al. 2008; Viiala & Olynyk 2008).

It can be expected from this evidence that it is possible to achieve a higher caecal intubation rate in patients attending for average risk screening than those attending for investigation of symptoms. US guidelines recommend a different intubation rate standard for screening and for symptomatic populations: 95% and 90%, respectively (Rex et al. 2002). Adjusted completion rates (for factors such as bowel prep or obstruction) are open to diverse interpretation, and it is recommended to use

unadjusted rates for the standard. The exception to this would be an obstruction leading to operative intervention. This is a clear-cut reason for adjusting the rate.

It is recommended that unadjusted caecal intubation rate (as defined above) be a prime indicator of quality of colonoscopy The acceptable standard is >90%; >95% is desirable (see also Ch. 3, Rec. 3.11, sect 3.3.2 and 3.3.3) **(III - A).**[Rec 5.41] There should be documentation and review of reasons for failed completion **(III - B).**[Rec 5.42]

Complete and correct identification of neoplastic lesions

The principal aim of screening FS and colonoscopy is to identify and, in appropriate cases, remove neoplastic lesions in order to lower the burden of colorectal cancer in the population.

Furthermore, a complete colonoscopy that has identified all the relevant pathology is a prerequisite for assessing future risk for inclusion in colonoscopy surveillance programmes (see Chapter 9). There is good evidence of varying rates of detection of high-risk lesions and of missed lesions in back-to-back colonoscopy studies (Rex et al. 1997). Rapid withdrawal at colonoscopy is associated with lower adenoma detection rates (Rex 2000a; Barclay et al. 2006; Millan et al. 2008). Internationally accepted guidelines on performance indicators of colonoscopy recommend monitoring direct or proxy markers of detection of suspicious lesions: polyps, adenomas or withdrawal times (Rex et al. 2002; Levin et al. 2005). In a recently published retrospective study based on data from a colonoscopy screening programme with a high percentage of participants with a family history of colorectal cancer, adenoma detection rate has been shown to be an independent predictor of interval cancer (Kaminski et al. 2010).

Counting polyps is relatively easy but capturing adenoma detection rates can be problematic if endoscopy and pathology databases are not linked. Withdrawal times are a proxy measure and inferior to measuring detection of polyps or adenomas.

There are now well-defined criteria for high risk and the evidence base underpinning these criteria is discussed in Chapter 9. It is recommended that these criteria be used as a marker of careful inspection of the colonic mucosa. These criteria also indicate which persons should enter into surveillance programmes. Therefore it is proposed that the rate of referral into surveillance programmes (whether they are part of the screening programme or not) be an essential outcome for evaluating the quality of inspection of colonic mucosa in the context of screening.

It is recommended that screening programmes adopt, as a minimum, the following outcomes to determine the quality of inspection of the colonic mucosa **(VI - A):**[Rec 5.43]

1. Referral into surveillance programmes (see above and Chapter 9); and
2. Withdrawal times from caecum to anus (in patients who have not had biopsy or therapy).

NOTE 1: Monitoring more than one outcome will support quality improvement. For example monitoring withdrawal times might indicate that an individual with low adenoma detection rates may need to withdraw more slowly. However, if acceptable withdrawal times are associated with poor detection rates another solution may be required.

NOTE 2: Different patient populations will have different prevalence rates of neoplastic lesions, thus the standards for different populations will differ.

NOTE 3: To permit monitoring of professional performance, the above minimum outcomes should be generated from complete, individual data sets recorded according to standardised procedures specified by programme rules.

Excision and retrieval of pathological material

Incomplete excision of a high-risk lesion is associated with an increase risk of development of cancer (Winawer et al. 1993). Incomplete removal of tissue may lead to misclassification of pathology (see Chapter 8). There are currently no validated methods of determining completeness of excision but it is possible to measure retrieval rates for pathological material. Chromoendoscopy may facilitate assessment of completeness of excision (see section 5.4.3). At this stage it is recommended that there be raised awareness of the importance of complete excision (or at the very least careful documentation of whether a lesion has been completely excised) and retrieval rates of excised tissue should be recorded.

Information provided for the pathologist

The quality of histopathology is affected by the information provided by the endoscopist and the extent to which the endoscopist and pathologist communicate with each other (see Chapter 7).

Information on histology request forms for suspicious colonic lesions should include (see also Chapter 7):

- Site of lesion;
- Size of the lesion (as estimated by the endoscopist);
- Nature of lesion, including whether it is ulcerated; and
- Completeness of excision as judged by the endoscopist

NOTE: An optimal colonoscopy report will contain this information and it is recommended that a copy of the report should be sent with the pathology request form.

5.4.5.2 Safety outcomes

Adverse outcomes can occur immediately or several days after the procedure. In this context an immediate adverse outcome is defined by an adverse outcome occurring before the patient leaves the endoscopy department. An adverse outcome occurring after this is a late outcome. Endoscopic services must have processes in place to identify and record adverse outcomes occurring after the patient leaves the endoscopy department **(VI - B).**[Rec 5.45]

Three methods are recommended:

- Contacting all patients within a defined time frame;
- 30-day mortality review of all screened patients; and
- 8-day unplanned admission review of all screened patients

It is appreciated that for some health care systems capturing 30-day mortality and 8-day readmissions may be challenging. Furthermore, it is clear that a person may be admitted or die for reasons that have nothing to do with the procedure. The key point is that if there are factors related to the procedure contributing to death or admission, they should be reviewed and an action plan created if the review indicates there is a need for a change in practice.

To simplify the collection of immediate adverse outcomes, it is recommended that unplanned admission on the same day as the endoscopic procedure be a key adverse outcome. It is recommended that the reason for the admission be recorded in the following categories. Furthermore, the primary reason for admission should be indicated **(III - A):**[Rec 5.44]

- Abdominal pain;
- Suspected or confirmed perforation;

- Bleeding;
- Cardio-respiratory event; or
- Other (specify).

5.5 After the procedure

5.5.1 Recovery facilities and procedures

A person having an endoscopy needs a period of recovery, particularly if they have received sedation. There should be a designated area for recovery and sufficient equipment for them to recover (such as chairs and trolleys).

Auditable outcomes: Patient feedback on recovery collected when the patient has recovered from sedation

5.5.2 Emergency equipment and protocols

The recovery area should be equipped with adequate resuscitation and monitoring equipment, and there should be policies and procedures in place for monitoring patients and dealing with emergencies **(VI - B).**[Rec 5.15]

Auditable outcomes: Regular audit of resuscitation equipment check

5.5.3 Patient information – post procedure

Ideally patients should be informed about the outcome of their procedure before leaving the endoscopy unit and given written information that supports a verbal explanation, particularly if they have had sedation **(VI - A).**[Rec 5.26] They need to be told (orally and with written information) whether any follow up will be arranged (written or outpatient), by whom and during what timescales. Oral and written information must contain an explanation of what to do in the event there are problems, and patients should be given a contact telephone number (24 hours/day, 7 days/week) in case of a procedure-related complication.

Auditable outcomes: Patient feedback on adequacy and helpfulness of post-procedure information

5.5.4 Patient feedback

It is essential to obtain patient feedback on a regular basis in order to correct issues that concern patients that health professionals are unaware of. This feedback can be expected to contain considerable

praise for the service provided, and such positive feedback will have a strong motivating effect on staff to provide an even better service.

5.5.5 Communication to other health professionals

The outcome of screening examinations should be communicated to the primary care doctor (or equivalent) so that it becomes part of their core patient record (see Ch. 2, Sect. 2.4.3.4.2; Ch. 10, Rec.10.31) **(II - B).**[Rec 5.27] In some EU countries the consent of the patient is needed for transmitting the information to the primary care doctor. There should be pre-defined clinical pathways for patients found to require further intervention for cancer, incompletely removed lesions and difficult-to-remove lesions (and failsafe mechanisms to ensure that interventions do occur) **(II - B).**[Rec 5.28]

Auditable outcomes: Time to definitive treatment for patients with cancer; turnaround times for communicating pathology results to patients

5.5.6 Immediate and late safety outcomes

There should be a process in place for systematically recording immediate and late outcomes following screening colonoscopy. See above for types of outcomes and methods of assessment.

Auditable outcomes: Outcomes identified by this process

5.6 Guidelines

The endoscopy service should create and regularly review guidelines for the following, taking into account previous experience and results as well as relevant national and pan-European guidelines containing accepted, published recommendations and standards **(VI - B):**[Rec 5.50]

- Sedation;
- Monitoring after the use of conscious sedation;
- Antibiotic prophylaxis;
- Anticoagulants;
- Colonic cleansing;
- Endoscopic assessment of colorectal abnormalities;
- Endoscopic removal of lesions (both high- and low-risk);
- Marking of high-risk lesions;
- Further management of high-risk lesions; and
- Equipment.

5.7 Policies and processes

There should be policies, and processes to support them, for the following:

- Consent and patient information;
- Withdrawal of consent;
- Decontamination;
- Assessment of competence;
- Staff training;
- Transfer of care following complications;
- Completing the audit cycle; and
- Selection and assessment of equipment.

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Annex 5.1

Suggested quality indicators and auditable outcomes

Annex 5.1: Suggested quality indicators and auditable outcomes

		QI / AO	mandatory	desirable
1	Age and sex of patient	QI/AO	+	
2	Cancer detection rate (all cancers)	QI/AO	+	
3	Cancer detection rate (endoscopically removed cancers) [1]	QI/AO	+	
4	Referral rate into surveillance programmes (total and by risk category)	QI	+	
5	Adenoma excision and retrieval rate +/- withdrawal times	QI	+	
6.1	Numbers and detection rates of colorectal lesions, in total and broken down by: polypoid and non-polypoid (Paris classification: Ip Ls, IIb IIc sessile non-neoplastic)	QI/AO	+	
6.2	Numbers and rates in 6.1 broken down by sector of the colon (caecum; ascending, transverse, descending colon; sigmoid; rectum)	AO	+	
7.1	Numbers and detection rates of colorectal lesions, in total, and by predicted histology: 1) non-neoplastic (hyperplastic polyp, sessile serrated lesion, other), 2) neoplastic (low-grade adenoma, high-grade adenoma, submucosal carcinoma) and 3) uncommon lesions	QI/AO	+	
7.2	Numbers and rates in 7.1 broken down by sector of the colon (caecum; ascending, transverse, descending colon; sigmoid; rectum)	AO	+	
8.1	Numbers and detection rates of colorectal lesions, in total, and by confirmed histology: 1) non-neoplastic (hyperplastic polyp, sessile serrated lesion, other), 2) neoplastic (low-grade adenoma, high-grade adenoma, submucosal carcinoma) and 3) uncommon lesions	AO	+	
8.2	Numbers and rates in 8.1 broken down by sector of the colon (caecum; ascending, transverse, descending colon; sigmoid; rectum)	AO	+	
9.1	Numbers and rates of discrepant lesions broken down by categories in 7.1 and 8.1	AO	+	
9.2	Numbers and rates of discrepant lesions broken down by categories in 7.2 and 8.2	AO	+	
10	Withdrawal times from caecum to anus (in patients who have not had biopsy or therapy)	QI/AO	+	
11	Colonoscopy completion rate	QI	+	
12	Wait time: FOBT to colonoscopy	QI	+	
13	Wait time: FS to colonoscopy	QI	+	
14	Wait time: colonoscopy to pathology results	QI	+	
15	Wait time: FS to pathology results	QI	+	

16	Wait time: pathology results to definitive treatment	QI	+	
17	Unplanned admission on day of procedure: four options	AO	+	
18	Type of insufflation gas (air or $C0_2$)	AO	+	
19	Type of sedation used: three options	AO	+	
20	Comfort: only if conscious or no sedation used	AO		+
21	Adequacy of preparation	AO	+	
22	Delayed adverse outcomes: two options	AO	+	
23	Key endoscopic characteristics of polyps written on pathology request form: five key characteristics: number, site, size, completeness of excision, separate pots used for different sites (see also 6–9)	QI	+	
24	Lesions referred elsewhere for excision	AO	+	
25	Patient feedback on information and consent, booking, environment, comfort and aftercare	AO		+
26	Adverse incidents related to incomplete pre-assessment	AO	+	
27	Decontamination indicators	AO	+	

[1] Removed by endoscopic polypectomy and mucosectomy

Annex 5.2

Minimum requirements for endoscopic reporting

Annex 5.2: Minimum requirements for endoscopic reporting

Performance of a unit and staff can be affected by a number of factors.

Therefore for each endoscopically removed lesion it is important to record:

1. Specification of the procedure in which the lesion has been obtained
    - 1.1. Patient/client information
    - 1.2. Type of endoscopy (FS or CS)
    - 1.3. Team performing procedure (endoscopist(s) and ancillary staff
    - 1.4. Purpose of procedure
        - 1.4.1. Primary screening
            - 1.4.1.1. Initial screening or subsequent screening
            - 1.4.1.2. Interval to last primary screening procedure, if applicable
            - 1.4.1.3. Interval to last endoscopic examination if not the same as above
        - 1.4.2. Assessment of abnormal findings
            - 1.4.2.1. After positive screening test (indicate if FOBT or FS or other)
            - 1.4.2.2. After positive symptomatic test (indicate if FOBT or FS or other, e.g. symptoms)
            - 1.4.2.3. For repeat assessment of abnormal findings
        - 1.4.3. Surveillance
    - 1.5. Interval to last endoscopic procedure and type of procedure
2. Preparation, insufflation and sedation
    - 2.1. Bowel cleansing regimen
    - 2.2. Insufflation gas (air or CO_2)
    - 2.3. Type of anesthesia and substances used
    - 2.4. Kit
3. Caecal intubation
    - 3.1. End of caecum visualized
        - 3.1.1. Panoramic image of ileo-caecal valve and end of caecum? (Other imaging confirmation of caecal intubation?)
        - 3.1.2. Signs of inadequate preparation in caecum?
        - 3.1.3. Intubation time (time at beginning of procedure, time at visualization of end of caecum)
    - 3.2. End of caecum not visualized:
        - 3.2.1. Maximum extent of intubation/inspection of colonal mucosa
        - 3.2.2. Reasons for incomplete examination
4. End of procedure (withdrawal time from caecum)
5. Number of abnormalities detected:
6. For each abnormality detected:
    - 6.1. Location
        - 6.1.1. Distance in cm from ano-rectal junction
        - 6.1.2. Sector: caecum; ascending, transverse, descending colon; sigmoid; rectum

6.2. Size and morphology:

6.2.1. Maximum diameter in millimeters

6.2.2. Depth in mm and layer (mucosal/submucosal)

6.2.3. Mucous patch

6.2.4. Polypoid

6.2.5. Non-polypoid (Paris classification): Ip Ls, IIb, IIc sessile

6.3. Prediction of histology (endoscopic diagnosis)

6.3.1. Non-neoplastic (hyperplastic polyp, sessile serrated lesion, other)

6.3.2. Neoplastic (low-grade adenoma, high-grade adenoma[4], submucosal carcinoma)

6.3.3. Uncommon lesions

7. When endoscopic treatment is conducted

7.1. Complications (bleeding, use of coagulation, perforation, other adverse effects)

7.2. For each abnormality endoscopically treated:

7.2.1. Technique of resection (polypectomy, mucosectomy)

7.2.2. Information provided for the pathologist:

7.2.2.1. Location (see 5.1)

7.2.2.2. Size and morphology: (see 5.2)

7.2.2.3. Completeness of excision as judged by the endoscopist)

7.2.2.4. Prediction of histology (endoscopic diagnosis, see 5.3)

[4] Very rare mucosal carcinomas, if diagnosed, are included in “mucosal high grade neoplasia and are treated endoscopic biopsy/excision.

6

Professional requirements and training

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Recommendations[1]

General requirements

6.1 Colorectal cancer screening programmes should be operated by an adequately trained multidisciplinary team (see Ch. 8, Rec. 8.1) **(VI - A).**[Sect 6.2; 8.2]

6.2 Key performance indicators should be developed for the monitoring of a national or regional screening programme **(VI - B).**[Sect 6.2]

Administrative and Clerical Staff

6.3 National or regional colorectal cancer programmes should be run in conjunction with other screening programmes by an experienced administrative team **(VI - B).**[Sect 6.3]

6.4 All administrative and clerical staff in a colorectal screening programme should acquire a basic understanding of colorectal screening and specific courses should be developed for this purpose **(VI - A).**[Sect 6.3]

6.5 Management, communication and project management skills for the administrative staff of a colorectal screening programme should be acquired by means of formal courses **(VI - A).** [Sect 6.3]

Epidemiologist

6.6 A specifically trained epidemiologist should be seconded to a national or regional colorectal cancer screening programme **(VI - B).**[Sect 6.4]

6.7 Training of epidemiologists inexperienced in evaluation and monitoring in colorectal cancer screening should be organised as secondments to established screening centres running population-based screening programmes. Additional didactic courses on relevant aspects of the work should be attended depending on individual knowledge and experience **(VI - B).**[Sect 6.4]

Laboratory staff

6.8 A fully trained laboratory staff with appropriate management should be in place for a national or regional colorectal cancer screening programme and internal quality control and external quality assurance mechanisms should be put in place for the laboratory (see Ch. 4, Rec. 4.10 and 4.12) **(VI - A).**[Sect 6.5; 4.3.3.4; 4.3.4]

6.9 Training in the form of courses or secondments to existing laboratories should be available for all laboratory personnel **(VI - B).**[Sect 6.5]

6.10 A European laboratory network should be established in order to provide appropriate external quality assurance **(VI - C).**[Sect 6.5]

Primary care physicians

6.11 All general practitioners should be informed about national or regional colorectal cancer screening programmes and provided with appropriate infrastructure and training, including adequate training to be able to help people make informed decisions about CRC screening (see Ch. 2, Rec. 2.12; and Ch. 10, Rec. 10.21) **(II - C).**[Sect 6.6; 2.4.3.4.2; 10.4.2.3.2]

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[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.

Endoscopists

6.12 Endoscopists who participate in a colorectal cancer screening programme should be fully trained in colonoscopy or flexible sigmoidoscopy, depending on the procedure they perform in the programme **(V - A).**[Sect 6.7]

6.13 Endoscopists who participate in a colorectal cancer screening programme should be fully trained in biopsy and polypectomy **(V - A).**[Sect 6.7]

6.14 Endoscopists who intend to participate in a colorectal cancer screening programme should undergo assessment to ensure an adequate level of expertise before commencing practice within the programme **(VI - B).**[Sect 6.7]

6.15 Endoscopists who participate in a colorectal cancer screening programme should be able to demonstrate high completion rates, low morbidity and appropriate adenoma detection rates **(VI - B).**[Sect 6.7]

Radiologists

6.16 Radiologists participating in a colorectal cancer screening programme should have specialist training in colorectal imaging **(VI - A).**[Sect 6.8]

6.17 Radiologists working within a screening programme should participate in quality assurance where at least a proportion of radiological examinations are double-read **(VI - B).**[Sect 6.8]

Pathologists

6.18 Pathologists participating in a colorectal cancer screening programme should have specific training in colorectal pathology **(VI - B).**[Sect 6.9]

6.19 Pathologists participating in a colorectal cancer screening programme should develop a network with other pathologists in order to share experience (see also Ch. 7, Rec. 7.16) **(VI - B).**[Sect 6.9; 7.6; 7.7]

Surgeons

6.20 Surgeons treating patients with screen-detected disease should specialise (although not necessarily exclusively) in colorectal cancer surgery and should be able to demonstrate a high-volume practice **(III - B).**[Sect 6.10]

Nurses

6.21 Nurses participating in colorectal cancer screening programmes should have a specific training to equip them with the necessary skills, including adequate training to be able to help people make informed decisions about CRC screening (see Ch.10, Rec. 10.21) **(VI - C).**[Sect 6.11; 10.4.2.3.2]

Public Health

6.22 Public health physicians should be involved in national or regional colorectal cancer screening programmes and should be provided with appropriate training **(VI - C).**[Sect 6.12]

6.23 Where necessary, public health specialists should have access to courses or the ability to visit screening centres to obtain this specific training **(VI - C).**[Sect 6.12]

6.1 Introduction

The success of a colorectal cancer screening programme is dependant on specially trained individuals committed to implementation, provision and evaluation of a high quality, efficient service. The multi-disciplinary team that is responsible for a colorectal screening programme includes

- Administrative and clerical staff;
- Epidemiologists;
- Laboratory staff;
- Primary care physicians;
- Endoscopists;
- Radiologists;
- Pathologists;
- Surgeons;
- Nurses; and
- Public health specialists

All staff involved in the delivery of a colorectal cancer screening programme must have knowledge of the basic principles of colorectal cancer screening. To achieve this it would be appropriate for them to attend a course of instruction at an approved training centre prior to the commencement of the programme. The need for specialist training in screening differs between the different disciplines and is most important for those involved in the delivery of the service and diagnosis, e.g. laboratory staff, endoscopists, radiologists, pathologists and nurses. The surgical treatment of screen-detected cancer and post-operative treatment is not performed differently according to whether a cancer is screen detected or symptomatic, but there are certain considerations for the surgeon to take into account when treating a screen-detected cancer. Oncologists are not mentioned in this document, as, stage for stage, their role in the treatment of screen-detected disease is no different from that in symptomatic disease. High-quality screening performance is based on a multidisciplinary approach, and it is important that appropriate training packages are offered. Updating knowledge as part of continuing medical education should be encouraged.

Participation in training courses should be documented and certificates of attendance issued based on the levels of skill attained and evaluated. Specific training requirements in terms of quality and volume should determine eligibility for any certification or accreditation process which must be applied only to centres with sufficiently skilled personnel.

6.2 General requirements

The evidence that Multidisciplinary Teams (MDTs) improve outcomes for cancer patients is still scanty, but beginning to accumulate (Fleissig et al. 2006). However, there is general agreement that multidisciplinary services provide better patient care for a variety of conditions and in colorectal cancer, multidisciplinary management is strongly recommended (NHS Executive 2004). Effective communication between the various professionals of a colorectal multidisciplinary team is essential and training

courses should therefore focus on good inter-professional communication. Joint courses given for the multidisciplinary team may facilitate this goal.

Continuing education including refresher courses at various intervals is essential to gaining information on new developments and to improve the quality of the screening and diagnostic therapeutic processes. It is important to keep records of training activities as they are useful indices of the quality of a service. These would be part of a certification or accreditation review process.

Staff – all staff involved in the screening programme require basic knowledge of the foundation of the programme. Relevant topics are:

- Colorectal cancer epidemiology (incidence, prognosis, mortality);
- Introduction to screening theory;
- Screening terminology (sensitivity, specificity, predictive value, etc);
- Current screening practices (screening modalities used, methods of identifying target population, methods of invitation)
- Evaluation of screening effectiveness (key performance indicators)

Key performance indicators are essential for the effective monitoring of a national or regional colorectal cancer screening programme (Steele et al. 2009). As a bare minimum, the key performance indicators of a colorectal screening programme include:

- Uptake of screening test;
- Time between screening test and definitive diagnosis (where screening test is not colonoscopy);
- Proportion of those with a positive test undergoing colonoscopy (where colonoscopy is not the screening test);
- Colonoscopy completion rate;
- Colonoscopy complication rate;
- Positivity rate (for a non-endoscopic screening test);
- Cancer detection rate;
- Stage of cancer at diagnosis;
- Adenoma detection rate;
- Positive predictive value for cancer and adenomas; and
- Interval cancer rate.

Summary of evidence

- Optimal care is best provided by multidisciplinary teams **(VI).**
- Key performance indicators are essential for effective monitoring of a national or regional screening programme **(VI).**

Recommendations

Colorectal cancer screening programmes should be operated by an adequately trained multidisciplinary team (see Ch. 8, Rec. 8.1) **(VI - A).**[Rec 6.1]

Key performance indicators should be developed for the monitoring of a national or regional screening programme **(VI - B).**[Rec 6.2]

6.3 Administrative and clerical staff

A colorectal screening programme can be run under the umbrella of a screening programmes division associated with the national or regional health department where this exists. This allows the colorectal screening programme staff to benefit from the experience gained from other screening programmes. In the UK, the organisation of the colorectal screening programmes is overseen by a programme manager who reports to a national or regional screening coordinator responsible for all screening programmes. In addition to a programme manager each centre that is responsible for sending out invitations and/or organising screening tests for those who accept the invitations is overseen by a screening manager who is responsible for the efficient operation of the screening programme and managing the staff of the screening centre (Public Health Resource Unit 2008; Scottish Bowel Screening Programme 2010). The staffing of the screening centre depends on the structure of the programme itself; e.g. if it is a centralised programme, staff are required for identifying individuals to be invited, sending out invitations, replying to those who have undergone testing and, where appropriate, organising further investigations for those with positive tests. The basic training requirements for all screening administrative and clerical staff should include the following:

- Basic understanding of colorectal cancer, the potential benefits and harms of screening, and the prime importance of quality assurance
- Basic understanding of the colorectal cancer screening programme; and
- Basic information technology skills.

In addition, the centre manager requires:

- Advanced managerial skills; and
- Advanced communication skills (for dealing with queries, complaints etc).

In addition, the programme manager requires

- Advanced project management skills.

Management communication and project management skills can be acquired by means of formal courses. However the administrative structure required for a colorectal cancer screening programme will depend very much on local and national conditions and must be modified accordingly.

Summary of evidence

- No literature evidence was retrieved for this topic. National and regional screening programmes require an efficient administrative structure **(VI).**

Recommendations

National or regional colorectal cancer programmes should be run in conjunction with other screening programmes by an experienced administrative team **(VI - B).**[Rec 6.3]

All administrative and clerical staff in a colorectal screening programme should acquire a basic understanding of colorectal screening and specific courses should be developed for this purpose **(VI - A).** [Rec 6.4]

Management, communication and project management skills for the administrative staff of a colorectal screening programme should be acquired by means of formal courses **(VI - A).**[Rec 6.5]

6.4 Epidemiologist

As many disciplines contribute to providing data required for monitoring and evaluating a colorectal screening programme it is essential that a designated individual with relevant epidemiological expertise be assigned the task of overseeing the collection and analysis of the data required for evaluation. Assessing a programme's impact on colorectal cancer mortality is only possible if adequate provision has been made in the planning process for adequate collection and analysis of data (see Chapter 3).

Basic Training: The individual overseeing data collection and analysis requires training in clinical epidemiology and statistics.

Specific training: Training for epidemiologists involved in a colorectal cancer screening programme focuses on:

- Colorectal cancer epidemiology (incidence, prevalence, mortality, trends);
- Screening theory (pre-clinical disease, lead time, selection, length bias);
- Colorectal cancer screening terminology (sensitivity, specificity, positive predictive value etc);
- The colorectal screening programme (organisation, current screening modalities);
- Ethical and confidentiality issues;
- Setting up a colorectal cancer screening programme (identification and an invitation of target population, call-recall system, follow-up system);
- Strategies for data collection and management (use of appropriate databases, individual files, computerised archives, linkage to appropriate registries, classification of screening outcomes, quality control procedures and data collection);
- Statistical analysis and interpretation of results (performance indicators for evaluation, predictors of the impact of screening, assessing screening impact and effectiveness, cost-effectiveness calculations); and
- Presentation of data and report writing.

Acquisition of these skills may require specific courses for the individuals involved.

Summary of evidence

- No literature evidence was retrieved for this topic. Careful data collection and analysis is essential for the effective monitoring of a national and regional colorectal screening programme **(VI)**.

Recommendations

A specifically trained epidemiologist should be seconded to a national or regional colorectal cancer screening programme **(VI - B).**[Rec 6.6]

Training of epidemiologists inexperienced in evaluation and monitoring in colorectal cancer screening should be organised as secondments to established screening centres running population-based screening programmes. Additional didactic courses on relevant aspects of the work should be attended depending on individual knowledge and experience **(VI - B).**[Sect 6.7]

6.5 Laboratory staff

Where a screening programme is based on a laboratory test (in the case of colorectal cancer screening the only currently available laboratory test is faecal occult blood testing), it is self-evident that an adequately staffed laboratory is necessary. It is similarly self-evident that the training and skills required by the laboratory staff are dependent on the type of test (guaiac or immunochemical, qualitative or quantitative). The laboratory staff requires supervision by an appropriately qualified individual with expertise in clinical biochemistry (see Ch. 4, Rec. 4.11), and the day-to-day running of the laboratory must be managed by an appropriately skilled scientific officer. When faecal occult blood testing is being used as the primary test for a colorectal screening programme it is essential that this be done with appropriate internal quality control (IQC) and external quality assurance (EQAS) (see Ch. 4, Rec. 4.10 and 4.12, Sect. 4.3.3.4 and 4.3.4); and this requires centralisation, either on a national or regional basis, of the testing process (Public Health Resource Unit 2008; Scottish Bowel Screening Programme 2010). Delegation to individual practitioners is not appropriate.

The training required for the laboratory staff should include the following:

- A basic understanding of colorectal cancer and the benefits of early diagnosis (a basic understanding of the colorectal cancer screening process);
- Training in good laboratory practice;
- Training in the performance of the faecal occult blood test (the specific training will depend on whether a guaiac or immunochemical test is used and whether it is a qualitative or quantitative test); and
- Training in the use of the IT system used to record results.

In addition, the training required by the Laboratory Manager includes:

- Managerial skills;
- An appreciation of internal quality control and external quality assurance; and
- A thorough understanding of the interactions between the laboratory process and the whole screening programme.

An individual with expertise in clinical biochemistry is ultimately responsible for the operation of the laboratory and requires training in the following:

- An in-depth understanding of colorectal cancer (diagnosis, treatment, prognosis, staging and the importance of stage at diagnosis);
- An in-depth understanding of the colorectal cancer screening process (including screening theory and especially the potential benefits and harms of screening and the prime importance or quality assurance);
- Extensive knowledge of performance characteristics of different types of faecal occult blood test; and
- An in-depth understanding of the technology required to perform the faecal occult blood test.

In some parts of Europe the screening programme may not be based on faecal occult blood testing. Where it is, however, it is essential to ensure a uniformly high standard of testing, and a European laboratory network would facilitate this.

Summary of evidence

- No literature evidence was retrieved for this topic. Appropriately trained Laboratory staff are essential for a FOBT-based colorectal cancer screening programme **(VI).**

- No literature evidence was retrieved for this topic. Internal quality control and external quality assurance are essential to ensure consistency of FOBT reporting **(VI).**

Recommendations

A fully trained laboratory staff with appropriate management should be in place for a national or regional colorectal cancer screening programme and internal quality control and external quality assurance mechanisms should be put in place for the laboratory (see Ch. 4, Rec. 4.10 and 4.12, Sect. 4.3.3.4 and 4.3.4) **(VI - A).**[Rec 6.8]

Training in the form of courses or secondments to existing laboratories should be available for all laboratory personnel **(VI - B).**[Rec 6.9]

A European laboratory network should be established in order to provide appropriate external quality assurance **(VI - C).**[Rec 6.10]

6.6 Primary care physicians

There is ample evidence for the importance of involving primary care physicians in the implementation of colorectal cancer screening programmes (see Ch. 2, Rec. 2.8, 2.12 and 2.13; and Sect. 2.3.1 and 2.4.3). The role of primary care physicians in colorectal cancer screening will vary widely from one European country to another. In some instances the general practitioner (GP) is required to invite the target population, in some instances they are required to encourage their patients to participate in a centrally organised screening programme and in some instances they may not play a direct role in the screening programme but will clearly be required to answer questions on screening posed by their patients. It must be emphasised however, that general practitioners should not be encouraged to perform faecal occult blood tests on an individual basis as it is impossible to ensure adequate quality assurance for the performance of the test.

The training required of general practitioners working in an area where there is an active screening programme should include the following:

- A thorough knowledge of colorectal cancer (diagnosis, treatment, prognosis, staging and importance of stage at diagnosis;
- An in-depth understanding of the colorectal screening process (including screening theory and particularly the potential benefits and harms of screening, and the prime importance of quality assurance); and
- A thorough knowledge of the organisation of the local screening programme and the role of GPs within the programme.

Whenever a colorectal screening programme is introduced into a region it is essential that all GPs serving the region are informed, and that specific training events for GPs are made available, including adequate training to be able to help people make informed decisions about CRC screening (see Ch. 10, Rec. 10.21, and Sect. 10.4.2.3.2).

Summary of evidence

The involvement of primary care physicians (general practitioners) in a screening programme can enhance uptake **(I)** (see Chapter 2).

From evidence derived from two good-quality RCTs, it appears that educational programmes on CRC screening rationale, recommendation, CRC risk etc., towards primary care physicians are effective in improving CRC screening rates (Ferreira et al. 2005; Lane et al. 2008). However, a third RCT did not confirm such results (Walsh et al. 2005) **(II).**

Recommendations

All general practitioners should be informed about national or regional colorectal cancer screening programmes and provided with appropriate infrastructure and training, including adequate training to be able to help people make informed decisions about CRC screening (see Ch. 2, Rec. 2.12, Sect. 2.4.3.4.2; Ch.10, Rec. 10.21 and Sect. 10.4.2.3.2) **(II - C).**[Rec 6.11]

6.7 Endoscopists

Endoscopists carrying out either flexible sigmoidoscopy or colonoscopy as the primary screening test, or colonoscopy as the investigation following a positive primary screening test, are central to the delivery of a successful screening programme. It is essential that they be skilled in complete examination of the colonic mucosa and in recognising both cancers and pre-cancerous lesions (i.e. adenomas). It is also essential that they be skilled in biopsy and polypectomy technique such that they can carry out lower gastrointestinal endoscopy safely and effectively. If the endoscopy associated with a colorectal cancer screening programme has an appreciable morbidity or mortality, this has the potential to negate any benefit derived from the programme. Likewise if a high proportion of neoplastic lesions are missed on endoscopy, this will undermine the confidence of the population in the screening programme and has the potential to create a damaging “certificate of health” effect.

In order to ensure that only the highest quality of colonoscopy is delivered by the national screening programme in the United Kingdom, a specific assessment process has been introduced, and all colonoscopists wishing to participate in the programme must complete this successfully. The assessment consists of a test of knowledge and direct observation of procedural skills (Shorthouse 2009) (for level of competency for endoscopists see Ch. 5, Sect. 5.1.2).

Different countries will employ different types of health professionals to undertake endoscopy, including medically qualified gastroenterologists, medically qualified surgeons, nurse endoscopists and, in some instances, endoscopists who have neither a formal medical nor a nursing qualification.

In all cases, however, endoscopists working within a colorectal screening programme should meet national professional requirements for performing endoscopy (FS and/or colonoscopy depending on the type of programme and the role of the respective endoscopist) and should fulfil the following training requirements:

- Good knowledge of the normal large bowel, its anatomy and its physiology;
- Good knowledge of the disease processes that can affect the large bowel and its endoscopic appearance;
- An understanding of digital endoscopy technology including maintenance and cleaning;
- Full training in the performance of either flexible sigmoidoscopy or colonoscopy as required including appropriate accreditation where this is available;

- Full training in safe biopsy and polypectomy technique (note: in some instances where endoscopic mucosal resection or endoscopic sub-mucosal resection of extensive lesions is required, tertiary referral may be necessary); and
- Full training in managing complications of endoscopic procedures performed in screening and diagnosis, including local protocols for management of severe complications.

To ensure the requisite high quality of endoscopy within a screening programme, all participating endoscopists must engage in quality assurance, and they must provide the data and reports required to routinely generate returns on numbers of endoscopies performed, completion rates, morbidity rates (including perforation, bleeding and death) and both adenoma and cancer detection rates.

It is difficult to conclude which professional and training requirements for endoscopists can affect the efficacy, safety, tolerability, and accuracy of endoscopic procedures, but evidence suggests that the following patient variables should be identified and taken into account prior to FS or colonoscopy because they can be associated with more adverse events, more time duration, and incomplete examination:

- Use of anticoagulants e.g. warfarin;
- Female anatomy;
- Age of patient;
- ASA (American Society of Anaesthesiologists) physical status;
- Prior abdominal surgery;
- BMI; and
- Diverticular disease.

Furthermore, the conditions under which endoscopy is conducted also have an impact on performance (see Ch. 5, Rec. 5.21, 5.30, 5.37-39, Sect. 5.1.3. 5.3.3 and 5.4.5.1):

- Poor bowel preparation is associated with lower rate of complete colonoscopy;
- Deep sedation is associated with a greater rate of complete colonoscopy but also with a higher risk of cardiovascular events;
- The volume of colonoscopy is associated with completeness of examination and lower complication rates.

Recommendations

Endoscopists who participate in a colorectal cancer screening programme should be fully trained in colonoscopy and/or flexible sigmoidoscopy, depending on the procedure they perform in the programme (Atkin et al. 2004; Thomas-Gibson et al. 2007) **(V - A).**[Rec 6.12]

Endoscopists who participate in a colorectal cancer screening programme should be fully trained in biopsy and polypectomy (Atkin et al. 2004; Thomas-Gibson et al. 2007) **(V - A).**[Rec 6.13]

Endoscopists who intend to participate in a colorectal cancer screening programme should undergo assessment to ensure an adequate level of expertise before commencing practice within the programme(Atkin 2004) However another study did not confirm these results (Aslinia et al. 2006) **(VI - B).**[Rec 6.14]

Endoscopists who participate in a colorectal cancer screening programme should be able to demonstrate high completion rates, low morbidity and appropriate adenoma detection rates **(VI - B).**[Rec 6.15]

6.8 Radiologists

While the majority of European countries will employ colonoscopy as either the main investigative technique for a positive test or as the primary screening test, radiology expertise is required to investigate the colon in those individuals in whom a complete follow-up or surveillance colonoscopy is not achievable. It is essential that the radiological examination be carried out by an experienced gastrointestinal radiologist. There is evidence that the "miss rate" is highest in situations where a colonoscopy has been incomplete and a subsequent radiological examination has not detected pathology.

Radiologists working within the colorectal cancer screening programme have the following training requirements:

- Good knowledge of the normal colon, its anatomy and physiology;
- Good knowledge of the disease processes that can affect the colon and their radiological appearances;
- An understanding of the technology underlying barium enema and computer tomographic (CT) colography[2]; and
- Full training in the performance of either barium enema or CT colography or both, depending on local availability.

For quality assurance, a proportion of radiological examinations should be double-read. The use of virtual colonoscopy[1] following an incomplete colonoscopy assessment is increasing for patients with poor health. The same requirements, specific for training to barium enema, should apply to virtual colonoscopy.

Summary of evidence

- Currently the role of radiologists in the colorectal cancer screening programme is limited to the investigation of individuals who have undergone incomplete follow-up or surveillance colonoscopies **(V)**.

Recommendations

- Radiologists participating in a colorectal cancer screening programme should have specialist training in colorectal imaging **(VI - A).**[Rec 6.16]
- Radiologists working within a screening programme should participate in quality assurance where at least a proportion of radiological examinations are double-read **(VI - B).**[Rec 6.17]

6.9 Pathologists

Pathologists working within a colorectal cancer screening programme require full training in the histopathology of gastrointestinal disease with specific emphasis on colorectal cancer. These pathologists should be skilled in the following areas:

[2] CT colography is also known as virtual colonoscopy.

- The interpretation of biopsies taken from benign and malignant tumours of the colon and rectum;
- The preparation and histological interpretation of endoscopic polypectomy specimens; and
- The preparation and histological interpretation of surgical resection specimens.

The histological examination of a polypectomy specimen is a particularly demanding area within a screening programme, as large, complex endoscopically removed lesions are common and often exhibit equivocal features of possible invasive malignancy. It is also particularly important for a pathologist to be able to comment on the degree of differentiation, the presence or absence of lymphovascular invasion, and distance of invasive cancer from the resection margin in endoscopically excised pT1 i.e. "polyp" cancers.

In addition, quality control of surgery is particularly important within a screening programme, as it is essential that individuals with lesions detected at screening are afforded the highest possible standards of care (see Ch. 8). The pathologist has an essential role in the quality assurance of surgery by assessing the completeness of tumour excision in surgical resection specimens.

Pathologists working within a colorectal screening programme have the following training requirements:

- Good knowledge of the disease processes that can affect the colon and their histological appearances;
- An ability to distinguish between benign and malignant biopsy specimens;
- An ability to distinguish between benign and malignant polypectomy specimens;
- An ability to access the risk factors associated with recurrence after endoscopic excision of malignant polyps;
- An appreciation of immunohistochemistry where it relates to histological interpretation of colorectal tumours; and
- The ability to prepare a colorectal resection specimen, with particular emphasis on harvesting lymph nodes and assessing the circumferential resection margin.

Quality assurance in pathology is important and essential within a colorectal screening programme and image exchange is an important component of ensuring consistency of reporting, particularly with the interpretation of difficult endoscopically removed lesions (see Ch. 7, Sect. 7.7).

Summary of evidence

- Colorectal cancer screening results in increased workload for pathology departments, and creates significant demands in terms of the interpretation of complex histology of endoscopically removed lesions (see Ch. 7, Rec. 7.17 and 7.22, Sect. 7.6.5.2) **(V)**.

Recommendations

Pathologists participating in a colorectal cancer screening programme should have specific training in colorectal pathology **(VI - B).**[Rec 6.18]

Pathologists participating in a colorectal cancer screening programme should develop a network with other pathologists in order to share experience (see also Ch. 7, Rec. 7.16, Sect. 7.6 and 7.7) **(VI - B).**[Rec 6.19]

6.10 Surgeons

Most cancers and a small proportion of large adenomas detected within a colorectal screening programme will require surgical excision, and it is important that this be carried out as effectively and safely as possible. The beneficial effect of early detection of colorectal cancer is dependant on low mortality and morbidity rates associated with the subsequent surgery.

It is now recognised that both short- and long-term results of surgery for both rectal and colon cancer are highly surgeon-dependant and there is now good evidence that specialisation associated with high volume is associated with improved results (Morris & Platell 2007; Salz & Sandler 2008). It is therefore mandatory that all screen-detected cancers requiring surgery are treated by surgeons who specialise in colorectal surgery, preferably with a particular interest in cancer. It is also essential that these surgeons work in multidisciplinary teams with access to oncologists experienced in both adjuvant and palliative treatment of colorectal cancer (see Ch. 8, Rec. 8.1).

It follows that surgeons treating patients with screen-detected colorectal cancer should be fully trained and possess the appropriate qualifications for a colorectal surgeon. In addition to the specialist training that this entails, surgeons working within a colorectal screening programme have the following training requirements:

- An understanding of the basic principles of screening, with particular reference to colorectal cancer; and
- An understanding of the significance of pT1 cancers with reference to the need for completion surgery (see Ch. 8, Rec. 8.17).

Screen-detected cancers may be particularly suitable for laparoscopic resection, and it is essential that any surgeon utilising this technique is fully trained and, where appropriate, accredited. While some surgeons may be in a position to obtain appropriate training for laparoscopic surgery within their own institutions, this may not always be the case; and it is essential that surgeons wishing to carry out laparoscopic colorectal surgery should attend the appropriate courses and obtain the appropriate training wherever this is available.

Summary of evidence

- High quality of surgery in a colorectal cancer screening programme is essential to avoid creating unnecessary morbidity in patients requiring surgery for asymptomatic disease. Surgeon specialisation and volume are associated with short- and long-term outcome in colorectal cancer **(III).**

Surgeons

All surgeons treating patients with screen-detected disease should specialise (although not necessarily exclusively) in colorectal cancer surgery and should be able to demonstrate a high-volume practice **(III - B).**[Rec 6.20]

6.11 Nurses

Nurses have important roles throughout the colorectal screening pathway, from the initial contact with the screening invitees through diagnostic endoscopy both as an endoscopy nurse or as a nurse endoscopist, to the care of the patient requiring surgery (Public Health Resource Unit 2008; Scottish Bowel Screening Programme 2010). The importance of these roles will vary from country to country and indeed from region to region within countries. The nursing skills required to care for screening patients are essentially the same as those required to care for symptomatic colorectal patients in many situations. However, the specialist colorectal nurse may have a specific role to play, particularly in counselling individuals with positive screening tests. Such nurses are fully qualified and have experience in specialist colorectal nursing.

The training requirements for nurses in a colorectal cancer screening programme include the following:

- An in-depth understanding of colorectal cancer (diagnosis, treatment, prognosis, staging and importance of stage at diagnosis);
- An in-depth understanding of the colorectal screening process (including screening theory and particularly the potential benefits and harms of screening, and the prime importance of quality assurance); and
- Advanced communication skills.

Appropriate courses should be available for nurses involved specifically in colorectal cancer screening programmes to address these issues, including adequate training to be able to help people make informed decisions about CRC screening.

Recommendations

Nurses participating in colorectal cancer screening programmes should have a specific training to equip them with the necessary skills, including adequate training to be able to help people make informed decisions about CRC screening (see Ch.10, Rec. 10.21) **(VI - C).** [Rec 6.21]

6.12 Public health

The role of the public health specialist in a colorectal cancer screening programme is to ensure coordination of the component parts of the screening programme in such a way as to optimise delivery of the programme to the target population (Public Health Resource Unit 2008; Scottish Bowel Screening Programme 2010). This will include endeavouring to maximise uptake by means of health promotion initiatives and addressing inequality issues.

The role of the public health physician may vary from country to country and from region to region within countries, but public health specialists are well placed to act in a coordinating role.

Public health specialists engaging in colorectal cancer have the following training requirements:

- An in-depth understanding of colorectal cancer (diagnosis, treatment, prognosis, staging and the importance of stage at diagnosis);

- An in-depth understanding of the colorectal cancer screening process (including screening theory and particularly the potential benefits and harms of screening, and the prime importance of quality assurance);
- A full understanding of the mechanisms whereby colorectal cancer screening is delivered in their population; and
- Training in effective health promotion.

Courses or the ability to visit screening centres can provide this specific training.

Summary of evidence

- **No literature evidence was retrieved for this topic.** Public health Physicians have important roles within a Colorectal Cancer Screening Programme in terms of coordination and optimisation of delivery **(VI).**

Recommendations

Public health physicians should be involved in national or regional colorectal cancer screening programmes and should be provided with appropriate training **(VI - C).**[Rec 6.22]

Where necessary, public health specialists should have access to courses or the ability to visit screening centres to obtain this specific training **(VI - C).**[Rec 6.11]

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7

Quality assurance in pathology in colorectal cancer screening and diagnosis

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Recommendations[1]

7.1 Due to the improved diagnostic reproducibility of the revised Vienna classification, use of this classification in a format modified for lesions detected in screening is recommended to ensure consistent international communication and comparison of histopathology of biopsies and resection specimens **(IV – B).** Only two grades of colorectal neoplasia (low grade and high grade) should be used, to minimise intraobserver and interobserver error **(V - B).** The terms intra-mucosal adenocarcinoma or *in-situ* carcinoma should not be used **(VI - B).**[Sect 7.2; 7.3; 7.5.1]

7.2 The WHO definition of colorectal adenocarcinoma should be used: "an invasion of neoplastic cells through the muscularis mucosae into the submucosa" **(VI - A).**[Sect 7.5.1]

7.3 Adenocarcinomas should be reported according to the TNM classification. The version of TNM to be used should be decided nationally and should be stated e.g. pT1 pN0 pMX (Version 5) or pT4 pN2 pM1 (Version 7). These can be further abbreviated to pT1N0MX **(v5)** or to pT4N2M1 **(v7) (VI - B).**[Sect 7.6.5.1]

7.4 The WHO classification of adenomas into tubular, tubulo-villous and villous should be used **(VI - A).**[Sect 7.2]

7.5 Due to the increased risk of colorectal cancer associated with flat and/or depressed lesions they should be reported as non-polypoid lesions **(III)**, and further classified by the Paris classification **(V - B).**[Sect 7.2; 7.2.3]

7.6 The pathologist should verify the complete removal of neoplastic lesions (clear margins) and the absence of submucosal invasion in biopsy specimens. Currently we recommend that clearance of 1 mm or less indicates margin involvement **(VI - B)**. Cases of incomplete removal or uncertainty about submucosal invasion should be highlighted in the pathology report **(VI - B).**[Sect 7.6.3]

7.7 Sub-staging of T1 cancers should be performed to determine the risk of residual disease. Consideration should be given to the appropriate method, which may vary depending on the morphology of the lesion (Kikuchi/Haggitt or measurement). For non-polypoid lesions the Kikuchi stage and for pedunculated lesions Haggitt are currently recommended **(VI - C)**. High-risk features for residual disease such as lack of margin clearance (≤1 mm), poor differentiation and lymphatic and vascular invasion should be reported **(V - B)**. The multidisciplinary team should be consulted on whether or not surgical resection of pT1 adenocarcinoma is recommended; if surgical resection is recommended, consideration should be given to obtaining an opinion from a second histopathologist as variation exists in evaluating high-risk features **(VI - A).**[Sect 7.5.3]

7.8 The size of lesions should be carefully measured by the pathologist to the nearest mm on the haematoxylin and eosin slide, or on the fixed specimen when the largest dimension of the lesion cannot be reliably measured on the slide. Endoscopy measurements are less accurate and should only be used when strictly necessary, e.g. if the lesion is fragmented **(III - B)**. Given the small dimensions of the submucosal layer, infiltration into the submucosal level should be measured in microns from the bottom line of the muscularis mucosae **(VI - B).**[Sect 7.2.1; 7.6.3]

7.9 Programmes should have a policy on the methodology of, and should regularly monitor the accuracy of size measurements of endoscopically removed lesions. Deviation between the actual size and the measurements of pathologists and endoscopists should be minimised. Management decisions which depend on lesion size should take into account potential inaccuracy in the

[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.

size measurement. The multidisciplinary team should consider deviating from the recommended size categories in treatment and surveillance algorithms, if the review of a case indicates that there is sufficient reason to doubt the accuracy of the measurement. Such cases should be captured as an auditable outcome **(VI – B).**[Sect 7.2.1]

7.10 Hyperplastic polyps are non-neoplastic and their complete removal is optional. All other lesions in the serrated pathway should be excised and serrated lesions with neoplasia should be followed up (surveillance) as if they were adenomas **(VI- C).**[Sect 7.1; 7.2.4.4-5]

7.11 All biopsies and lesions identified in the screening programme and the subsequent resection specimen should be reported on a proforma **(IV - B)** in a timely manner and in a minimum of 90% of all cases. The proforma should be sent to the referring physician, the relevant cancer registry and the screening programme **(VI - B).**[Sect 7.6.5.2; 7.8]

7.12 Dissection of all specimens should be according to national guidelines. If national guidelines do not exist they should be created or adopted from elsewhere. An additional free text written report is optional, but must include all of the data required in the proforma **(VI - B).**[Sect 7.6.5.2]

7.13 The correlation between histological diagnosis of biopsy and surgical specimens should be reported. Any lack of correlation should be discussed by the multi-disciplinary team, and the results of this discussion should be documented **(III - B).**[Sect 7.8]

7.14 Pathologists must ensure that their proformas are received by the screening programme coordinators or a cancer registry for the purposes of clinical management, audit and quality assurance. Results from the key indicators of quality should be returned to the funding body: either the Health Authority or the national screening programmes' offices for analysis **(VI - B).**[Sect 7.8]

7.15 Statistics should include the frequency of colorectal cancer and the distribution of TNM stages and version used, as well as the distribution of the type of lesion, size, location, frequency of grades of neoplasia and villousness (villous, tubulo-villous or tubular) and presence of non-neoplastic lesions **(VI - B).**[Sect 7.8; 7.5.3.6]

7.16 There should be good communication between the members of the screening team with agreed terminology, regular meetings and clinical discussions **(VI - B).**[Sect 7.7]

7.17 Pathologists taking part in a colorectal cancer screening programme must participate regularly in multi-disciplinary team meetings, and twice a year in an external quality assurance programme that has external oversight of the results **(VI - B).**[Sect 7.6; 7.7]

7.18 Departments and individual pathologists should audit their own reporting practices for key features **(VI - B).**[Sect 7.7]

7.19 Pathologists reporting in a colorectal cancer screening programme must meet their national criteria for safety in reporting colorectal cancer **(VI - B).**[Sect 7.7]

7.20 Departments and pathologists taking part in screening programmes should audit the number of lymph nodes retrieved, the frequency of circumferential resection margin involvement and the frequency of high-risk features such as extramural vascular invasion, tumour perforation and peritoneal invasion reported **(VI - B).**[Sect 7.7]

7.21 Pathologists reporting in a colonoscopy screening programme should not report high-grade neoplasia in more than 5% of lesions and those in an FOBT programme in not more than 10% of lesions **(VI - B).**[Sect 7.7]

7.22 Pathologists should attend one refresher training course every year on the pathology of colorectal neoplasia to maintain quality **(VI - B).**[Sect 7.6]

7.23 Laboratories participating in a screening programme must be able to demonstrate participation in a laboratory technical external quality assurance programme and hold external accreditation for their services **(VI - C).**[Sect 7.7]

Further detailed information can be found in the annex to this chapter.

7.1 Introduction

The pathology service plays a very important role in colorectal cancer screening since the management of participants in the programme depends on the quality and accuracy of the diagnosis. Pathology affects the decision to undergo further local and/or a major resection as well as surveillance after screening. The adoption of formal screening programmes leads to improvement not only in the management of early but also advanced disease by the introduction of guidelines, quality standards, external quality assurance and audit. In screening programmes, the performance of individuals and programmes must be assessed and it is advantageous if common diagnostic standards are developed to ensure quality, recognise areas where sufficient evidence is still lacking, and initiate high-quality studies to answer these questions. The present chapter suggests practical guidelines for pathology within a colorectal screening programme. We have concentrated on the areas of clinical importance in the hope of standardising these across the European Union. In the associated annex we deal with some of the more difficult areas and suggest topics for future research. We have included guidelines for the reporting and management of resected specimens in an attempt to move towards agreed minimum European standards of pathology in these areas as well. This is the first edition of what will be a continuing process of revision as new data emerge on the pathology, screening and management of colorectal cancer. We hope to set minimum standards that will be followed in all programmes and to encourage the development of higher standards amongst the pathology community and screening programmes.

Many lesions are found within a screening programme some of which are of little or no relevance to the aim of lowering the burden of colorectal cancer in the population. The range of pathology differs between the different approaches, with faecal occult blood programmes yielding later, more advanced disease than flexible sigmoidoscopy and colonoscopy screening. Programme activities must focus on the identification and appropriate management of invasive colorectal cancer and its precursors. The management of pre-invasive lesions involves surveillance to allow the prevention of future disease, whereas management of adenocarcinoma focuses on immediate treatment and decisions on local removal, or radical surgery with the potential for operative mortality. Overuse of radical surgery must be avoided and recommendations for its use must be balanced with the risks to the patient.

There are a number of lesions, especially in the serrated pathway leading from hyperplastic polyps to other serrated lesions and in some cases to adenocarcinoma, that may be difficult to diagnose and for which knowledge of their natural history and clinical implications is limited (Snover et al. 2005). Further work is required in this area, but until we understand these lesions better it is recommended that all serrated lesions, with the exception of hyperplastic polyps, be fully removed **(V - B).**[Rec 7.10]

Few data were present in the literature on this issue. This paucity of data is caused in part by a lack of standardisation in terminology and limited observer agreement. Furthermore, a lack of prospective studies precludes a clear indication of the optimal treatment and surveillance strategy for lesions in the serrated pathway. For more information, see the annex to this chapter. The screening programme will also identify other non-serrated neoplastic and non-neoplastic lesions and provide important data on such conditions.

7.2 Classification of lesions in the adenoma-carcinoma sequence

A colorectal adenoma is defined as a lesion in the colon or rectum containing unequivocal epithelial neoplasia. Classification of adenomas should include grading of neoplasia according to the revised Vienna classification that has been modified for the European Guidelines to obtain a two-tiered system of low-grade and high-grade neoplasia (Table 7.1); see also Kudo et al. (2008). This modified grading system aims to minimise intra- and inter-observer variation and facilitate management of endoscopically detected lesions by improving correlation between histopathology of biopsies and resection specimens (Tominaga et al. 2009). Classically, adenomas are divided into tubular, tubulo-villous or villous types and demarcation between the three is based on the relative proportions of tubular and villous components, according to the "20% rule" described in the WHO classification of tumours in the digestive tract (WHO 2000). At least 20% of the estimated volume of an adenoma should be villous to be classified as a tubulo-villous adenoma and 80% villous to be defined as a villous adenoma. All other lesions are classified as tubular (WHO 2000) **(VI - A).**[Rec 7.4] The reproducibility of villousness increases when collapsing the categories into only two: tubular vs. any villous component (i.e. anything >20% villous). Adenomas can be endoscopically polypoid, flat or depressed. Due to the increased risk of colorectal cancer associated with flat and/or depressed lesions **(III)** they should be reported as non-polypoid lesions (see Sect. 7.2.3). The Paris endoscopic classification of superficial neoplastic lesions should be used to describe the gross appearance of colorectal adenomas **(V - B).**[Rec 7.5] Key features to report in a programme are size, villousness, the grading of neoplasia, the recognition of invasion and features suggesting the need for further intervention either local or radical. The size of adenomas is important for their risk of containing an adenocarcinoma but it is also related to the need for subsequent surveillance, or colonoscopy.

The two-tiered grading of mucosal colorectal neoplasia recommended in the European Guidelines (see Table 7.1) is based on the revised Vienna Classification that has improved diagnostic reproducibility, particularly for non-polypoid lesions (Schlemper et al. 2000; Schlemper, Kato & Stolte 2001; Dixon 2002; Stolte 2003; Suzuki et al. 2006) **(IV - B).**[Rec 7.1] The recommended two-tiered grading system also permits translation of histopathology findings of Western and Japanese pathologists into a uniform system for classification of colorectal neoplastic lesions.

In screening programmes the use of the term advanced adenoma has developed and is sometimes used to categorise adenomas for management. In this context an advanced adenoma is one that is either ≥10 mm or contains high-grade mucosal neoplasia or a villous component.

The hyperplastic polyp must be distinguished from other serrated lesions due to its extremely low malignant potential. The significance of other lesions in the serrated spectrum is controversial and our knowledge is still developing; traditional serrated adenomas and mixed polyps with neoplasia should be considered as adenomas for the purpose of follow-up (surveillance). More details are provided in the annex.

7.2.1 Measurement of size of adenomas

Size (largest diameter) is an important objective measurement best performed by the pathologist (Schoen, Gerber & Margulies 1997) from the slide, as is recommended in the EU Guidelines for breast cancer screening (EC Working Group on Breast Screening Pathology 2006). Endoscopy measurements are less accurate and should only be used when strictly necessary **(III - B)**.[Rec 7.8] Pathology meas-

urements are auditable, accurate, simple to perform and able to assess the size of the adenomatous component of mixed lesions. Although the quality of evidence is low, there are some indications that different modalities of advanced adenoma measurement (endoscopic measurement vs. pathologist's measurement before and after fixation, slide preparation) can affect diagnostic reproducibility and the detection rate of advanced adenomas. An overestimation or underestimation of a large or a small polyp is important when the misjudgement crosses the 10 mm threshold. It seems that the use of the pathologist's measurement is currently the most accurate. If the lesion is too large for the maximum dimension to be measured by this method, because it cannot be represented on a single slide, the measurements taken at the time of specimen dissection should be used. If a biopsy is received or the specimen is fragmented it should be stated that it cannot be accurately assessed for size by the pathologist and the endoscopy measurements should be used. Measurements should exclude the stalk if it is composed of normal mucosa however the distance to the excision margin should be noted. The size of adenomas is used to determine the need for surveillance and therefore must be measured accurately to the nearest millimetre (and not rounded-up to the nearest 5 or 10 mm). Where the lesion is mixed or only part of a lesion is adenomatous, measurement should be performed on the adenomatous component.

Programmes should have a policy on the methodology of, and should regularly monitor the accuracy of size measurements of endoscopically removed lesions. Deviation between the actual size and the measurements of pathologists and endoscopists should be minimised. Management decisions that depend on lesion size should take into account potential inaccuracy in the size measurement. The multidisciplinary team should consider deviating from the recommended size categories in treatment and surveillance algorithms, if the review of a case indicates that there is sufficient reason to doubt the accuracy of the measurement. Such cases should be captured as an auditable outcome **(VI - B).**[Rec 7.9]

7.2.2 Tubular, tubulo-villous and villous adenomas: the typing of villousness

The 20% rule only applies to wholly excised polyps and to intact sections of lesions large enough to provide reliable proportions. For small fragmented lesions or superficial polyp biopsies, the presence of at least one clearly identifiable villus merits classification as “at least tubulo-villous”. Definitions of the types of villousness are presented in the annex.

7.2.3 Non-polypoid adenomas

The role of the pathologist in the evaluation of non-polypoid adenomas is to confirm the adenomatous nature of the lesion, and to determine the grade of neoplasia as well as the depth of depression in the case of a depressed non-polypoid lesion (see below). Since the expression “flat adenoma” is not well defined it is recommended to group together all adenomatous lesions other than polypoid into the category of “non-polypoid adenomas” and avoid the term “flat”. Non-polypoid adenomas correspond to an endoscopical diagnosis of neoplasia in the subtypes IIa, IIb and IIc according to the Paris classification. Completely flat adenomas (type IIb) and depressed lesions (type IIc) are rarely found in the colon and rectum, while slightly elevated lesions (type IIa) are frequent. In the literature, the height of non-polypoid adenomas has been described histologically as not exceeding twice the height of normal mucosa, thus measuring less than 3 mm in height. This definition may be difficult to apply due to fixation artefacts and in slightly depressed lesions since the adjacent mucosa may be thinner than the normal epithelium. The endoscopic diagnosis of a non-polypoid lesion should be reported according to the Paris classification (The Paris Classification 2003; Suzuki et al. 2006; Kudo et al. 2008; Soetikno et al. 2008) **(III - B).**[Rec 7.5] We were unable to retrieve studies that specifically address the

topic of the differences in the detection rates of non-polypoid colorectal neoplasms among the different types of screening programmes (FOBT vs. FS vs. TC), although a prevalence of 9–10% of non-polypoid colorectal neoplasm (flat and depressed) was recently reported by Western pathologists in a large cross-sectional study (Soetikno et al. 2008). Depressed lesions (type IIc) should be mentioned in the histological report for clinico-pathological correlation. Special care should be taken for centrally depressed lesions, especially when the depression is deeper than half of the adjacent lesion. These are reported to have a higher frequency of high-grade neoplasia and invasion at a smaller size than other flat or depressed lesions (Kudo et al. 2008). Non-polypoid adenomas can show so-called lateral spread with poor delineation of the margins thus making endoscopic removal difficult.

7.2.4 Serrated lesions

7.2.4.1 Terminology

These lesions have in common a serrated morphology, but depending on other characteristics, the potential to develop into invasive adenocarcinoma differs considerably. Serrated lesions vary from the *hyperplastic polyp*, which although relatively common, has no implications for the screening programme unless very numerous, proximally located or of a large size (>10 mm), to *sessile serrated lesions* (sometimes referred to as *sessile serrated polyps/sessile serrated adenomas*), *traditional serrated adenomas*, or *mixed lesions/mixed polyps*. Serrated lesions are infrequent, the evidence base is poor and recommendations are not well established, but until further evidence is forthcoming we recommend the following:

7.2.4.2 Hyperplastic (metaplastic) polyp

Hyperplastic polyps (HPs) are often small lesions (<5 mm in diameter), frequently found in the left (distal) colon. They are composed of simple elongated crypts with a serrated structure in the upper half. These polyps usually show some proliferation in the basal (non-serrated) part of the crypts (regular proliferation). Nuclei are small, regular and basally orientated. There is no hyperchromasia, and stratification of the upper half of the crypts has a serrated appearance without cytological atypia.

Hyperplastic polyposis should be excluded in cases with giant hyperplastic polyps (>10 mm), or multiple hyperplastic polyps in the right colon, or in first-degree relatives of individuals with hyperplastic polyposis.

7.2.4.3 Sessile serrated lesions

We recommend the use of the term sessile serrated lesion (SSL) for serrated lesions with structural alterations that do not show mucosal neoplasia. This term should replace the use of sessile serrated polyp and sessile serrated adenomas until better definitions are created.[2] It is not recommended to use the latter terms in screening programmes because it would add additional ill-defined categories that may confuse practitioners.

[2] The term *sessile serrated polyp* has been proposed elsewhere for serrated lesions that cannot be definitely classified into the category of *hyperplastic polyps* or *serrated adenomas* (Snover et al. 2005), especially in cases with technical inconsistencies such as tangential cuts or superficial biopsies. The same terminology has been propsed for lesions with minimal and focal structural alterations in the absence of cytological atypia (Torlakovic et al. 2008).

7.2.4.4 Traditional serrated adenomas

If the lesion shows a serrated morphology as well as mucosal neoplasia (cytological abnormalities), it is considered to be a traditional serrated adenoma (TSA) (Longacre & Fenoglio-Preiser 1990). It should be reported as such (TSA) and treatment and surveillance should be the same as for adenomas. See annex and Chapter 9 for details. This pragmatic recommendation recognises the neoplastic nature of these lesions. The non-serrated features found in such lesions (e.g. size and grade of neoplasia) and any co-existing pathology (e.g. number of neoplastic lesions) should be taken into account in selecting an appropriate surveillance protocol **(VI - C).**[Rec 7.10]

7.2.4.5 Mixed polyp

These are lesions with combinations of more than one histopathologic type in the serrated spectrum (hyperplastic polyps, sessile serrated lesions, traditional serrated adenomas) or at least one type in combination with adenoma (Jass et al. 2006). The important feature to recognise for the screening programme is the presence of neoplasia. The respective types of lesion in a mixed polyp should be reported and the term "mixed polyp" should only be used in brackets after the diagnosis of the individual components (e.g. adenoma and hyperplastic polyp, or traditional serrated adenoma plus adenoma). Mixed polyps should be completely removed. If there is an adenomatous component, the lesion should be followed up (surveillance) in the same manner as for adenomas, taking into account the size and the grade of the adenomatous component. **(VI - C).**[Rec 7.10]

7.3 Grading of neoplasia

The revised Vienna classification has been adopted here, but in a simplified form suitable for screening and diagnosis, by removing the indefinite category between "negative for neoplasia" and "low-grade neoplasia". This category has no clinical value and unlike inflammatory bowel disease is likely to be chosen very infrequently. Excluding it reduces the number of categories and simplifies the subsequent management choices. The advantages of the revised Vienna Classification on which the European screening classification is based are that it improves diagnostic reproducibility (Schlemper et al. 2000; Dixon 2002; Stolte 2003; Suzuki et al. 2006) **(IV - B).** The modified format with a two-tiered grading of mucosal colorectal neoplasia aims to further reduce inter-observer variation (Fenger et al. 1990) **(V - B).**[Rec 7.1] It encompasses the diagnostic categories used in the Eastern and the Western schools and each level has a clinical consequence. In the revised Vienna classification the term neoplasia is used which is synonymous with the formerly used term "dysplasia". In the two-tiered grading system recommended in the European Guidelines, mucosal low-grade neoplasia corresponds to neoplasia of the same grade in the revised Vienna classification; mucosal high-grade neoplasia likewise corresponds to neoplasia of the same grade in the revised Vienna classification. Invasive submucosal neoplasia in the European classification corresponds to carcinoma invading the submucosa or beyond in the Vienna classification (see Table 7.1).

7.3.1 Low-grade neoplasia

Low-grade neoplasia is an unequivocal neoplastic condition confined to the epithelial glands. It should not be mistaken for inflammatory or regenerative changes. Alterations characteristic for low-grade

neoplasia start from one gland and develop into a microadenoma that then grows to become macroscopically visible. Caution should be exercised in patients with chronic inflammatory bowel disease where the diagnosis of a neoplastic sporadic adenoma has implications different from that of neoplasia in colitic mucosa.

7.3.2 High-grade neoplasia

The changes of high-grade neoplasia should involve more than just one or two glands (except in tiny biopsies of polyps), and should therefore be identifiable at low-power examination. Caution should be exercised in over-interpreting isolated surface changes that may be due to trauma, erosion or prolapse.

Table 7.1: Adaptation of the revised Vienna classification[1] for colorectal cancer screening

1. NO NEOPLASIA:[2]
Vienna Category 1 (Negative for neoplasia)

2. MUCOSAL LOW GRADE NEOPLASIA:
Vienna Category 3 (Mucosal low-grade neoplasia
Low-grade adenoma
Low-grade dysplasia);
Other common terminology
mild and moderate dysplasia;
WHO: low-grade intra-epithelial neoplasia

3. MUCOSAL HIGH GRADE NEOPLASIA:
Vienna: Category 4.1–4.4 (Mucosal high grade neoplasia
High-grade adenoma/dysplasia
Non-invasive carcinoma (carcinoma *in situ*)
Suspicious for invasive carcinoma
Intramucosal carcinoma);
Other common terminology
severe dysplasia;
high-grade intraepithelial neoplasia;
WHO: high-grade intraepithelial neoplasia
TNM: pTis

4. CARCINOMA invading the submucosa or beyond:
4a. Carcinoma confined to submucosa
Vienna: Category 5 (Submucosal invasion by carcinoma);
TNM: pT1
4b. Carcinoma beyond submucosa
TNM: pT2-T4

[1] For revised Vienna classification see Dixon (2002), for WHO classification see WHO (2000), for TNM see (TNM classification of malignant tumours, 5th edition 1997; TNM Classification of malignant tumours, 6th edition 2002; TNM Classification of Malignant Tumours, 7th edition 2009).

[2] Category 2 of the Vienna Classification (indefinite) is not recommended for screening.

High-grade neoplasia is diagnosed on structure, supplemented by an appropriate cytology. Hence its presence is nearly always suspected by the low-power appearances where complex structural abnor-

malities are present in structures whose epithelium looks thick, blue, disorganised and with focal cell debris and necrosis.[3] The structural features are:

- complex glandular crowding and irregularity (note that the word "complex" is important and excludes simple crowding of regular tubules that might result from crushing);
- prominent glandular budding;
- a cribriform appearance and "back to back" glands; and
- prominent intraluminal papillary tufting.

While many of these features often co-exist in high-grade neoplasia, individually they are neither necessary nor usually sufficient. Indeed they may occasionally occur in lower grades of neoplasia and that is why it is necessary to further scrutinise the cytological features for signs of high-grade neoplasia. The cytological features of high-grade neoplasia are:

- loss of cell polarity or nuclear stratification. High-grade neoplasia should show at least 2–5 nuclear rows and preferably a variable number of rows within individual glands. The nuclei are haphazardly distributed within all three thirds of the height of the epithelium. No maturation of the epithelium is seen towards the luminal surface;
- neoplastic goblet cells (retronuclear/dystrophic goblet cells);
- cytology includes vesicular or/and irregular round nuclei with loss of polarity whereas spindle-like palisading nuclei are a sign of low-grade intraepithelial neoplasia;
- markedly enlarged nuclei, often with a dispersed chromatin pattern and a prominent nucleolus;
- atypical mitotic figures; and
- prominent apoptosis, focal cell debris and necrosis.

Again, these features usually coexist in high-grade neoplasia, and caution must be exercised in using just one. It should be emphasised again that they should occur in a background of complex structural abnormality. Marked loss of polarity and nuclear stratification sometimes occurs on the surface of small, structurally regular, tubular adenomas that otherwise have a lower grade of neoplasia, probably as a result of trauma, and must not be used to classify a lesion as high grade. The only exception to the rule is when the specimen consists of just a small biopsy from a polyp, when there is insufficient tissue to assess the architecture properly. In this situation it is permissible to label florid cytological abnormalities alone as high-grade neoplasia, but this will usually lead to re-excision of the whole polyp, when it will be possible to assess the whole lesion properly.

Also included within high-grade neoplasia is the presence of definite invasion into the lamina propria of the mucosa but not invasion through the mucscularis mucosae.

[3] High-grade neoplasia also contains the subgroup of intramucosal carcinoma used by some pathologists but not recommended here. For details see the annex.

7.4 Other lesions

7.4.1 Inflammatory polyps

Experience from United Kingdom pilot sites has shown that inflammatory-type polyps are relatively common. Whilst they are most usually seen as a complication of chronic inflammatory bowel disease, particularly ulcerative colitis, they are also seen in association with diverticulosis, mucosal prolapse and at the site of ureterosigmoidostomy. Furthermore, sporadic, single inflammatory-type polyps (inflammatory cap polyp, cloacogenic inflammatory polyp, myoglandular polyp, granulation tissue polyp etc.) are well described in the colorectum. As the reporting pathologist may not know the true context of such polyps, we recommend that all such polyps be classified as “post inflammatory polyp”. The term inflammatory pseudopolyp (or even just “pseudopolyp”) should be avoided. Biopsies with mucosal prolapse syndrome should be identified and reported as such and not as neoplastic conditions.

7.4.2 Juvenile polyps

Juvenile polyps are spherical in shape, show an excess of lamina propria, and have cystically dilated glands. The expanded lamina propria shows oedema and mixed inflammatory cells. Experience from the UK faecal occult blood pilot sites suggests that occasional juvenile-type polyps are identified, even in the screening age group (Jass et al. 1988). Juvenile polyps are most common in children but occasional examples are seen in adults. We advise that any polyp showing juvenile polyp-type features should be classified as “juvenile polyp” for the purposes of diagnostic reporting in a screening programme. Juvenile polyps often show epithelial hyperplasia but neoplasia is very rare. Single sporadic juvenile polyps have a smooth surface, can be found in all age groups and often are eroded. So-called “atypical juvenile polyps” show different morphological features, with a multilobated architecture, intact surface mucosa and (usually) a much more pronounced epithelial component. They are a characteristic feature of juvenile polyposis (JP).

7.4.3 Peutz-Jeghers polyps

Whilst these polyps are usually seen in the Peutz-Jeghers syndrome, occasional examples are demonstrated as single, sporadic polyps in the colon. There remains uncertainty as to whether “inflammatory myoglandular polyp” represents a similar entity. As with juvenile polyposis, it would seem most unlikely, given the rarity of the syndrome and the age of the screening population, that Peutz-Jeghers syndrome would be diagnosed as part of a screening programme. Although Peutz-Jeghers polyps are classified as hamartomas, they have a very organised structure. They have a central core of smooth muscle with conspicuous branching, each branch being covered by colorectal-type mucosa that appears hyperplastic but not neoplastic. As with sporadic juvenile polyps, solitary Peutz-Jeghers-type polyps are most unlikely to demonstrate foci of neoplasia.

7.4.4 Serrated (hyperplastic) polyposis

This condition is characterised by one or more of the following conditions (Burt & Jass 2000):

- At least 5 histologically diagnosed serrated polyps proximal to the sigmoid colon, of which 2 are >10 mm;
- Any number of serrated polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with hyperplastic polyposis; and/or
- More than 30 serrated polyps of any size, but distributed throughout the colon.

As mentioned in Section 7.2.4.2, hyperplastic polyposis should be excluded in cases with giant hyperplastic polyps (>10 mm), hyperplastic polyps in the right colon or in first-degree relatives of individuals with hyperplastic polyposis.

7.4.5 Cronkhite-Canada syndrome

We believe it is most unlikely that such cases will present via a screening programme and the true diagnosis may not be recognised by pathological assessment. However if Cronkhite-Canada syndrome is suspected, the pathologist should contact the endoscopist and ask for clinical details to ensure the diagnosis.

7.4.6 Neuroendocrine tumour

It is recommended to use the term “neuroendocrine tumour” rather than carcinoid in accordance with the WHO classification. These lesions are usually benign, small lesions and do not give rise to diagnostic difficulty.

7.4.7 Colorectal intramucosal tumours with epithelial entrapment and surface serration

Entrapment and pseudoinvasion of glands into the submucosal layer must be distinguished from invasive carcinoma. If in doubt, the relevant findings should be stated in the written report. If evaluation is problematic, step sections, a second opinion and further biopsies from the polypectomy ulcer should be considered.

7.4.8 Non epithelial polyps

- Lipoma
- Leiomyoma of the muscularis mucosae
- Ganglioneuroma
- Gastrointestinal schwannoma
- Neurofibroma

- GIST
- Various forms of vascular tumour
- Perineurioma
- Fibroblastic polyp
- Epithelioid nerve sheath tumour
- Inflammatory fibroid polyp

7.5 Assessment of the degree of invasion of pT1 colorectal cancer

pT1 cancers are those showing invasion through the muscularis mucosae into the submucosa but not into the muscularis propria.

7.5.1 Definition of invasion

We recommend the use of the WHO definition (WHO 1989; WHO 2000) of an adenocarcinoma as **an invasion of neoplastic cells through the muscularis mucosae into the submucosa (VI- A).**[Rec 7.2] The term intramucosal carcinoma should be substituted by mucosal high-grade neoplasia according to the WHO classification and the modified classification of neoplasia recommended in the European Guidelines based on the revised Vienna classification (see Table 7.1). We recognise that this will not allow detailed comparison with Japanese series where, contrary to the previous US and European literature, a diagnosis of carcinoma can be made on cases of neoplasia without submucosal invasion, or even on the basis of marked intraepithelial atypia. The TNM classification (TNM classification of malignant tumours, 5th edition 1997; TNM Classification of malignant tumours, 6th edition 2002; TNM Classification of Malignant Tumours, 7th edition 2009) allows carcinoma *in situ* (Tis) but this does not improve on the revised Vienna classification and should not be used. Please see annex for details **(VI - D).**[Rec 7.1]

Careful consideration should be given to the potential for surgical overtreatment of misclassified early T1 cancers. Screening programmes require explicit criteria for the diagnosis and staging of early adenocarcinoma because unnecessary radical resection will raise the morbidity and mortality in colorectal cancer screening programmes. Please see annex for further discussion of this point. Post-operative mortality (within 30 days) ranges between 0.6% and 4.4% in T1 cancers depending on the population, age of patient and quality of services available. Achieving the optimum balance between removing all disease by resection and minimising harm is very important.

7.5.2 Epithelial misplacement

Epithelial misplacement of adenomatous epithelium into the submucosa of a polyp is a well-recognised phenomenon (Muto, Bussey & Morson 1973). It is commonly seen in prolapsing polyps in the sigmoid colon. Experience suggests that this will be one of the most difficult areas of pathological diagnostic

practice in FOBT screening. Sigmoid colonic polyps are particularly prone to inflammation, a feature that tends to enhance the neoplastic changes present. When associated with epithelial misplacement, the potential for misdiagnosis of these lesions as early carcinoma become much greater. In cases of epithelial misplacement, surrounding lamina propria and haemosiderin-laden macrophages are found. Sub-mucosal mucinous lakes may be seen. These do not warrant an immediate diagnosis of invasion and must be interpreted in association with the surrounding features.

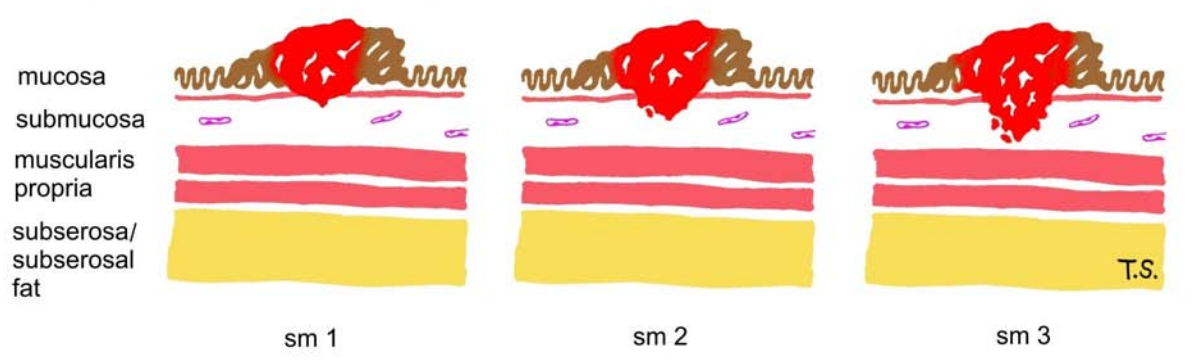
7.5.3 High risk pT1 adenocarcinoma

pT1 tumours provide many difficulties in a screening programme and the current evidence base for management of these lesions is poor and based on symptomatic patients (Coverlizza et al. 1989; Cooper et al. 1995; Volk et al. 1995; Blumberg et al. 1999; Hassan et al. 2005) **(V - B).**[Rec 7.7] With regard to the correlation between clinical outcomes and tumour pathology, a clear indication of an increased risk of residual disease, lymph-node metastasis, haematogenous metastasis and mortality was observed after endoscopic polypectomy and subsequent surgical resection of poorly differentiated tumours (i.e. tumours with incomplete excision, poor grade of histological differentiation, venous and lymphatic invasion, tumour budding). Some pathology features, such as tumour budding and lymphatic and venous invasion appeared as possible prognostic factors for increased risk of lymph node metastasis but a clear guideline cannot be drawn as this correlation was not statistically significant in all studies. The available methods for sub-staging and differentiation grading are shown below. The most appropriate method depends on the morphology of the lesion and depth of invasion, e.g. non-polypoid – Kikuchi levels, and polypoid - Haggitt levels. In the future more quantitative measurements should be investigated as suggested by the Japanese.

7.5.3.1 Sub-staging pT1

In pT1 tumours the frequency of lymph node metastasis in tumours that involve the superficial, middle and deep thirds of the submucosa, i.e. so-called Kikuchi levels sm1, sm2 and sm3 (Figure 7.1) (Kudo 1993; Kikuchi et al. 1995) has been reported to be 2%, 8% and 23%, respectively (Nascimbeni et al. 2002).

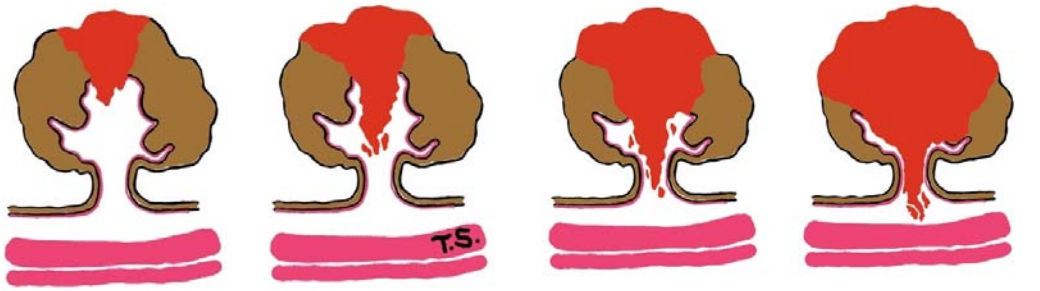
Figure 7.1: Kikuchi levels of submucosal infiltration modified from Nascimbeni et al. (2002)



In pedunculated polypoid lesions, Haggitt identified the level of invasion into the stalk of the polyp (Figure 7.2) as being important in predicting outcome and found that level 4 invasion, in which the tumour extended beyond the stalk of the polyp into the submucosa, but did not invade the muscularis propria, was an adverse factor (Haggitt et al. 1985).

However, both the Kikuchi (for non-polypoid tumours) and the Haggitt (for pedunculated tumours) systems may be difficult to use in practice, especially if there is fragmentation or suboptimal orientation of the tissue, and one study found lymph node metastases in 6/24 Haggitt level 3 lesions. More recently Ueno et al. (2004) have proposed use of the depth (>2000 µm) and width (>4000 µm) of invasion measured in microns beyond the muscularis mucosae provides a more objective assessment of lymph node metastatic potential (2.5% vs. 18.2% when submucosal invasion width is < or ≥4000 µm, respectively; and 3.9% vs. 17.1%, when submucosal invasion depth is < or ≥2000 µm, respectively; and this approach has been adopted in Japan. Each classification has advantages and disadvantages.

Figure 7.2: Haggitt levels of invasion in polypoid carcinomas



Level 1: invasion of the submucosa but limited to the head of the polyp

Level 2: invasion extending into the neck of polyp

Level 3: invasion into any part of the stalk

Level 4: invasion beyond the stalk but above the muscularis propria

Kikuchi cannot be used in the absence of muscularis propria; Haggitt is not applicable in non-polypoid lesions, and measurement depends on a recognisable submucosa from which to measure. In view of the uncertainty and lack of consensus, a firm evidence-based recommendation for one method of assessing local invasion cannot yet be made. At present we recommend the Kikuchi stage for non-polypoid lesions and Haggitt for pedunculated lesions **(VI - C)**. All three approaches must be evaluated in further large series from multiple programmes to derive adequately evidence-based recommendations.

7.5.3.2 Tumour grade in pT1 lesions

Poorly differentiated carcinomas are identified by the presence of either irregularly folded, distorted and often small tubules or the lack of any tubular formation and showing marked cytological pleomorphism. In the absence of good evidence we recommend that a grade of poor differentiation should be applied in a polyp cancer when ANY area of the lesion is considered to show poor differentiation. Poor differentiation should equate to the WHO categories of poor and undifferentiated tumours (Washington et al. 2009). The frequency should not exceed 20%. According to the WHO classification (WHO 1989), budding of the tumour cells at the front of invasion should not influence grading of the tumour. Please see annex for details.

7.5.3.3 Lymphovascular invasion in pT1 adenocarcinomas

Definite invasion of endothelium-lined vascular spaces in the submucosa is generally regarded as a significant risk for lymph node or distant metastasis. Sometimes retraction artefact around tumour aggregates can make assessment uncertain, in which case this uncertainty should be recorded and the observation should be interpreted in a multidisciplinary conference in the light of any other adverse

histological features. At the moment there are no consistent data available on the additional use of immunohistochemistry, but this might be helpful in distinguishing retraction artefacts from lymphatic (e.g. LEM D 2-40) or capillary spread (e.g. CD 34).

7.5.3.4 Margin involvement in pT1 adenocarcinomas

It is important to record whether the deep (basal) resection margin is involved by invasive tumour (that may be a reason for further surgery) and whether the lateral mucosal resection margin is involved by carcinoma or the pre-existing mucosal neoplasia (in which case a further local excision may be attempted) **(VI - B).**[Rec 7.6]

There has been considerable discussion and controversy in the literature over what degree of clearance might be regarded as acceptable in tumours that extend close to the deep submucosal margin (Cooper et al. 1998). It is important that clearance be measured and recorded in the report. All would agree that a clearance of 0 mm, and most would agree that a clearance of <1 mm is an indication for further therapy, others would use <2 mm. We currently recommend that clearance of 1 mm or less indicates margin involvement **(VI - B)**. However, this may be handled by removal of any residual polyp endoscopically.

7.5.3.5 Tumour cell budding in pT1 adenocarcinomas

Tumour cell budding, i.e., the presence of small islands or single infiltrating tumour cells at the front of tumour invasion, has been described in the Japanese literature as an unfavourable prognostic factor if present in a marked degree (Sakuragi et al. 2003; Ueno et al. 2004; Masaki et al. 2006). Budding has been assessed either as slight, moderate or marked; or as present/absent (Deinlein et al. 2003; Wang et al. 2005). However, its reproducibility has been criticised, the diagnostic criteria vary (Prall 2007) and the ability to predict metastasis compared to the previously discussed factors is unproven. Further research is needed in this area to identify the optimum method and its reproducibility before tumour cell budding can be recommended for routine use as an indicator of metastasis. Please see annex for details.

7.5.3.6 Site

The site of origin of each specimen should be individually identified by the clinician and provided to the pathologist on the request form **(VI - B).**[Rec 7.15] This should preferably include both the segment of the bowel and the distance in cm from the anus. The pathologist should record this information on the proforma. This is important as the risk of lymph node metastases from a T1 adenocarcinoma has been reported to vary depending on the site of the lesion (Okuyama, Oya & Ishikawa 2002).

7.6 Specimen handling

Specimen handling is an important issue, as poor handling and dissection procedures can impair diagnostic accuracy. Specimen handling starts with the endoscopic removal of the specimen and ends with the histopathological diagnosis and report. The need for a close relationship between endoscopists and histopathologists is stressed.

7.6.1 Submission of specimens

It is recommended to place specimens in separate containers, one for each lesion, to avoid confusion about exact location; if lesions are small, individual cassettes or multicassettes can be used. Biopsies from the same lesion can be placed in the same container. For endoscopic resections it is helpful to pin out specimens by inserting pins through the periphery of the specimen onto cork or thick paper. Too much tension on the specimen could result in artificially thinned lesions. Needles should not be placed directly through a lesion but at the margin. Besides patient data, an exact description on location should be provided (e.g. cms from anocutanous line), as well as size and morphology (stalked polyp, non-polypoid – Paris classification, etc.). Additional information about central depression or focal erosion or ulceration or coexistent chronic inflammatory bowel disease can be useful. Endoscopic pictures can also be submitted with the specimen(s).

7.6.2 Fixation

Fixation should be by buffered 10% formalin; this equals a roughly 4% paraformaldehyde concentration, as formalin is 30–40% paraformaldehyde. Specimen(s) can shrink due to formalin fixation, therefore measurements taken after fixation can differ from those prior to fixation. Fixation in alcohol is not recommended and if any other fixatives are used a comparative study of size of adenomas after fixation should be performed prior to use to avoid excessive shrinkage of adenomas to avoid under treatment.

7.6.3 Dissection

The pathologist should verify the complete removal of neoplastic lesions (clear margins) and the absence of submucosal invasion in biopsy specimens. Currently we recommend that clearance of 1 mm or less indicates margin involvement **(VI - B)**. Cases of incomplete removal or uncertainty about submucosal invasion should be highlighted in the pathology report **(VI - B).**[Rec 7.6] Lesion size should be given in millimetres. Size should be carefully measured identifying the maximum diameter of the adenomatous component as well as the distance to the margin of excision(s) to within a mm **(V - B).**[Rec 7.8]

Given the small dimensions of the submucosal layer, infiltration into the submucosal level should be measured in microns from the bottom line of the muscularis mucosae **(VI - B).**[Rec 7.8]

7.6.3.1 Polypoid lesions

Polyps must be sliced and totally embedded. Special attention should be paid to the resection margin, which should be identified and described (dot-like, broad, stalked, etc.) and either dissected tangentially into an extra cassette or sliced in a way that allows complete assessment.

7.6.3.2 Mucosal excisions

Mucosal excisions need to be pinned out on a cork board or on another suitable type of material, fixed, described and dissected allowing the identification of involvement of the deep and lateral surgical margins. Particular attention should be paid to any areas of ulceration or induration for signs of invasion. Inking margins is recommended.

7.6.3.3 Piecemeal removal

If it is possible to reconstruct a lesion removed piecemeal it may be helpful, but this is not commonly the case. It is good practice to embed the entire lesion to allow exclusion of invasive malignancy. Occasionally, whole embedding will not be possible.

7.6.4 Sectioning and levels

Three or more levels should be cut through each block and stained with haematoxylin and eosin.

7.6.5 Surgically-removed lesions

7.6.5.1 Classification

The staging of colorectal cancer can be undertaken by a number of different systems. The two used in Europe are TNM and the older Dukes classification. Originally the Dukes classification system placed patients into one of three categories (stages A, B, C) (see Table 7.2). This system was subsequently modified by dividing stage C into stage C1 and C2 and the addition of a fourth stage (D). More recently, the Union Internationale Contra le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) has introduced the TNM staging system, that places patients into one of four stages (Stage I-IV). TNM is superior to Dukes because of the greater information it yields, but there are currently major issues due to the periodic reclassification of this system that can lead to stage migration.

Table 7.2: Modified Dukes stage

Dukes A	Tumour penetrates into, but not through the muscularis propria (the muscular layer) of the bowel wall.
Dukes B	Tumour penetrates into and through the muscularis propria of the bowel wall but does not involve lymph nodes.
Dukes C	**C1**: There is pathological evidence of adenocarcinoma in one or more lymph nodes but not the highest node. **C2**: There is pathological evidence of adenocarcinoma in the lymph node at the high surgical tie.
Stage D	Tumour has spread to other organs (such as the liver, lung or bone).

TNM has a number of versions, so the version used should be noted in brackets (e.g. v5, v6, v7). Table 7.3 permits comparison of the most recent versions, 5, 6 and 7 (TNM classification of malignant tumours, 5th edition 1997; TNM Classification of malignant tumours, 6th edition 2002; TNM Classification of Malignant Tumours, 7th edition 2009). However, there are differences between the versions, particularly regarding the notes on T and N classification. There is also variation between countries as to the TNM classification used. For example, TNM 5 is recommended in the United Kingdom, Holland, Belgium and Denmark and is growing in popularity in other countries.

In the USA version 7 is used. TNM 7 appears to be more subjective than TNM 5 due to the notes on N classification and the category N1c, promoting stage migration from II to III (Quirke et al. 2007; Jass et al. 2008; Quirke et al. 2010). National results should be reported with the version of TNM used in a given country **(VI - B).**[Rec 7.3]

Table 7.3: TNM classification of tumours of the colon and rectum

T – Primary Tumour	Clinical Classification	5th Edition (1997)	6th Edition (2002)	7th Edition (2009)
TX	Primary tumour cannot be assessed	+	+	+
T0	No evidence of primary tumour	+	+	+
Tis[1]	Carcinoma in situ: intraepithelial or invasion of lamina propria	+	+	+
T1	Tumour invades submucosa	+	+	+
T2	Tumour invades muscularis propria	+	+	+
T3	Tumour invades through muscularis propria into subserosa or into non-peritonealised pericolic or perirectal tissues	+	+	+
T4[2,3]	Tumour directly invades into other organs or structures and/or perforates visceral peritoneum	+	+	+
T4a	Perforates visceral peritoneum	-	-	+
T4b	Directly invades other organ or structures	-	-	+
N – Regional Lymph Nodes				
NX	Regional lymph nodes cannot be assessed	+	+	+
N0	No regional lymph node metastasis	+	+	+
N1	Metastasis in 1 to 3 regional lymph nodes	+	+	+
N1a	1 node	-	-	+
N1b	2-3 nodes	-	-	+
N1c	Satellites[4] in subserosa, *without* regional nodes	-	-	+
N2	Metastasis in 4 or more regional lymph nodes	+	+	+
N2a	4-6 nodes	-	-	+
N2b	7 or more nodes	-	-	+
M – Distant Metastasis				
MX	Distant metastasis cannot be assessed	+	+	-
M0	No distant metastasis	+	+	+
M1	Distant metastasis	+	+	+
M1a	Metastasis confined to one organ (liver, lung, ovary, non-regional lymph node(s))	-	-	+
M1b	Metastasis in more than one organ or the peritoneum	-	-	+

	Stage Grouping					
Stage	**T- Tumour**	**N - Node**	**M - Metastasis**	**5th Edition (1997)**	**6th Edition (2002)**	**7th Edition (2009)**
Stage 0	Tis	N0	M0	+	+	+
Stage I	T1,T2	N0	M0	+	+	+
Stage II	T3,T4	N0	M0	-	-	+
Stage IIA	T3	N0	M0	+	+	+
Stage IIB	T4	N0	M0	+	+	-
Stage IIB	T4a	N0	M0	-	-	+
Stage IIC	T4b	N0	M0	-	-	+
Stage III	Any T	N1,N2	M0	-	-	+
Stage IIIA	T1,T2	N1	M0	+	+	+

	Stage Grouping, cont'd					
Stage	**T- Tumour**	**N - Node**	**M - Metastasis**	**5th Edition (1997)**	**6th Edition (2002)**	**7th Edition (2009)**
Stage IIIA	T1,T2	N1c	M0	-	-	+
Stage IIIA	T1	N2a	M0	-	-	+
Stage IIIB	T3,T4	N1	M0	+	+	-
Stage IIIB	T3,T4a	N1/N1c	M0	-	-	+
Stage IIIB	T2,T3	N2a	M0	-	-	+
Stage IIIB	T1,T2	N2b	M0	-	-	+
Stage IIIC	Any T	N2	M0	+	+	-
Stage IIIC	T4a	N2a	M0	-	-	+
Stage IIIC	T3,T4a	N2b	M0	-	-	+
Stage IIIC	T4b	N1,N2	M0	-	-	+
Stage IV	Any T	Any N	M1	+	+	-
Stage IVA	Any T	Any N	M1a	-	-	+
Stage IVB	Any T	Any N	M1b	-	-	+

	Notes		
No.	**5th Edition**	**6th Edition**	**7th Edition**
1	Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or lamina propria (intramucosal) with no extension through muscularis mucosae into the submucosa. (Note: the authors of the European Guidelines for quality assurance in pathology in CRC screening and diagnosis recommend not using this category. Respective lesions should be reported as mucosal high-grade neoplasia, see Section 7.3.)		
2	Direct invasion in T4 includes invasion of other segments of the colon or rectum by way of the serosa, e.g. invasion of sigmoid colon by a carcinoma of the cecum.		Direct invasion in T4b includes invasion of other organs or segments of the colon or rectum by way of the serosa, as confirmed on microscopic examination, or for tumours in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria
3		Tumour that is adherent to other organs or structures, macroscopically, is classified T4. However, if no tumour is present in the adhesion, microscopically, the classification should be pT3.	Tumour that is adherent to other organs or structures, macroscopically, is classified cT4b. However, if no tumour is present in the adhesion, microscopically, the classification should be pT1-T3, depending on the anatomical depth of wall invasion.
4	A tumour nodule greater than 3 mm in diameter in perirectal or pericolic adipose tissue without histological evidence of a residual lymph node in the nodule is classified as regional lymph node metastasis. However, a tumour nodule up to 3 mm in diameter is classified in the T category as discontinuous extension i.e. T3.	A tumour nodule in the pericolic/perirectal adipose tissue without histological evidence of a residual lymph node in the nodule is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour it should be classified in the T category and also coded as V1 (microscopic venous invasion) or V2, if it was grossly evident, because there is a strong likelihood that it represents venous invasion.	Tumour deposits (satellites), i.e. macroscopic or microscopic nests or nodules, in the pericolorectal adipose tissue's lymph drainage area of a primary carcinoma without histological evidence of residual lymph node in the nodule, may represent discontinuous spread, venous invasion with extra-vascular spread (V1/2) or a totally replaced lymph node (N1/2). If such deposits are observed with lesions that would otherwise be classified as T1 or T2, then the T classification is not changed, but the nodule is recorded as N1c. If a nodule is considered by the pathologist to be a totally replaced lymph node (generally having a smooth contour), it should be recorded as a positive lymph node and not as a satellite, and each nodule should be counted separately as a lymph node in the final pN determination. (Note of the authors of the European Guidelines for quality assurance in pathology in CRC screening and diagnosis: introduction of N1c category leads to stage shift from II to III for some tumours)

7.6.5.2 Practical issues

High-quality reporting of colorectal cancer is very important both to the clinicians treating the patients and to the cancer registry. The introduction of a 'minimum' data proforma template allows more complete reporting compared with interpretation of free text reports by medical staff (Quirke & Williams 1998; Cross, Feeley & Angel 1998; Rigby et al. 1999; Branston et al. 2002; Oppong et al. 2002; Beattie et al. 2003; Wei et al. 2004; Eon et al. 2006). All biopsies and lesions identified in the screening programme and the subsequent resection specimens should be reported on a paper or electronic proforma **(II - B)** in a timely manner and in a minimum of 90% of all cases. The proforma should be sent to the referring physician, the relevant cancer registry and the screening programme **(VI - B).** Rec 7.11

Dissection should be according to national guidelines such as those for the United Kingdom; Royal College of Pathologists (Williams, Quirke & Shepherd 2007a; Williams, Quirke & Shepherd 2007b; Williams, Quirke & Shepherd 2007c) and the NHS Bowel Cancer Screening publication (NHS Bowel Cancer Screening Programme 2007), the Scottish clinical guidelines (SIGN 2003), the Dutch guidelines (Vereniging integrale kankercentra 2008a; Vereniging integrale kankercentra 2008b), the German guidelines (Schmiegel et al. 2008), or the Italian guidelines (Risio et al. 2006). For examples of these guidelines see the list of websites in Appendix 4 of the full Guidelines document. If national guidelines do not exist they should be created or adopted from elsewhere **(VI - B)**. An additional free text written report is optional, but needs to include all of the data required in the proforma **(VI - B).** Rec 7.12

Pathologists need access to a high-quality, binocular microscope with at least the following objectives: 5x, 10x, 20x and 40x and that fulfils national guidelines such as those of the Sector Committee for Pathology and Neuropathology of the German Accreditation Body (DAP-TM-30 2007).

A computer is required for identifying previous material from a given patient and for filling in proformas electronically and online if secure online services are available. Adequate time must be available for dissection, reporting, and attendance at meetings of the screening team and the colorectal cancer multidisciplinary team **(VI - B).** Rec 7.17 Time and funding are required for pathologists to attend national meetings on the screening programme and continued training in histopathology of colorectal neoplasia. Pathologists should attend one refresher training course every year on the pathology of colorectal neoplasia to maintain quality. **(VI - B).** Rec 7.22

7.7 Standards and quality indicators

There should be good communication between members of the screening team with agreed terminology, regular meetings and clinical discussions **(VI - B).** Rec 7.16

An external quality assurance programme should be put in place, specifying a minimum of two slide circulations per year of an adequate number of slides **(VI - B).** Rec 7.17 This may be via clusters or cells of pathologists using glass slides, or can be electronic using images or virtual slides (Risio et al. 2010) distributed via DVD or the web (see http://www.virtualpathology.leeds.ac.uk). There should be external oversight of such programmes. In the absence of evidence-based guidelines we recommend that pathologists reporting in a colonoscopy programme should not report high-grade neoplasia in more than 5% of lesions and those in an FOBT programme in not more than 10% of lesions **(VI - B).** Rec 7.21

The pathologists reporting in the programme must meet their national criteria for safety in reporting colorectal cancer **(VI - B).**[Rec 7.19] Departments and pathologists taking part in screening programmes should audit their own reporting practices for key features, including the number of lymph nodes retrieved, the frequency of circumferential resection margin involvement (CRM) and the frequency of high-risk features such as extramural vascular invasion and peritoneal invasion reported **(VI - B).**[Rec 7.18, 7.20] In the UK, national standards suggest that the number of nodes retrieved should be above a median of 12, CRM positivity in rectal cancer should be below 15%, extramural vascular invasion reported in more than 25%, and peritoneal invasion in more than 20%. The laboratory must be able to demonstrate participation in a laboratory technical external quality assurance programme, such as Clinical Pathology Accreditation UK (http://www.cpa-uk.co.uk/), the ISO/IEC accreditation developed by the Sector Committee for Pathology and Neuropathology of the German Accreditation Body (http://www.dakks.de/, see also Rocken & Manke (2010)), or other national standards **(VI - C).** [Rec 7.23]

7.8 Data collection and monitoring

Lesions reported in the screening programme should be reported by proforma **(II - B)** or structured reporting, and the data returned to the screening programme or national tumour registries. This will include all lesions identified and the subsequent resection specimen. This should occur in a minimum of 90% of all cases **(VI - B).**[Rec 7.11]

Studies have shown discrepancy between the histopathology of biopsies and total removal by polypectomy, EMR and surgical specimens. Colorectal cancer was detected in surgical specimens in over 20% of biopsies diagnosed with high-grade neoplasia (Gondal et al. 2005). Sub-mucosal invasion was detected in surgical specimens in over 25% of cases with mucosal neoplasia (Tominaga et al. 2009). Therefore the correlation between histological diagnosis of biopsies and resections should be reported. Any lack of correlation should be discussed by the multi-disciplinary team and the results of this discussion should be documented **(III - B).**[Rec 7.13]

Pathologists must ensure that their proformas are received by the screening programme coordinators or a cancer registry for the purposes of clinical management, audit and quality assurance **(VI - B).** [Rec 7.14]

Results from the key indicators of quality should be returned for analysis to the funding body: either the Health Authority or the national screening programme's offices **(VI - B).**[Rec 7.14]

Statistics should include the frequency of colorectal cancer and the distribution of TNM stages and version used; as well as the distribution of the type of lesion, size, location, frequency of grades of dysplasia and villousness (villous, tubulo-villous or tubular) and presence of non-neoplastic lesions. **(VI - B).**[Rec 7.15]

7.9 Images

A selection of images and digital slides showing the histopathology of lesions commonly detected in screening programmes, as well as some images illustrating pitfalls in histopathologic interpretation is provided in the internet at http://www.virtualpathology.leeds.ac.uk (go to: “European Guidelines for quality assurance in pathology in colorectal cancer screening and diagnosis - Imaging library”). The site has been created to establish an initial, quality-assured repository for images illustrating the present chapter. The images are provided for reference and have been reviewed by pathologists from at least three European countries. We encourage colleagues to submit further images which they feel could be instructive or otherwise useful in illustrating or further developing the European Guidelines.

We also aim to extend the scope of this site in the future to promote pan-European and international collaboration in training and in expanding the evidence base for further advances in colorectal cancer screening and diagnosis.

7.10 References

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Annex

Annotations of colorectal lesions

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7A.1 Introduction

European Guidelines for quality assurance of pathology in colorectal cancer screening and diagnosis should provide multidisciplinary standards and best practice recommendations that can be implemented routinely across the EU. The authors therefore chose to limit the scope of Chapter 7 and to describe in greater detail in an annex some issues raised in the chapter, particularly details of special interest to pathologists. We also felt that an annex would be the appropriate place to point out new insights not yet widely adopted in Europe in routine practice that may be included in future updates of the Guidelines.

7A.2 Grading of neoplasia

In the present Guidelines, a classification system for colorectal neoplasia has been recommended based on a modified version of the revised Vienna classification (Section 7A.3). For readers not yet familiar with the Vienna classification, it may be helpful to note that it is the first classification to include a clinical recommendation for each neoplastic category. Furthermore, the system was developed to improve diagnostic reproducibility in the interpretation of biopsy specimens and subsequent resection specimens (Schlemper, Kato & Stolte 2000; Schlemper et al. 2000; Schlemper, Kato & Stolte 2001). Strictly speaking, the Vienna classification is only valid for biopsy specimens, since a clinical recommendation should follow. However, to avoid diagnostic inconsistencies, the Vienna classification can be used for resection specimens as well.

In the Vienna classification and hence in the European Guidelines, the term *neoplasia* rather than *dysplasia* is used to refer to epithelial tumours associated with chronic inflammatory diseases. Whereas the Vienna classification differentiates between strictly intraepithelial lesions and those involving the lamina propria, the European Guidelines only refer to *mucosal neoplasia* that may or may not involve the lamina propria (see Section 7A.3). More importantly, the EU Guidelines recommend a two-tiered grading of mucosal neoplasia. The pathologist must decide whether a neoplastic mucosal lesion can be categorised as low or as high grade; for criteria, see Table 7A.1.

As always in neoplasia, the lesion should reach the mucosal surface (no epithelial maturation). Undermining edges of an adjacent carcinoma should be excluded.

The criteria in Table 7A.1 can be weighted. The most important criteria for the diagnosis of carcinoma are the lateral expansion and the number of nuclear rows. In carcinoma, the number of nuclear rows should change within a single gland. High-grade neoplasia is diagnosed when the nuclear rows do not exceed 2–5 nuclei, and the glands do not show lateral expansion. Low-grade neoplasia is diagnosed when the nuclear rows do not exceed 2–3 nuclei (Wolber & Owen 1991; Ajioka et al. 1994; Ajioka et al. 2000).

In histopathology, the entity of carcinoma *in situ* is generally defined as carcinoma confined to the epithelial layer. In squamous epithelium such an entity can be readily diagnosed. In columnar epithelium, an analogous entity should theoretically also exist. However, to date there are no exact criteria that would permit diagnosis and that would enable the histopathologist to distinguish high-grade intraepithelial neoplasia from mucosal carcinoma that is invasive in the lamina propria. Therefore,

throughout the entire gastrointestinal tract, use of the term *carcinoma in situ* is not recommended for respective lesions in columnar epithelium. The term *intramucosal carcinoma* is widely introduced in the upper GI tract but not yet in the lower GI tract (see also Section 7A.4.5). We prefer the term mucosal neoplasia to intraepithelial neoplasia as high-grade dysplasia can contain epithelial neoplasia and invasion into the lamina propria according to the TNM classification.

Table 7A.1: Grading of gastrointestinal neoplasia

	Normal	**Low-grade mucosal / intraepithelial neoplasia (LGMN)**	**High-grade mucosal / intraepithelial neoplasia (HGMN)**	**Invasive Cancer**
Glands	non-branching	villous	branching, cribriform, irregular, solid	branching, cribriform, irregular, solid
Expansion	up/down	till surface	till surface	lateral expansion
Epithelial differentation	up/down	top-down and exceptional down-top	no maturation towards surface	
Goblet cells	+ +	(+)	-/(+) retronuclear, atypic	
Nuclear rows	1	2–3	2–5	changing
Nuclear size	small, basal	palisading	enlarged	vesicular
Chromatin	few	+	+ +	+ + / + + +
Nucleoli	none	none	few small	several/ prominent

Modified from (Borchard et al. 1991; Borchard 2000; Vieth & Stolte 2005)

7A.3 Classification of serrated lesions

7A.3.1 Terminology

The terminology is still under discussion. Serrated lesions can be regarded as a continuous spectrum of colorectal lesions with increasingly more pronounced serrated morphology starting with a *hyperplastic polyp* and progressing to *sessile serrated lesions* (*SSLs*, sometimes referred to as *sessile serrated adenomas* or *sessile serrated polyps*), *traditional serrated adenomas* (*TSA*), and leading, finally, to *adenocarcinoma*. Not only the adenomatous component but also other alterations associated with more pronounced serrated morphology may potentially progresses to cancer (see Table 7A.2).

The situation involving *sessile serrated lesions* is complicated as these lesions only reveal complex structural abnormalities, not adenomatous changes. Therefore, these lesions are neither adenomatous

nor are they neoplastic. This is why Kudo et al. (2008) and Lambert et al. (2009) recommended that these lesions no longer be called adenomas; instead they should be referred to as *sessile serrated lesions* (SSLs). Few of these lesions are reported to rapidly progress to invasive carcinoma, (Oono et al. 2009). Those few cases that do progress rapidly, particularly in the right colon, may be expected to appear more frequently as interval cancers. *Traditional serrated adenomas* (TSAs), unlike SSLs, do contain adenomatous alterations, albeit sometimes quite subtle (Longacre & Fenoglio-Preiser 1990); they are therefore termed correctly and treatment and surveillance should correspond to that of adenomas (see Chapters 8 and 9).

Due to the continuous spectrum in the serrated pathway to colorectal cancer, lesions with combinations of serrated morphology and adenomatous cytology can be observed. If more than one histopathologic type in the serrated spectrum (HP, SSL, TSA) is discernible in a given lesion, or at least one type in combination with adenomatous tissue, such lesions are referred to as *mixed polyps*.

The different histopathologic types (e.g. HP and SSL, SSL and TSA, adenoma and SSL, etc.) must be stated in the diagnosis.

Table 7A.2: Continuous spectrum of serrated lesions and possible combinations of histopathologic types. Every lesion can give rise to adenocarcinoma. Most of the adenocarcinomas are believed to derive from adenomatous components.

Lesion	Neoplasia	Risk of malignant transformation
Hyperplastic polyp	no	minimal
Sessile serrated lesion	no	slightly increased but exact data are missing (rapid transformation may be possible in a short time)
Traditional serrated adenoma	yes	increased and suggested worse prognosis than carcinomas arising in sessile serrated lesions
Mixed polyp	yes	increased, but exact data are not available
Adenoma (tubular, villous)	yes	increased, 17 years on average

7A.3.2 Hyperplastic polyp

Hyperplastic polyps (HPs) are composed of elongated crypts (no complex architecture) with serrated architecture in the upper half of the crypt. These polyps usually show some proliferation in the basal (non-serrated) part of the crypts (regular proliferation). Nuclei are small, regular, basal-orientated and lacking hyperchromasia, but with stratification of the upper (serrated) half of the crypts, and without cytological or structural signs of neoplasia.

Differences in the appearance of the cytoplasma permit recognition of three types:

- Microvesicular type (MVHP);
- Goblet-cell-rich type (GCHP); and
- Mucin-poor type (MPHP)

The microvesicular variant greatly predominates, but distinction between types is subject to wide interobserver variation, especially in small lesions, and is not always possible. Currently, routine subclassification is therefore neither feasible, nor has it been shown to be beneficial.

At the molecular level the microvesicular variant of HP may be the precursor lesion for sessile serrated lesion, and a goblet-cell-rich HP may be the precursor lesion for a traditional serrated adenoma (Torlakovic et al. 2003; O'Brien 2007; O'Brien et al. 2008). Routine distinction of these types is not necessary.

7A.3.3 Sessile serrated lesion

Sessile serrated lesions are described in the literature as “sessile serrated adenoma” and are often found in the right colon. This is a misnomer since sessile serrated lesions do not contain adenomatous changes (Higuchi & Jass 2004; Kudo et al. 2008; Lambert et al. 2009).

To date, four synonymously used terms exist for these lesions: sessile serrated adenoma (Torlakovic & Snover 1996), superficial serrated adenoma (Oka et al. 2004), Type 1 serrated adenoma (Jaramillo, Tamura & Mitomi 2005), and serrated polyp with abnormal proliferation (Torlakovic et al. 2003).

We recommend using only the term *sessile serrated lesion* and avoiding use of any other terms for this entity. This recommendation is given in full awareness that sessile serrated lesions do not show histological signs of an adenoma, but, like adenomas, they should be excised if detected during an endoscopic examination. Currently even in the hands of expert GI pathologists the agreement on the sub-types of serrated lesions is only moderate (Wong et al. 2009).

The vast majority of SSLs will not progress to adenocarcinoma. Histological criteria of these sessile, usually larger lesions include an abnormal proliferation zone with structural distortion, usually most pronounced in dilatation of the crypts, particularly near the base. Abundant mucus production is usually also observed as pools of mucin in the lumen of the crypts and on the surface of the mucosa. SSLs are found mainly in the right colon and may be misdiagnosed as hyperplastic polyps. Clues to the correct diagnosis include location and large size. As discussed above, cytological signs of “neoplasia” are lacking, but structural abnormalities are present, i.e. glandular branching (Higuchi & Jass 2004).

Sessile serrated lesions have an elevated serration index and serration in the basal half of crypts with basal dilation of crypts. The epithelium/stroma-ratio is believed to be >50% in SSL. There is crypt branching with horizontal growth (above muscularis mucosae; e.g. T- and L-shaped glands) and often pseudoinvasion into the submucosal layer, rectangular dilation of whole crypts with and without presence of mucus, increased number of goblet cells at the base of the crypts, vesicular nuclei with prominent nucleoli and proliferation zone in the middle of the crypts. Currently there is insufficient evidence available in the literature for weighting of these criteria.

A well-oriented polypectomy is mandatory for the identification of such histological features. Correct assessment of the deepest portions of the mucosa is impossible in superficial or tangentially cut lesions (O'Brien 2007; O'Brien et al. 2008).

Further criteria include an often asymmetrical expansion of the proliferation zone into the middle third of crypts. Often mild cytological atypia (slightly enlarged vesicular nuclei, nucleoli) is found without clear signs of neoplasia (dysplasia).

BRAF-Mutations depend on the type and location of lesion (see Table 7A.3).

Other abnormalities include:

- The majority of SSL and TSA show CIMP and promoter methylation of hMLH1
- BRAF mutations in 8–10% of all CRC (27–76% of CIMP and sporadic MSI-H CRC)
- BRAF mutations in the majority of SSL and TSA (also microvesicular variant of HP, especially proximal), but rarely (0–5%) in adenoma. (Toyota et al. 1999; Toyota et al. 2000; Ogino et al. 2006; Jass 2007; Samowitz et al. 2007; Ogino et al. 2007; Shen et al. 2007; Grady & Carethers 2008; Kawasaki et al. 2008; Ogino & Goel 2008; Suehiro et al. 2008; Ogino et al. 2009).

Table 7A.3: Prevalence of serrated lesions with BRAF Mutation: A prospective study of patients undergoing colonoscopy

Lesion	**Number** (n=414) (% of all lesions)	**Proximal location** (% of BRAF mutations)	**Distal location** (% of BRAF mutations)
Hyperplastic polyp	120 (29%)	35 (29%)	85 (71%)
Sessile serrated lesion	36 (9%)	27 (75%)	9 (25%)
Trad. serrated adenoma	3 (1%)	2 (66%)	1 (33%)
Mixed polyp	7 (2%)	4 (57%)	3 (43%)
Tubular adenoma	237 (57%)	176 (74%)	61 (26%)
Villous adenoma	11 (3%)	6 (55%)	5 (45%)

Source: modified from (Spring et al. 2006)

The frequency of sessile serrated lesions in small retrospective series is estimated at 2–11% of all mucosal lesions in the colon (Jass et al. 2006; Carr et al. 2009); between 8% and 23% are misdiagnosed as hyperplastic polyps with an interobserver variation of up to 40% (Torlakovic et al. 2003; Goldstein et al. 2003; Montgomery 2004; Higuchi, Sugihara & Jass 2005).

Table 7A.4: Comparison of proliferative activity in adenoma, hyperplastic polyps, sessile serrated lesion and traditional serrated adenoma

Ki-67	**Adenoma**	**Hyperplastic polyps**	**Sessile serrated lesion**
upper 1/3	68.8%	0.1%	1.6%
middle 1/3	48.7%	9.1%	20.3%
lower 1/3	29.6%	60.3%	64.9%

Source: modified from (Higuchi, Sugihara & Jass 2005; Sheridan et al. 2006)

The histological features separating HPs from SSLs constitute a continuous spectrum, and intermingled features can often be seen. This could explain the moderate interobserver concordance

(k=0.47) and the overlapping proliferative activity, and may justify establishing semi-quantitative criteria for diagnosis (e.g. >30% of undifferentiated cells) (Sandmeier, Seelentag & Bouzourene 2007; Farris et al. 2008). Only a few immunohistochemical markers (Ki67, Ki67 + CK20, MUC6) have been tested for differentiating HPs and SSAs, and their usefulness in colorectal screening and diagnosis remains to be validated (Torlakovic et al. 2008; Owens, Chiosea & Kuan 2008). At present, such an additional immunohistochemical analysis cannot be recommended (see Table 7A.4).

In all likelihood, lesions formerly interpreted as *mixed hyperplastic and adenomatous polyp* are, in fact, SSLs complicated by conventional neoplasia (Sheridan et al. 2006). Special care must be taken in such cases to document the respective histopathologic components in such mixed polyps. Sometimes the conventional neoplastic part shows features other than in classical adenomas. The nuclei are prominent, less palisading and smaller than in classical adenomas. It is not clear whether this type of morphology is distinct for serrated lesions and whether any clinical implications can be drawn.

Prospective studies with risk stratification are needed to develop more precise methods of diagnosis and recommendations for classification. Sessile serrated lesions appear to take a long time (average 17 years) to develop into an invasive carcinoma. In contrast, an ill-defined, small subsample of SSLs seems to rapidly progress (Sheridan et al. 2006; Oono et al. 2009). Therefore, SSLs should be completely excised, particularly if they are located on the right side of the colon (O'Brien et al. 2008; Noffsinger 2009).

Diagnosis on a biopsy is not adequate to exclude SSL since the most severe histologic changes might only appear focally within a lesion that otherwise appears to be a hyperplastic polyp (Schreiner, Weiss & Lieberman 2010).

The German guidelines for colorectal cancer (Schmiegel et al. 2008) recommend complete removal and follow-up of SSL similar to adenomas. An intensive surveillance protocol is recommended for sessile serrated lesions (surveillance colonoscopy after 3–5 years subsequent to complete excision of non-neoplastic SSL, after one year following excision of SSL HGIEN (Schmiegel et al. 2008).

The UK guidelines (NHS Bowel Cancer Screening Programme 2007; Williams, Quirke & Shepherd 2007a; Williams, Quirke & Shepherd 2007b; Williams, Quirke & Shepherd 2007c) recommend complete excision but classify these lesions in the same risk category as hyperplastic polyps. The existing evidence base is not definitive as to the level of risk, and follow up decisions should be made locally until more evidence is forthcoming.

7A.3.4 Traditional serrated adenoma

Traditional serrated adenomas show neoplastic crypts with a serrated structure (WHO 2000). Compared to hyperplastic polyps, the most striking diagnostic feature of traditional serrated adenomas are the complex serrated morphology and the eosinophilic, “dysplastic” cytoplasm that still can be identified in cases with invasive adenocarcinoma. These lesions also frequently show *BRAF* mutations and CIMP with *hMLH1*.promoter.methylation. Additionally, so-called intraepithelial microacini can be observed in the upper half of the mucosa (ectopic crypt formation). Often these lesions are located in the distal colon and can be found more frequently in elderly female individuals (Longacre & Fenoglio-Preiser 1990; Higuchi & Jass 2004; Torlakovic et al. 2008).

7A.3.5 Mixed polyp

A mixed polyp may contain partially hyperplastic, classical adenomatous or traditional serrated adenoma or sessile serrated lesion components. Rather than a continuous spectrum such lesions most probably represent several evolutionary lines, depending on the order of certain abnormalities in genes such as APC, BRAF and KRAS (O'Brien 2007; O'Brien et al. 2008). It has to be determined whether mixed polyps represent serrated lesions complicated by conventional neoplasia (Snover et al. 2005).

Focal, hyperplastic-like narrowing of the basal region of a few crypts in SSL and the findings of flat sectors or *ectopic crypt formation* in SSL/TSA (Torlakovic et al. 2008) are examples of combinations of serrated and adenomatous components. However, these features add no information of further diagnostic value; they probably result from the continuous developing nature of serrated lesions. We therefore recommend that the diagnosis of *mixed polyp* should be restricted to the definition given in Section 7A.3.1. Mixed polyps are serrated lesions in which more than one histopathologic type in the serrated spectrum (HP, SSL, TSA) is discernible in a given lesion or at least one type in combination with classical (unserrated) adenomatous tissue. The different histopathological types must be mentioned in the diagnosis, e.g. mixed polyp (HP and SSL, adenoma and SSL).

7A.3.6 Risk of progression

The vast majority of hyperplastic polyps and serrated lesions will not undergo malignant transformation. Only a fraction, especially in the group of sessile serrated lesions, may progress to rapidly aggressive carcinoma (Spring et al. 2006; Carr et al. 2009).

Hyperplastic polyps rarely progress to carcinoma. A single case report can be found in the literature (Watanabe & Suda 1984) and a second (unpublished) case has been reported in southern Germany. Interestingly, these carcinomas show features of gastric differentiation.

Little evidence is available on which the risk of colorectal cancer associated with serrated lesions other than hyperplastic polyps could be reliably judged. The risk assessment for sessile serrated lesions is not yet defined, but a subset of these lesions appears to give rise to carcinoma often less than a few millimetres in size. In a series of 110 traditional serrated adenomas, 37% exhibited foci of significant neoplasia and 11% contained areas of intramucosal carcinoma (Longacre & Fenoglio-Preiser 1990). Mixed polyps (e.g., HP/TSA/SSL or HP/adenoma) seem to have at least the same rate of progression to colorectal carcinoma as adenomas, and the risk might be higher (Leggett et al. 2001; Hyman, Anderson & Blasyk 2004).

7A.4 Assessment of T1 adenocarcinoma

Careful assessment in T1 adenocarcinoma is mandatory because a decision is required on local excision or a major operation.

7A.4.1 Size

Firstly, accurate measurement is very important, and measurement must be to the nearest mm (and not rounded-up to the nearest 5 or 10 mm). The maximum size of the lesion should be measured from the histological slide and if the lesion is disrupted or too large, from the formalin-fixed macroscopic specimen. If a biopsy is received it should be stated that size cannot be assessed.

7A.4.2 Tumour grade

Poorly differentiated carcinomas are identified by the presence of either irregularly folded, distorted and often small tubules, or the lack of any tubular formation and showing marked cytological pleomorphism. In the absence of good evidence, we recommend that a grade of poor differentiation should be applied in a pT1 cancer when ANY area of the lesion is considered to show poor differentiation. It should be noted that this is not in accordance with the WHO classification that recommends a certain proportion of lesion showing poor differentiation before diagnosing a lesion as G3. Poor differentiation includes undifferentiated and poorly differentiated as defined by the WHO classification (Washington et al. 2009).

7A.4.3 Budding

Budding describes the biological behaviour of the tumour at the front of invasion (Deinlein et al. 2003). Budding or tumour cell dissociation (Gabbert et al. 1992) can be divided into slight, moderate and marked and is known from the Japanese literature of the 1950s (Imai 1954) and 1990s (Kobayashi et al. 1994).

At this time, evidence is lacking concerning reproducibility of the numerous methods for tumour budding measurement (see Table 7A.5). It is good practice but not mandatory to document the presence or absence of single tumour cells at the front of invasion, and we therefore recommend providing this additional information in the written report with an explanatory comment, as budding has been suggested as a prognostic factor in colorectal cancer (Nakamura et al. 2008; Ogawa et al. 2009; Sy et al. 2010).

7A.4.4 Site

The site of origin of each specimen should be individually identified by the clinician and reported to the pathologist on the histopathology request form. The pathologist should record this on the proforma. This is important information because the risk of lymph node metastasis from a T1 adenocarcinoma varies depending on the site and size of the lesion (rectum vs. other locations) (Poeschl et al. 2010).

Table 7A.5: Measurement of tumour budding.

Source: modified from (Konishi & Morson 1982; Haggitt et al. 1985; Cooper et al. 1995; Volk et al. 1995; Nascimbeni et al. 2002; Ueno et al. 2004; Nakamura et al. 2008)

Author	Year	pT	Count	Magnif.	Object.	Area (mm2)	Classification	Cut- off	Notes
Ueno	2004		H&E		20x	0, 785	negative/positive	5	
Ueno	2002		H&E		25x	0, 385	<10/>10	10	degree of grading agreement
Ueno	2004		H&E	250	25x	0, 385	low (<10)/high (>10)	10	
Shinto	2005		IHC:MNF 116		20x		low (<10)/high (>10) moderate (10-19), severe (>20)		identification of cytoplasmic fragments
Shinto	2006	3	IHC:MNF 116		20x		low (<10)/high (>10) moderate (10-19), severe (>20)		scoring of cytoplasmic fragments called now podia
Okuyama	2002	1 and 2	H&E	n.a.	n.a.	n.a.	present/absent	1	endoscopically resected tumors were excluded
Okuyama	2003	3	H&E	n.a.	n.a.	n.a.	present/absent	1	
Okuyama	2003	3	H&E	n.a.	n.a.	n.a.	present/absent	1	
Prall	2005		IHC:MNF 116	250		0, 785	low/high	25	ROC metastatic progression; 0-120 buds range; 14 median 20,46 mean
Kazama	2006	1	IHC: CAM5.2 and AE1/AE3	n.a.	n.a.	n.a.	present/absent	1	
Kanazawa	2007		H&E	n.a.	n.a.	n.a.	none/mild/ moderate/marked		
Nakamura	2008		H&E	n.a.	n.a.	n.a.	None/mild/ =low moderate/marked=high		
Choi	2007	2 or more	H&E		20x		(0-3)/(4-5)/(6-10)/(11-38)		
Park	2005	2 or more	H&E		20x		(0-3)/(4-5)/(6-9)/(10-38)		mean intesity: (+/-SD) 6,6+/-5,6
Hori	2005		H&E	200	40x			0,05	5% of the horizontal length of the invasive front
Yasuda	2007		H&E				present/absent		
Ishikawa	2008		IHC:MNFIIb	400			negative/positive	5	

7A.4.5 Definition of invasion

In columnar epithelium, it is difficult to define the onset of invasive carcinoma and reliably distinguish it from high-grade intraepithelial neoplasia. Criteria such as single tumour cells are more likely to be seen in more advanced carcinomas, but not in early carcinomas. Desmoplastic stromal reactions are also seldom seen in very early carcinomas. However, basal membrane structures are frequently discernible in well-differentiated early carcinomas (Borchard et al. 1991; Borchard 2000; Vieth & Stolte 2005), so that definitions using “invasion through the basement membrane” are incorrect.

The WHO definition of adenocarcinoma in use when the EU Guidelines were developed excluded diagnosis of intramucosal carcinoma in the colon or rectum, in contrast to the accepted WHO definitions for the stomach, oesophagus and small bowel. In the latter cases, a decision on surgical vs. local therapy is made based on respective protocols. Comparable lesions in the colon and rectum are reported as high-grade mucosal neoplasia because a carcinoma in the colon is defined by infiltration of the submucosa according to the WHO classification.

The discussion on this issue among the authors of the pathology chapter in the EU Guidelines reflects, among other things, concern about potential overtreatment of early T1 carcinomas which are detected much more frequently in a screening setting. The clinical management of a lesion where invasion of the lamina propria has occurred is no different from that where high-grade changes are confined to the glands. This legitimate concern as to increased morbidity and mortality due to miscommunication of diagnostic criteria may be dealt with more effectively in the future, as multidisciplinary management of lesions detected in and outside of screening programmes advances. The authors hope that such advances and their effective dissemination will be stimulated by the publication of the new EU guidelines. This, in turn, may lead to revision of the current WHO definition of colorectal adenocarcinoma in a future revision of the WHO classification of gastrointestinal tumours. Pathologists should report on what version of the WHO and TNM classifications their diagnosis is based.

In those cases in which intramucosal colorectal cancer is suspected, and particularly in countries in which this diagnosis is documented in addition to the WHO terminology, explicit comments by the pathologist are recommended. Based on the cytological characteristics of the case, the pathologist should indicate whether local endoscopic or surgical removal is recommended, and the basis for this recommendation should be indicated. This recommendation should be discussed in a multidisciplinary conference prior to surgery. The Japanese criteria for such stratification have been published by Watanabe & Suda (1984). The updated Paris classification based on a workshop in February 2008 in Kyoto (Kudo et al. 2008) permits such subclassification based on improved grouping and explains in detail the grading criteria (Lambert et al. 2009).

The use of the term colonic carcinoma in situ introduced by the TNM system is inadequate because the criteria are too vague and cannot be used for columnar epithelium.

A subclassification of all carcinomas into low risk and high risk based on risk of lymph node involvement should always be undertaken. For exact criteria, please see Chapter 7 and the updated Paris classification (Kudo et al. 2008; Lambert et al. 2009).

Perineural invasion

Perineural invasion (PNI) was recently described as an independent risk factor for colorectal cancer (Liebig et al. 2009a; Poeschl et al. 2010). PNI is significantly associated with high tumour stage, grade and metastases. Furthermore, PNI serves as an independent predictor of disease-free and cancer survival (Liebig et al. 2009a; Poeschl et al. 2010). Recently, an association with other criteria indicating an aggressive course of disease, such as lymphatic vessel permeation, venous invasion, tumour growth pattern and budding (Jass, Love & Northover 1987) were described by Poeschl et al. (2010). Also, it was described that PNI-positive tumours are more likely to be incompletely resected and more

likely to progress after Mayo regimen chemotherapy than PNI-negative tumours. Lately Poeschl et al. were able to show that PNI is an additional independent factor for local tumour relapse.

It is recommended to record PNI in routine sections of colorectal cancer. According to recent studies (Liebig et al. 2009a; Liebig et al. 2009b; Poeschl et al. 2010; Marshall et al. 2010) immunohistochemistry or special stains are not necessary to detect PNI. Prospective studies are needed to show the clinical relevance of PNI, its relationship to other features such as lymphatic and vascular invasion and the benefit of alternative treatment for such more aggressive tumours that are PNI positive.

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8

Management of lesions detected in colorectal cancer screening

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Recommendations[1]

General requirements for treatment of colorectal cancer and pre-malignant lesions

8.1 Colorectal neoplasia should be managed by a multi-disciplinary team **(VI - A).**[Sect 8.2]

8.2 The interval between the diagnosis of screen-detected disease and the start of definitive management should be minimised and in 95% of cases should be no more than 31 days **(VI - B).**[Sect 8.2]

8.3 Colonoscopy should always be done with therapeutic intent i.e. the endoscopist carrying out screening or follow-up colonoscopy should have the necessary expertise to remove all but the most demanding superficial lesions (see Ch. 5) **(VI - A).**[Sect 8.2; 5.1.2]

Management of pre-malignant colorectal lesions

8.4 Pre-malignant lesions detected at screening endoscopy should be removed **(III - A).**[Sect 8.3]

8.5 Lesions that have been removed should be retrieved for histological examination (see also Ch. 7, Rec. 7.11) **(VI - A).**[Sect 8.3.5; 7.6.5.2; 7.8]

8.6 Colorectal lesions should only be removed by endoscopists with adequate training in techniques of polypectomy (See Chap. 6, Rec 6.13) **(V - A).**[Sect 8.3]

8.7 Large sessile lesions of the rectum should be considered for transanal surgical removal **(II - B).**[Sect 8.3.4]

8.8 For large sessile rectal lesions, transanal endoscopic microsurgery (TEM) is the recommended method of local excision **(II - B).**[Sect 8.3.4]

8.9 Consideration should be given to tertiary referral for patients with large sessile colorectal lesions **(V - B).**[Sect 8.3.3]

8.10 Patients with large pre-malignant lesions not suitable for endoscopic resection should be referred for surgical resection **(VI - A).**[Sect 8.3]

8.11 Appropriate precautions should be taken prior to endoscopic excision of colorectal lesions in patients on anticoagulants **(V - C).**[Sect 8.3.7]

8.12 In patients with bare coronary stents, polypectomy should be delayed for at least one month from placement of the stents, when it is safe to discontinue clopidogrel temporarily **(V - B).**[Sect 8.3.7]

8.13 In patients with drug-eluting coronary stents, polypectomy should be delayed for 12 months from placement of the stents, when it is safe to discontinue clopidogrel temporarily **(V - B).**[Sect 8.3.7]

8.14 In patients with drug-eluting coronary stents, when early polypectomy is deemed essential, it can be delayed for only 6 months from placement of the stents, when it is probably safe to discontinue clopidogrel temporarily **(VI - C).**[Sect 8.3.7]

8.15 Aspirin therapy can **(IV – C)** - and in patients with stents should - be continued prior to and during polypectomy **(VI – B).**[Sect 8.3.7]

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[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.

Management of pT1 colorectal cancer

8.16 If there is clinical suspicion of a pT1 cancer, a site of excision should be marked with submucosal India ink **(VI - C).**[Sect 8.4.1]

8.17 Where a pT1 cancer is considered high-risk for residual disease consideration should be given to completion colectomy along with radical lymphadenectomy, both for rectal cancer **(II - A)** and colon cancer **(VI - A)**. If surgical resection is recommended, consideration should be given to obtaining an opinion from a second histopathologist as variation exists in evaluating high risk features (see also Ch. 7, Rec. 7.7) **(VI - B).**[Sect 8.4.2; 7.5.3]

8.18 After excision of a pT1 cancer, a standardised follow-up regime should be instituted **(VI - A).** The surveillance policy employed for high-risk adenomas is appropriate for follow-up after removal of a low-risk pT1 cancer (see Ch. 9, Rec. 9.16) **(III - B).**[Sect 8.4.3; 9.5.1]

Management of colon cancer

8.19 If a complete colonoscopy has not been performed either because the primary lesion precluded total colonoscopy, or for any other reason for failure to complete colonoscopy, the rest of the colon should be visualised radiologically before surgery if at all possible. This should be performed ideally by CT colography, or if this is not available, by high-quality double-contrast barium enema. If for any reason the colon is not visualised prior to surgery, complete colonoscopy should be carried out within 3 to 6 months of colectomy **(VI - B).**[Sect 8.5.1]

8.20 Patients with a proven screen-detected cancer should undergo pre-operative staging by means of CT scanning of the abdomen and pelvis **(V - B).** Routine chest CT is not recommended **(III - D).**[Sect 8.5.1]

8.21 Patients with screen-detected colon cancer that has not been adequately resected endoscopically should have surgical resection by an adequately trained surgeon **(III - A).**[Sect 8.5.2]

8.22 Where appropriate, laparoscopic colorectal surgery should be considered **(I - A).**[Sect 8.5.2]

Management of rectal cancer

8.23 If a complete colonoscopy has not been performed either because the primary lesion precluded total colonoscopy, or any other reason for failure to complete colonoscopy, the rest of the colorectum should be visualised radiologically before surgery if at all possible. This should be performed ideally by CT colography, or if this is not available, by high-quality double-contrast barium enema. If for any reason the colon is not visualised prior to surgery, complete colonoscopy should be carried out within 6 months to 1 year of excision of the rectal cancer **(VI - B).**[Sect 8.6]

8.24 Patients with a proven screen-detected rectal cancer should undergo pre-operative staging by means of CT scanning of the abdomen and pelvis **(VI - B)**. Routine chest CT is not recommended **(III - D).**[Sect 8.6.1]

8.25 Patients with a proven screen-detected rectal cancer should ideally undergo pre-operative local staging by means of MRI scanning of the pelvis in order to facilitate planning of pre-operative radiotherapy **(III - B)**, although high-quality multi-slice CT scanning may provide adequate information **(VI - C).**[Sect 8.6.1]

8.26 All patients undergoing radical surgery for rectal cancer should have mesorectal excision **(II - A)** by an adequately trained specialist surgeon **(VI - A).**[Sect 8.6.3]

8.27 Patients undergoing surgery for rectal cancer may be considered for laparoscopic surgery **(I - B).**[Sect 8.6.3]

8.28 All patients undergoing surgery for rectal cancer (and certainly those predicted on imaging to have T3/4 cancers and/or lymph node metastases) should be considered for pre-operative adjuvant radiotherapy with or without chemotherapy **(I - A).**[Sect 8.6.2]

8.29 Local excision alone should only be performed for T1 sm1 rectal cancers, and if the patient is fit for radical surgery **(III - B).**[Sect 8.6.5]

8.30 In the patient in whom there is doubt about fitness for radical surgery, local excision of more advanced rectal cancer should be considered **(III - B).**[Sect 8.6.5]

8.31 In patients in whom local excision for rectal cancer is planned, consideration should be given to pre-operative CRT **(III - C).**[Sect 8.6.5]

8.32 If a local excision is carried out, and the pT stage is T1 sm3 or worse, then radical excision should be performed if the patient is fit for radical surgery **(II- B).**[Sect 8.6.5]

8.1 Introduction

Mortality reduction for colorectal cancer is the main endpoint of any colorectal screening programme but it must be appreciated that all screening modalities will detect substantial numbers of individuals with adenomas (Levin et al. 2008) as well as a lesser number of lesions in the serrated pathway, some of which should be treated as adenomas (see Ch. 7, Sect. 7.1, 7.2 and 7.2.4).[2] As adenomas are recognised to be pre-malignant (Leslie et al. 2002) screening has the potential to reduce the incidence of the disease if these lesions are adequately managed. To achieve the dual aims of mortality and incidence reduction it is essential that all the elements of the screening service achieve and maintain high levels of quality. The screening process can only be successful if it is followed by timely and appropriate management of screen-detected lesions.

In essence the management of screen-detected adenomas and carcinomas does not differ, stage for stage, from that required for symptomatic disease with the proviso that sub-optimal management can negate the benefit of screen detection. Screening does however detect a different spectrum of disease compared with that diagnosed in the symptomatic population (i.e. higher proportion of early disease) and there are some considerations in the management of screen-detected disease that should be emphasised. In this Chapter of the EU Guidelines the management of **endoscopically detected pre-malignant lesions, pT1 cancers**, as well as **colon cancer and rectal cancer** which is not limited to the submucosa are dealt with separately and discussion is focused on issues pertinent to screening. Accordingly, adjuvant chemotherapy and the management of advanced disease are not discussed.

8.2 General requirements for treatment of colorectal cancers and pre-malignant lesions

It is widely agreed that colorectal neoplasia is best managed by a multi-disciplinary team with expertise in surgery, endoscopy, pathology, radiology, radiotherapy, medical oncology, specialist nursing, genetics and palliative care (SIGN 2003), working in close collaboration with primary care **(VI - A).**[Rec 8.1] The interval between the diagnosis of screen-detected disease and the start of definitive management is a time of anxiety for the patient and affords the opportunity, if prolonged, for disease progression. For these reasons, standards aimed at minimising delay have set the maximum interval at 31 days (NHS 2007) **(VI - B).**[Rec 8.2] It should be noted that colonoscopy is not merely a diagnostic procedure, but has therapeutic capacity (Cotton & Williams 1996), and it is essential that the endoscopist carrying out screening colonoscopy has the necessary expertise to remove all but the most demanding polyps (see Ch. 5, Sect. 5.1.2) **(VI - A).**[Rec 8.3]

[2] Serrated lesions can be classified as hyperplastic polyp, sessile serrated lesions, traditional serrated lesions and mixed polyps. The hyperplastic polyp must be distinguished from other serrated lesions due to its extremely low malignant potential. The significance of other lesions in the serrated spectrum is controversial and our knowledge is still developing. Hyperplastic polyps are non-neoplastic and their complete removal is optional. All other lesions in the serrated pathway should be excised and serrated lesions with neoplasia should be followed up (surveillance) as if they were adenomas (Ch. 7, Sect. 7.1, 7.2 and 7.2.4, Rec. 7.10).

Recommendations

- Colorectal neoplasia should be managed by a multi-disciplinary team **(VI - A).**[Rec 8.1]
- The interval between the diagnosis of screen-detected disease and the start of definitive management should be minimised and in 95% of cases should be no more than 31 days **(VI - B).**[Rec 8.2]
- Colonoscopy should always be done with therapeutic intent i.e. the endoscopist carrying out screening or follow-up colonoscopy should have the necessary expertise to remove all but the most demanding lesions (see Ch. 5, Sect. 5.1.2) **(VI - A).**[Rec 8.3]

8.3 Management of pre-malignant colorectal lesions

(Note: the terms "pre-malignant lesion" and "polyp" are used in the following text as it is impossible to be certain of the histology of colorectal lesions prior to removal, although the intention is to treat adenomas and in some cases also serrated lesions with neoplasia or the potential to develop neoplasia, as mentioned in Section 8.1.)

There is abundant evidence that colorectal adenomas are pre-malignant (Leslie et al. 2002), and it follows that a lesion found during colonoscopy that could be an adenoma should be removed **(III - A).**[Rec 8.4] Lesions should only be removed by endoscopists with adequate training in techniques of polypectomy, (see Chapter 6, Rec. 6.13) **(V - A).**[Rec 8.6]

For the purposes of management, polyps may be classified as small (≤5 mm), pedunculated, large (≥10 mm) sessile colonic and large sessile rectal. Patients with large adenomas not suitable for endoscopic resection should be referred for surgical resection **(VI - A).**[Rec 8.10]

8.3.1 Small lesions

In order to obtain a representative histological specimen and to achieve definitive treatment, lesions >5 mm are removed by snaring. Those ≤5 mm may be removed with biopsy forceps or cold snaring. Hot biopsy forceps may be used to ensure destruction of polyp tissue when the endoscopist is not confident about removing all the abnormal tissue with ordinary forceps. One randomised controlled trial has compared hot biopsy with cold biopsy followed by bipolar coagulation and concluded that both were equally effective and safe (Paspatis et al. 2005). There is also evidence that hot biopsy is associated with a higher risk of haemorrhage than cold biopsy, particularly in the right colon (Weston & Campbell 1995; Parra-Blanco et al. 2000). Cold snaring may also be used safely for polyps ≤6 mm (Uno et al. 1997; Deenadayalu & Rex 2005).

Lesions <10 mm do not usually present major technical difficulties in endoscopic excision by snare electrocoagulation. It should however be born in mind that, particularly on the right side of the colon, the muscle wall is thin and even with small polyps (when they are sessile) sub-mucosal injection of saline is necessary to elevate the adenoma away from the underlying muscle wall prior to excision (Cotton & Williams 1996).

8.3.2 Pedunculated adenomas/polyps

The polyp on a stalk or the pedunculated adenoma is usually amenable to snare excision even when very large (≥20 mm) (Church 2003; Perez Roldan et al. 2004). In most instances it is appropriate to apply snare electro-coagulation directly to the stalk of the adenoma (Dell'Abate et al. 2001) . However, in those with thick stalks, and certainly those where the stalk is greater than 10 mm in diameter, pre-injection with 1 in 10 000 adrenaline (Hsieh et al. 2001) or the placement of a detachable nylon loop around the stalk below the site of coagulation (Brandimarte & Tursi 2001) can reduce the risk of bleeding. There is evidence from a randomised controlled trial that pre-injection with adrenaline is effective in reducing immediate bleeding after polypectomy (Hsieh et al. 2001).

If after transection of the stalk arterial bleeding is seen the stalk is grasped with the diathermy loop and held (without electro-coagulation) for 5 minutes; this should at least temporarily control the bleeding. The stalk can then be injected with adrenaline and scleroscent or nylon loop can be placed around the stalk remnant. Depending on the size and position of the stalk, the placement of one or two clips may be used as an alternative (Cotton & Williams 1996).

8.3.3 Large sessile colonic adenomas/lesions

With large sessile colonic lesions the choice is between formal surgical resection of the affected part of the colon and endoscopic resection at colonoscopy. The decision as to which strategy to adopt will depend on the ability of the colonoscopist and the availability of a tertiary referral centre where advanced endoscopic techniques can be used (Perez Roldan et al. 2004) **(V - B).**[Rec 8.9]

For sessile adenomas up to about 20 mm, complete excision may be possible using snare electro-coagulation after elevating the lesion by sub-mucosal injection of saline or saline plus adrenaline. The saline injection has two main functions; firstly, elevating the lesion facilitates the placement of a snare around it, and secondly, it protects the underlying muscle from damage thereby reducing the risk of perforation. For lesions >20 mm a similar technique may be employed but piecemeal excision is necessary (Doniec et al. 2003; Stergiou et al. 2003), and argon plasma coagulation can be used as an adjunct to this technique in order to destroy residual adenoma tissue (Garcia et al. 2004; Boix et al. 2007). If a lesion does not lift with sub-mucosal injection, snaring should not be attempted as this indicates involvement of the underlying muscle (Cotton & Williams 1996). For large carpeting lesions, endoscopic sub-mucosal resection using elevation with saline and a specially designed sheath for the colonoscope and a needle knife may be possible (Jameel et al. 2006). It must be appreciated, however, that this is a very advanced technique and at the present time it is only available in a few specialist tertiary referral centres.

8.3.4 Large sessile rectal adenomas/lesions

While sessile rectal adenomas ≤20 mm in diameter may be treated by snare electro-coagulation as described for colonic adenomas, the very large carpeting lesions may be treated by surgical transanal excision **(II - B).**[Rec 8.7] For low lesions this may be achieved using conventional transanal techniques utilising specifically designed retractors (e.g. the Pratt Bivalve Retractor, the Lone Star Retractor). For lesions of the mid and upper rectum however where access using conventional techniques is difficult either endoscopic sub-mucosal dissection (ESD) or transanal endoscopic microsurgery (TEM) may be employed. There is evidence from a randomised controlled trial that TEM results in less local recurrence than conventional local excision (Middleton, Sutherland & Maddern 2005) **(II - B).**[Rec 8.8] In

some situations where there is very extensive carpeting of the rectum it may be necessary to carry out a total proctectomy. Reconstruction can then be effected by means of a hand-sewn colo-anal anastomosis.

8.3.5 Retrieval of lesions

Whenever a lesion has been removed endoscopically it should be retrieved for histological examination firstly to assess the completeness of excision and secondly to confirm the benign nature of the lesion **(VI - A).**[Rec 8.5] Under most circumstances it is feasible to trap the excised lesion using the snare and to retrieve it in this fashion. Very small polyps may be retrieved by applying suction to the biopsy channel and employing a polyp trap. When there are multiple lesions or multiple fragments of a lesion, specifically designed endoscopic retrieval bags (e.g. Rothnet) can be employed (NHS 2007).

8.3.6 Management of incomplete endoscopic excision

Incomplete excision is most common when a large sessile lesion has been removed piecemeal, but it may occur in any situation. If residual lesion tissue is seen at the time of initial polypectomy, this should be excised using snare electrocoagulation where possible. Small areas of residual tissue that are not amenable to snare electrocoagulation may be treated with direct electrocoagulation or obliteration using argon beam therapy (Brooker et al. 2002; Regula et al. 2003; Boix et al. 2007).

If there is doubt about completeness of excision at the time of initial polypectomy or if the subsequent histopathology report indicates that there may have been incomplete excision, a repeat endoscopic examination of the treated area should be carried out within 3 months. Residual abnormal tissue seen at that time can be treated as outlined above. In the situation where residual adenoma is impossible to eradicate, surgical resection of the affected part of the large bowel may be required.

8.3.7 Management of pre-malignant lesions in patients taking anti-coagulants/anti-aggregants

Appropriate precautions should be taken prior to endoscopic excision of colorectal lesions in patients on anticoagulants **(V - C).**[Rec 8.11] The existing evidence (Timothy et al. 2001; Hui et al. 2004; Yousfi et al. 2004; Friedland & Soetikno 2006; Kim et al. 2006; Makar & Ginsberg 2006; Kimchi et al. 2007) relating to management of anticoagulants and antiplatelet therapy in patients undergoing endoscopic procedures is summarised in recent guidelines (Veitch et al. 2008) and indicates that the use of anti-coagulants (warfarin) is associated with the significantly increased risk of bleeding after polypectomy while the use of aspirin or other NSAIDS or antiplatelet agents is not. However, the potent anti-platelet agent clopidogrel may pose a risk, especially in combination with aspirin, and although the available data are scarce, caution is advised. The following issues must be considered when deciding the management of patients taking anti-coagulants or anti-platelet therapy:

- The risk of discontinuing anti-coagulation;
- The bleeding risk associated with polypectomy;
- The morbidity and mortality rates of thromboembolic complications versus those of bleeding complications; and
- The timing of cessation and reinstitution of anti-coagulants or anti-platelet therapy.

Warfarin is discontinued 3 to 5 days before the procedure. Patients at high-risk of thromboembolic events receive subcutaneous low-molecular-weight-heparin (LMWH) which is stopped at least 8 hours before the procedure. The LMWH can be resumed 6 hours after the procedure.

Another option is to perform an initial diagnostic colonoscopy followed if necessary by a second colonoscopy for polypectomy using LMWH bridge therapy. If the high-risk of thromboembolism is potentially transient (e.g. deep venous thrombosis), the best option is to delay the polypectomy until the risk is decreased.

Ideally, and certainly until further evidence is available relating specifically to polypectomy, individuals taking clopidogrel must stop this medication at least 7 days before polypectomy is performed where it is safe to do so. However, in patients with coronary stents, stopping clopidogrel within 1 month for bare stents and within 12 months for drug-eluting stents carries a high-risk of acute thrombosis of the stent and myocardial infarction. In patients such as these, endoscopic polypectomy must be delayed for the appropriate period of time **(V - B).**[Rec 8.12; 8.13] In patients with drug-eluting coronary stents, when early polypectomy is deemed essential, it can be delayed for only 6 months from placement of the stents, when it is probably safe to discontinue clopidogrel temporarily **(VI - C).**[Rec 8.14] Aspirin therapy can **(IV - C)** - and in patients with stents should - be continued **(VI - B).**[Rec 8.15]

8.3.8 Synopsis

Summary of evidence

- Colorectal adenomas are recognized as pre-malignant **(III).**
- Colonic adenomas can be removed by biopsy forceps, cold snaring, electrocoagulation snares or, when large and sessile, by endoscopic sub-mucosal resection **(V).**
- Rectal adenomas, when not suitable for colonoscopic excision, can be removed by surgical transanal excision with or without the use of transanal endoscopic microsurgery (TEM) or endoscopic sub-mucosal dissection (ESD) **(II).**
- Large colonic or rectal adenomas can be treated by surgical resection of the affected area if endoscopic resection is not possible **(V).**
- The use of sub-optimal technique for polypectomy can result in perforation with attendant morbidity and mortality **(V).**
- Removal of adenomas in an anticoagulated patient can result in potentially fatal haemorrhage **(V).**
- Stopping clopidogrel within 1 month of the placement of bare coronary stents can result in acute thrombosis of the stent and myocardial infarction **(III).**
- Stopping clopidogrel within 12 months of the placement of drug-eluting coronary stents can result in acute thrombosis of the stent and myocardial infarction, **(III)** although if absolutely essential it *may* be stopped temporarily at 6 months **(IV).**

Recommendations for management of colorectal pre-malignant lesions

- Pre-malignant lesions detected at screening endoscopy should be removed **(III - A).**[Rec 8.4]
- Lesions that have been removed should be retrieved for histological examination **(VI- A).**[Rec 8.5]
- Colorectal lesions should only be removed by endoscopists with adequate training in techniques of polypectomy **(V - A).**[Rec 8.6]
- Large sessile lesions of the rectum should be considered for transanal surgical removal **(II - B).**[Rec 8.7]

- For large sessile rectal lesions, transanal endoscopic microsurgery (TEM) is the preferred method of local excision **(II - B).**[Rec 8.8]
- Consideration should be given to tertiary referral for patients with large sessile colorectal lesions **(V - B).**[Rec 8.9]
- Patients with large pre-malignant lesions not suitable for endoscopic resection should be referred for surgical resection **(VI - A).**[Rec 8.10]
- Appropriate precautions should be taken prior to endoscopic excision in patients on anticoagulants **(V - C).**[Rec 8.11]
- In patients with bare coronary stents, polypectomy should be delayed for at least one month from placement of the stents, when it is safe to discontinue clopidogrel temporarily **(V - B).**[Rec 8.12]
- In patients with drug-eluting coronary stents, polypectomy should be delayed for 12 months from placement of the stents, when it is safe to discontinue clopidogrel temporarily **(V - B).**[Rec 8.13]
- In patients with drug-eluting coronary stents, when early polypectomy is deemed essential, it can be delayed for only 6 months from placement of the stents, when it is probably safe to discontinue clopidogrel temporarily **(VI - C).**[Rec 8.14]
- Aspirin therapy can **(IV - C)** and in patients with stents should - be continued prior to and during polypectomy **(VI - B).**[Rec 8.15]

8.4 Management of pT1 cancers

8.4.1 Primary management

A pT1 cancer can be defined as an invasive cancer that is confined to the submucosa. pT1 cancers are also commonly referred to as polyp cancers because they are generally detected and removed endoscopically. Although the evidence base relating to the management of these lesions is weak (Bentrem et al. 2005; Endreseth et al. 2005; Hahnloser et al. 2005; Floyd & Saclarides 2006; Chok & Law 2007), there has been one narrative review of this subject, and the recommendations given here are derived from the evidence cited in this review (Mitchell & Haboubi 2008).

The primary management of a pT1 cancer is, by definition, identical to that of an adenoma (see Sect. 8.3). In most cases the diagnosis of pT1 cancer is made on histological examination of the endoscopically excised lesion but the following features raise the suspicion of a polyp cancer:

- Lesion is larger than 20 mm;
- Lesion is uncharacteristically hard; or
- Lesion is ulcerated.

Identification of a previous polypectomy site may be difficult and can cause problems for the surgeon in deciding on the anatomical region to be removed if completion surgery (see below) is required. This problem can be overcome by injecting India ink sub-mucosally at the site of a suspected pT1 cancer at the time of its removal **(VI - C).**[Rec 8.16] India ink tattooing should be performed distal to the lesion and include at least three quadrants of the bowel. Care should be taken to avoid “Indian ink peritonitis” by initial raising of the mucosa with saline.

pT1 cancers can be categorised into low-risk and high-risk lesions according to their likelihood of being associated with lymph node metastases:

- Low risk: Well or moderately differentiated and no lymphovascular invasion; rate of lymph node metastases <5%
- High risk: Poorly differentiated and/or lymphovascular invasion; rate of lymph node metastases ~35%

The significance of venous invasion is currently unknown.

8.4.2 Completion surgery

Patients with a histologically confirmed, completely removed low-risk pT1 cancer do not require additional surgery, due to their low risk of lymph node metastases. In patients with a high-risk polyp cancer with clear margins (RO), the multidisciplinary team should be consulted on whether completion surgery involving removal of the part of the large bowel in which the polyp was situated, along with radical lymphadenectomy, for both rectal cancer **(II - A)** and colon cancer **(VI - A)** is recommended.[Rec 8.17] If surgical resection is recommended, consideration should be given to obtaining an opinion from a second histopathologist, as variation exists in evaluating high risk features (See also Ch. 7, Sect. 7.5.3 and Rec. 7.7) **(VI - B).**[Rec 8.17] The precise nature of the surgery will of course depend on the site of the pT1 cancer. It may be difficult to precisely locate the site of the previous polypectomy and for this reason inking of the site at the time of initial polypectomy is advised when there is any clinical suspicion of polyp cancer (see above).

It should be noted that if a suspected pT1 cancer has been *incompletely* removed, lack of invasion beyond the submucosa cannot be guaranteed, and thus even in the situation where the lesion is well or moderately differentiated with no lymphovascular invasion, further treatment is required. This will usually take the form of completion surgery, although repeat endoscopic excision may be possible and appropriate in some situations.

In summary, current consensus would classify a pT1 cancer as high-risk requiring completion surgery in the following circumstances:

- When invasive cancer is seen at or within 1 mm of the resection margin;
- Where the cancer is poorly differentiated; or
- Where there is evidence of lymphovascular invasion within the resected specimen.

8.4.3 Follow-up

After excision of a pT1 cancer, a standardised follow-up regime should be instituted **(VI - A).**[Rec 8.18] After removal of a low-risk pT1 cancer, many endoscopists consider the surveillance policy employed for high-risk adenomas to be appropriate follow-up (see Ch. 9, Sect. 9.5.1, Rec. 9.16) **(III - B).**[Rec 8.18] In the case of removal of a high-risk pT1 cancer without additional completion surgery for whatever reason, a more intensive programme of follow-up would be appropriate because of the increased risk of cancer recurrence. It is suggested that such patients benefit from quarterly endoscopic inspection of the polypectomy site for 1 year and then bi-annual inspection for a further 2 years. After this, the surveillance protocol for high-risk adenomas can be adopted. Given the increased risk of extramural recurrence in patients with high-risk pT1 cancers without completion surgery, it is

also appropriate to use cross-sectional imaging of the abdomen on a bi-annual basis for a period of 3 years.

8.4.4 Synopsis

Summary of evidence

- When invasive cancer is present in a polypectomy specimen, the risk of residual disease is associated with distance from the resection margin, degree of differentiation and degree of lymphovascular invasion **(III).**
- The precise site of a polyp within the colon is difficult to define at colonoscopy **(VI).**

Recommendations for management of pT1 cancers

- If there is clinical suspicion of a pT1 cancer a site of excision should be marked with sub-mucosal India ink **(VI - C).**[Rec 8.16]
- Where a pT1 cancer is considered high-risk for residual disease, consideration should be given to completion colectomy along with radical lymphadenectomy, for both rectal cancer **(II - A)** and colon cancer **(VI - A)**.[Rec 8.17] If surgical resection is recommended, consideration should be given to obtaining an opinion from a second histopathologist as variation exists in evaluating high risk features (see also Ch. 7, Sect. 7.5.3 and Rec. 7.7) **(III - A).**[Rec 8.17]
- After excision of a pT1 cancer, a standardised follow-up regime should be instituted **(VI - A).** The surveillance policy employed for high-risk adenomas is appropriate for follow-up after removal of a low-risk pT1 cancer (see Ch. 9, Sect. 9.5.1, Rec. 9.16) **(III - B).**[Rec 8.18]

8.5 Management of colon cancer

The management of screen-detected colon cancer is not materially different from that of the management of symptomatic cancer. Management of pT1 colon cancer has been dealt with in Section 8.4. The following summary deals with management of colon cancer which is not limited to the submucosa; it is derived from evidence based guidelines (SIGN 2003; Otchy et al. 2004; Schmiegel et al. 2005; Labianca et al. 2010; NCCN 2010a).

8.5.1 Preoperative staging

Once the diagnosis of colon cancer has been made (usually by means of colonoscopic biopsy) it is essential to a) ensure that the whole colon has been visualised for second primaries or adenomas and b) screen the patient for metastatic disease.

The reason for visualising the whole colon is that 5% of patients with a colorectal cancer will have a synchronous cancer, and more will have adenomas that require removal.

If a complete colonoscopy has not yet been performed, either because the primary lesion precluded total colonoscopy or any other reason, the rest of the colorectum should be visualised radiologically

before surgery, if at all possible. This should be performed ideally by CT colography, or if this is not available, by high quality double contrast barium enema. If for any reason the entire colon is not visualised prior to surgery then a complete colonoscopy should be carried out within 3 to 6 months of excision of the colon cancer **(VI - B).**[Rec 8.19]

In terms of screening for metastatic disease, patients with a proven screen-detected cancer should undergo pre-operative staging by means of CT scanning of the abdomen and pelvis **(V - B).** Routine chest CT is not recommended **(III - D).**[Rec 8.20]

8.5.2 Surgery

As with all patients with colon cancer, the quality of surgery for screen-detected cancers is central to the outcome. Safe, high-quality surgery is essential for screen-detected cancers given that surgery-related mortality will result in greater shortening of life for patients with screen-detected cancers compared with those with symptomatic cancers.

The exact nature of the colectomy will of course depend on the anatomical location of the tumour but in general terms the most common operations will be a right hemicolectomy for tumours in the caecum or ascending colon, an extended right hemicolectomy for tumours in the transverse colon up to the splenic flexure, a left hemicolectomy for tumours between the splenic flexure and the sigmoid colon and a sigmoid colectomy for tumours of the sigmoid colon.

There is accumulating evidence that radicality of surgery is associated with better long-term outcomes and it is recommended that all of these operations be carried out with a full lymphadenectomy that involves flush ligation of the feeding vessels at the superior mesenteric artery or aorta as appropriate (West et al. 2008b). There is also increasing evidence that outcomes after surgery for colon cancer, both short- and long-term, are dependent on the degree of specialisation and experience of the surgeon (McArdle & Hole 2004). Thus patients with screen-detected colon cancer that has not been adequately resected endoscopically should have surgical resection by an adequately trained surgeon **(III - A).**[Rec 8.21]

Increasingly, laparoscopic surgery is being used to treat colon cancer, and screen-detected colon cancer is often amenable to this approach. The evidence suggests that advantages of laparoscopic surgery are related to short-term rather than long-term outcomes, but randomised controlled trials indicate that it is oncologically safe (Kuhry et al. 2008). Thus where appropriate, laparoscopic colorectal surgery should be considered **(I - A).**[Rec 8.22] However, it is essential that if laparoscopic surgery is employed, the oncological principles outlined above are adopted. It is also essential that the surgeons carrying out laparoscopic surgery be fully trained in this technique.

8.5.3 Synopsis

Summary of evidence

- High-quality surgery is the optimal primary treatment for colon cancer **(III).**
- In appropriately selected patients laparoscopic colon cancer surgery can offer better short-term outcomes **(I).**

Recommendations for management of colon cancer

- If a complete colonoscopy has not been performed either because the primary lesion precluded total colonoscopy, or for any other reason for failure to complete colonoscopy, the rest of the

colon should be visualised radiologically before surgery if at all possible. This should be performed ideally by CT colography, or if this is not available, by high-quality double-contrast barium enema. If for any reason the colon is not visualised prior to surgery, complete colonoscopy should be carried out within 6 months to 1 year of colectomy **(VI - B).**[Rec 8.19]

- Patients with a proven screen-detected cancer should undergo pre-operative staging by means of CT scanning of the abdomen and pelvis **(V - B).** Routine chest CT is not recommended **(III - D).**[Rec 8.20]
- Patients with screen-detected colon cancer that has not been adequately resected endoscopically should have surgical resection by an adequately trained surgeon **(III - A).**[Rec 8.21]
- Where appropriate, laparoscopic colorectal surgery should be considered **(I - A).**[Rec 8.22]

8.6 Management of rectal cancer

The management of screen-detected rectal cancer is not materially different from that of the management of symptomatic rectal cancer. Management of pT1 rectal cancer has been dealt with in Section 8.4. The following summary deals with management of rectal cancer which is not limited to the submucosa; it is derived from evidence based guidelines (SIGN 2003; Schmiegel et al. 2005; Tjandra et al. 2005; Glimelius, Pahlman & Cervantes 2010; NCCN 2010b). However, the issue of how to treat small rectal cancers that are technically suitable for local excision is particularly germane to screen-detected disease, and particular emphasis is placed on this area.

8.6.1 Pre-operative staging

Pre-operative staging considerations are the same as those for colon cancer, including visualisation of the entire colon, (see Section 8.5.1 and Recommendations 8.19 and 8.20).[Rec 8.23; 8.24] In addition, however, it is important that the primary tumour be imaged in order to assess the need for neoadjuvant therapy. It is recommended that MRI of the pelvis be carried out for this purpose **(III - B)**, although high-quality multi-slice CT scanning may provide adequate information **(VI - C).**[Rec 8.25] It should also be borne in mind that large rectal adenomas may harbour invasive malignancy, and it is recommended that all of these should be evaluated pre-operatively by transrectal ultrasound in order to assess the likelihood of possible invasive malignancy. Endoscopic ultrasound may also be helpful in distinguishing T1 from T2 tumours.

8.6.2 Neoadjuvant therapy

For many years it has been recognised that adjuvant radiotherapy given either pre-operatively or post operatively reduces the risk of local recurrence after radical excision of rectal cancer. There is now good evidence that pre-operative treatment is superior to post-operative treatment (SIGN 2003; NCCN 2010b) and it follows that all patients with rectal cancer (and certainly those predicted on imaging to have T3/4 cancers and/or lymph node metastases) should be considered for pre-operative radiotherapy with or without concomitant chemotherapy **(I - A).**[Rec 8.28] It is not possible to be

prescriptive regarding the regime as this is dependant on pre-operative assessment of the individual tumour, the fitness of the patient (particularly with regard to chemotherapy), and on local protocols.

8.6.3 Surgery

Radical surgery for rectal cancer consists of either anterior resection or abdomino-perineal excision of the rectum. The latter operation is reserved for tumours where it is impossible to mobilise the tumours sufficiently to achieve an anastomosis, and in specialist practice this accounts for less than 40% of all rectal cancers.

The main principle of rectal cancer surgery is to obtain an adequate circumferential margin clearance of the tumour and to this end all rectal cancers treated by radical surgery are best served by the technique of mesorectal excision **(II - A).**[Rec 8.26] In cancers of the upper rectum it is acceptable to transect the mesorectum 50 mm distal to the tumour, but in cancers of the lower two thirds, total mesorectal excision is required. Evidence is accumulating that when an abdomino-perineal excision is carried out, wide excision of the pelvic floor is required to obtain adequate tumour clearance (West et al. 2008a).

There is now very good evidence that the quality of the surgery is strongly correlated with local recurrence and survival (Quirke et al. 2009), and, as with colon cancer, both short- and long-term outcomes are dependent on the degree of specialisation and experience of the surgeon (McArdle & Hole 2004). Therefore all patients undergoing radical surgery for rectal cancer should have mesorectal excision by an adequately trained specialist surgeon **(VI - A).**[Rect 8.26]

The same general considerations regarding laparoscopic surgery for colon cancer apply to rectal cancer (see Sect. 8.5.2 and Rec. 8.22) **(I - B).**[Rec 8.27] It should be considered, however, that a recent Cochrane Review concluded that laparoscopic surgery for the upper rectum is feasible, but more randomised trials are required to assess the long-term outcome (Kuhry et al. 2008).

8.6.4 Post-operative radiotherapy

Post-operative radiotherapy plus concomitant chemotherapy is indicated when a rectal tumour has been removed without pre-operative radiotherapy and where the resection margins are threatened by invasive cancer (Sengupta & Tjandra 2001; Min et al. 2007; Park et al. 2008) **(III)**.

8.6.5 Management of small rectal cancers

A major effect of a screening programme is to increase the number of small primary cancers that are diagnosed, and because the rectum can be accessed transanally this opens up the possibility of local excision for small rectal cancers. This can be achieved using conventional approaches with specifically designed retractors (e.g. the Pratt Biovalve Retractor and the Lone Star Retractor) or, if the tumour is in the mid- or upper rectum, using transanal endoscopic microsurgery (TEM) (Tytherleigh, Warren & Mortensen 2008). If a decision is made to locally excise a proven rectal cancer, this must be done along with an underlying full-thickness disk of rectal muscle and a margin of normal tissue of at least 5 mm in order to maximise the chance of complete excision. It must be recognised that this is only

suitable for posterior rectal tumours or low anterior rectal tumours. A full-thickness excision of a high anterior rectal tumour, particularly in a female, can result in perforation into the peritoneal cavity.

The main issue surrounding local excision of early rectal cancers is the risk of recurrence, and the evidence is such that most surgeons consider the risk of local recurrence after local excision to be considerably higher than that after radical rectal excision (Tytherleigh, Warren & Mortensen 2008). The risk of recurrence is dependent on the depth of invasion of the primary tumour, tumour diameter, lymphovascular invasion and degree of differentiation (Bach et al. 2009). T2 tumours are associated with at least a 20% risk of recurrence after local excision (You et al. 2007); T1 tumours are associated with a lesser risk of local recurrence, but again this is dependent on the depth of invasion. Kikuchi sm1 level tumours (superficial one third of the sub-mucosa) are associated with a negligible risk of local recurrence and can be safely treated by local excision (Kikuchi et al. 1995). Kikuchi level sm2 tumours (superficial two thirds of sub-mucosa) are associated with an 8% risk of local recurrence, and Kikuchi level sm3 tumours (full thickness involvement of the sub-mucosa) are associated with almost the same risk of local recurrence as T2 tumours. Thus under most circumstances radical surgery for sm2 and sm3 tumours is indicated. If a local excision is made and the pT stage is T1 sm3 or worse then radical excision should be carried out provided the patient is fit enough for radical surgery **(II - B).**[Rec 8.32]

There is, however, a school of thought that local excision combined with radiotherapy plus or minus chemotherapy may produce acceptable local recurrence rates in T1, T2 and even T3 tumours; however the evidence to support this comes from relatively small case series. A recent review of the literature examined the use of pre-operative chemoradiation (CRT) and local excision, and found that local recurrence was 0% for those with pT0 tumours (i.e. complete response to CRT), 2% for pT1 tumours, 7% for pT2 tumours and 21% for pT3 tumours (Borschitz et al. 2008). (Note: in this context, pT refers to the *histopathological* T stage determined on the resection specimen after CRT).

There have been two RCTs comparing local excision by means of TEM and radical resection. One compared TEM alone with radical resection for T1 carcinoma (Winde et al. 1996), and the other compared TEM plus pre-operative CRT with radical surgery for T2 tumours (Lezoche et al. 2008). Both demonstrated significantly shortened operating times, less blood loss, less analgesic usage and shorter duration of hospitalisation with the TEM approach, but although neither demonstrated a difference in local recurrence rates, neither trial was sufficiently powered to examine this outcome.

In summary, with the exception of sm1 T1 cancers, there is a significant risk of local recurrence after local excision, although this may be modified by pre-operative CRT.

This view is supported by two recent systematic reviews (Middleton, Sutherland & Maddern 2005; Suppiah et al. 2008). Therefore, local excision alone should only be performed for T1 sm1 rectal cancers and if the patient is fit for radical surgery **(III - B).**[Rec 8.29] Furthermore, in patients in whom local excision for rectal cancer is planned, consideration should be given to pre-operative CRT **(III - C).**[Rec 8.31]

If however there is doubt about the fitness of the patient for radical surgery, local excision of more advanced rectal cancer could be considered **(III - B).**[Rec 8.30]

8.6.6 Synopsis

Summary of evidence

- The quality of surgery for rectal cancer, particularly with respect to circumferential margin involvement and the plane of surgery are strongly associated with outcome in terms of local recurrence and survival **(III)**.

- Although the evidence is not as extensive as for colon cancer, there is evidence that laparoscopic surgery for rectal cancer may be associated with better short-term outcomes without significant detriment **(I)**.
- Preoperative radiotherapy is associated with improved local recurrence rates and improved survival in appropriate patients undergoing radical surgery for rectal cancer **(I)**.
- Although small rectal cancers can be excised locally, local recurrence rates are higher than with radical surgery, with the exception of early (sm1) T1 cancers **(III)**.
- If a rectal cancer can be downstaged to pT0 or pT1 with CRT, local excision is associated with low local recurrence rates **(V)**.

Recommendations for management of rectal cancer

- If a complete colonoscopy has not been performed either because the primary lesion precluded total colonoscopy, or any other reason for failure to complete colonoscopy, the rest of the colorectum should be visualised radiologically before surgery if at all possible. This should be performed ideally by CT colography, or if this is not available, by high-quality double-contrast barium enema. If for any reason the colon is not visualised prior to surgery, complete colonoscopy should be carried out within 3 to 6 months of excision of the rectal cancer **(VI - B).**[Rec 8.23]
- Patients with a proven screen-detected rectal cancer should undergo pre-operative staging by means of CT scanning of the abdomen and pelvis **(VI - B).** Routine chest CT is not recommended **(III - D).**[Rec 8.24]
- Patients with a proven screen-detected rectal cancer should ideally undergo pre-operative local staging by means of MRI scanning of the pelvis in order to facilitate planning of pre-operative radiotherapy **(III - B)**, although high-quality multi-slice CT scanning may provide adequate information **(VI - C).**[Rec 8.25]
- All patients undergoing radical surgery for rectal cancer should have mesorectal excision **(II - A)** by an adequately trained specialist surgeon **(VI - A).**[Rec 8.26]
- Patients undergoing surgery for rectal cancer may be considered for laparoscopic surgery **(I - B).**[Rec 8.27]
- All patients undergoing surgery for rectal cancer (and certainly those predicted on imaging to have T3/4 cancers and/or lymph node metastases) should be considered for pre-operative adjuvant radiotherapy with or without chemotherapy **(I - A).**[Rec 8.28]
- Local excision alone should only be performed for T1 sm1 rectal cancers and if the patient is not fit for radical surgery **(III - B).**[Rec 8.29]
- In the patient in whom there is doubt about fitness for radical surgery, local excision of more advanced rectal cancer should be considered **(III - B).**[Rec 8.30]
- In patients in whom local excision for rectal cancer is planned, consideration should be given to pre-operative CRT **(III - C).**[Rec 8.31] If a local excision is carried out, and the pT stage is T1 sm3 or worse, then radical excision should be performed if the patient is fit for radical surgery **(II - B).**[Rec 8.32]

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9

Colonoscopic surveillance following adenoma removal

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Guiding principles

1. Patients with previous adenomas are at increased risk for recurrent adenomas and thus eventually colorectal cancer. This risk is thought to depend on findings during baseline colonoscopy, in particular the number, size and histological grade of removed adenomas. This allows categorisation of patients into different risk groups. The indication and interval for surveillance is determined primarily by the presumed risk for recurrence of advanced adenomas and cancer, and secondarily also by age, co-morbidity, and patient wishes.
2. The primary aims of colonoscopic surveillance are to reduce the morbidity and mortality from colorectal cancer by removing high risk adenomas before they have had a chance to become malignant, and by detecting invasive cancers at an early, curable, stage.
3. Colonoscopy is a costly, invasive and scarce resource. Therefore colonoscopy surveillance should be undertaken only in those at increased risk and at a minimum frequency required to provide adequate protection against the development of cancer.
4. If colonoscopy surveillance is undertaken, it should be performed to the highest standard.
5. The surveillance strategy should be based on an assessment of the risk of developing advanced adenomas and colorectal cancer after a baseline colonoscopy.
6. Patients can be divided into low, intermediate and high risk groups, and the interval to the first follow-up examination can vary accordingly. A reassessment can be made based on findings at the first and subsequent follow-up examinations.
7. The risk stratification is predicated on an assumption that the initial and subsequent colonoscopies are of high quality and that there is complete removal of any detected lesions.
8. Surveillance colonoscopy consumes considerable endoscopic resources and may prevent a country that has difficulty meeting demand from sustaining reasonable waiting times. Screening programmes should have a policy on surveillance with a hierarchy of action for different risk groups based on resource availability.

Recommendations[1]

Risk stratification (see Figure 1)

9.1 Patients can be divided into low, intermediate and high risk groups with respect to their risk of developing advanced adenomas and cancer based on findings at baseline colonoscopy. The surveillance strategy can vary accordingly **(III - A).**[Sect 9.1; 9.3.1-3]

9.2 A readjustment of the strategy can be made based on findings at the first and subsequent surveillance examinations **(III - C).**[Sect 9.1; 9.4.1]

9.3 **Low risk**. Patients with only one or two small (<10 mm) adenomas are at low risk, and should be returned to the screening programme **(III - A).**[Sect 9.3.1]

9.4 **Intermediate risk.*** Patients with three or four small adenomas or at least one adenoma of size ≥10 mm and <20 mm are at intermediate risk **(III - A)** and should be offered surveillance at 3-yearly intervals **(II - A)**. After one negative exam, the interval can be extended to 5 years **(V - C)**. After two consecutive normal exams, the patient can return to routine screening **(VI - C).**[Sect 9.3.2; 9.4.1]

* Some programmes may wish to include small (<10 mm) adenomas with a villous component or with high grade neoplasia[2] in this group **(III - C).**[Sect 9.2.2.3; 9.3.1]

9.5 **High risk.** If either of the following is detected at any single examination (at baseline or follow-up): 5 or more adenomas, or an adenoma ≥20 mm, the patient is at high risk and an extra examination should be undertaken within 12 months, to check for missed synchronous lesions, before initiating 3-yearly surveillance **(III - B).** After two consecutive normal exams, the interval can be extended to 5-yearly **(V - C).** In the absence of evidence on the safety of stopping surveillance in the high risk group, surveillance should continue, taking into account Recommendations 9.10 and 9.11 **(VI - C)**.[Sect 9.3.3; 9.4.1]

Quality of colonoscopy and removal of colorectal lesions

9.6 The risk stratification is based on accurate detection and complete removal of adenomas otherwise risk status will be underestimated **(III - A).**[Sect 9.1; 9.2.1.1]

9.7 Exams should be performed only after adequate bowel preparation i.e. without any residual stool or liquid in the lumen that could mask any suspicious area (see also Ch. 5, Rec. 5.22) **(VI – A)**. Exams should be complete to the caecum and there should be slow, careful inspection of the colonic mucosa during withdrawal of the scope (See Ch. 5, Rec. 5.35) **(I - A).**[Sect 9.2.1.1; 5.3.3; 5.4.5.1]

9.8 Patients with a failed colonoscopy should, if possible, undergo repeat colonoscopy or an alternative complete colonic examination, particularly if they are in the high risk group **(VI - B).**[Sect 9.2.1.2]

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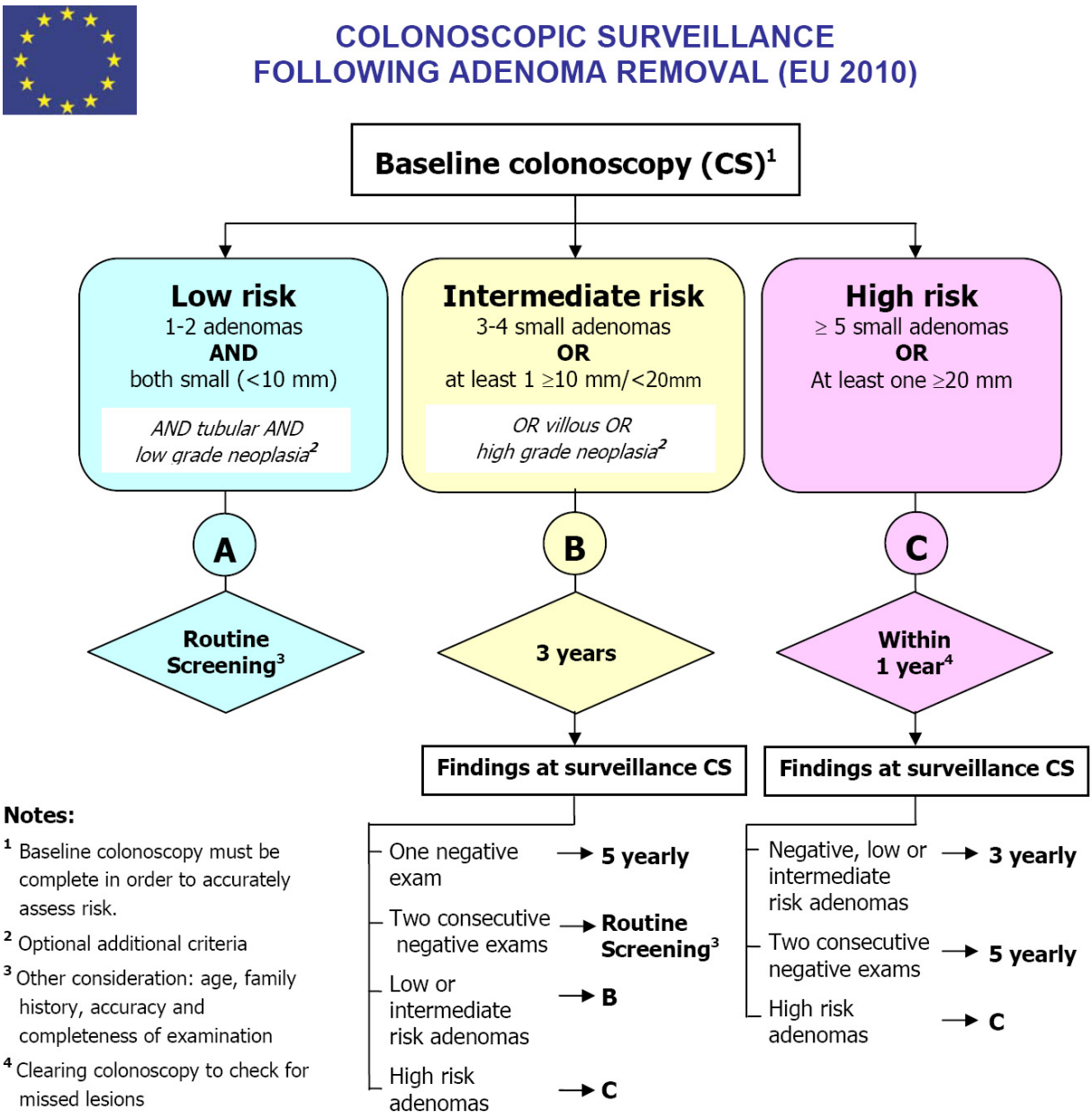
[1] **Sect** (superscript) after each recommendation in the list refers the reader to the section/s of the Guidelines dealing with the respective recommendation.

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

[2] For consistency between the chapters of the European Guidelines, size and histopathology of endoscopically removed colorectal lesions are described using the scale (*mm*) and terminology (*neoplasia* rather than *dysplasia*) as recommended in Chapter 7 *Quality assurance in pathology in colorectal cancer screening and diagnosis*. This terminology is used in the Guidelines even though *cm* and *dysplasia* are used to report size and histopathology in other publications.

Figure 9.1: Recommended surveillance following adenoma removal. (For explanation see Recommendations 9.1–9.20 and Sections 9.3–9.5)



9.9 The site of large sessile lesions removed piecemeal should be re-examined at 2–3 months. Small areas of residual tissue can then be treated endoscopically, with a further check for complete eradication within 3 months. India ink tattooing aids recognition of the site of excision at follow-up. If extensive residual lesion is seen, surgical resection must be considered, or alternatively, referral to a colonoscopist with special expertise in advanced endoscopic excision. **(VI - B).**[Sect 9.2.1.3]

Stopping surveillance

9.10 The decision to undertake each colonoscopic surveillance examination should depend not only on adenoma characteristics, but also on the patient's age and wishes, and the presence of significant co-morbidity. The patient status should be established prior to attendance for each examination **(VI - A).**[Sect 9.4.2]

9.11 The cut-off age for stopping surveillance is usually 75 years, but this should also depend upon patient wishes and co-morbidity **(VI - A).**[Sect 9.4.2]

9.12 Following cessation of surveillance, individuals should be returned to the population screening programme **(VI - C).**[Sect 9.4.2]

Family history

9.13 Recommendations should not differ for patients with a family history who are found to have adenomas, unless it is suspected that they have one of the dominantly inherited conditions. **(III - B).**[Sect 9.2.3.2]

Symptoms

9.14 New symptoms should be assessed on the basis that a recent clearance colonoscopy reduces the chance of advanced adenomas and cancers but does not eliminate the risk altogether **(III - A).**[Sect 9.4.3]

Role of faecal occult blood testing

9.15 The potential benefit of supplementing colonoscopy exams with faecal occult blood testing is presumed to be too small to warrant double testing; therefore it is recommended to stop faecal occult blood testing in individuals who are undergoing surveillance **(VI - C).**[Sect 9.4.4]

Guideline following local removal of a pT1 cancer

9.16 By their nature locally removed pT1 cancers are high risk lesions and therefore should undergo a surveillance strategy similar to the high risk adenoma group **(III - B).**[Sect 9.5.1]

Guideline following detection of serrated adenomas

9.17 For surveillance purposes, serrated adenomas (traditional serrated adenomas and mixed polyps with at least one adenomatous component) should be dealt with like any other adenoma; there are no data to suggest that different surveillance intervals are required **(VI - C).**[Sect 9.5.2; 7.2; 7.2.4.4; 7.2.4.5]

Guideline following detection of hyperplastic polyps or other non-neoplastic serrated lesions

9.18 There is no evidence that patients in whom only small, distally located hyperplastic polyps are detected are at increased risk for colorectal cancer; therefore they should be offered routine screening **(III - A).**[Sect 9.5.3; 7.2.4.2]

9.19 One or more large (≥10 mm) hyperplastic polyps or other non-neoplastic serrated lesions anywhere in the colon or multiple smaller lesions of these types in the proximal colon may confer an increased risk, but there are no data available to indicate appropriate surveillance intervals **(VI - B).**[Sect 9.5.3]

Quality improvement

9.20 Every screening programme should have a policy on surveillance. The policy may limit surveillance to the high risk group if sufficient resources are not available to include people with lower risk **(VI - B).**[Sect 9.7]

9.21 The responsibility of programme management to assure the quality of screening services includes quality assurance of surveillance. For surveillance, the same principles, methods and

standards of quality assurance apply that are elucidated elsewhere in the first edition of the European Guidelines **(VI - B).**[Sect 9.7]

9.22 Adherence to the Guidelines should be monitored **(VI - A).**[Sect 9.7.1]

9.23 Surveillance histories should be documented and the results should be available for quality assurance **(VI - A).**[Sect 9.7.2]

9.24 The occurrence of colorectal cancer in any individual in whom adenomas or pT1 cancers have been detected at a previous exam should be captured as an auditable outcome for any surveillance programme **(VI - B).**[Sect 9.7.3]

9.1 Introduction

The adenoma is the precursor of the vast majority of colorectal cancers and is the most frequently detected lesion when colonoscopy is performed, either as a primary screening test or for investigation of a positive stool test (Imperiale et al. 2000; Lieberman et al. 2000; Schoenfeld et al. 2005). Hyperplastic polyps are also frequently detected during endoscopic examinations, but most are of no clinical significance.

The previous chapter has dealt with the management of colorectal lesions detected during endoscopy: they are invariably removed for histopathological assessment unless they are smaller than 3 mm and located in the distal rectum, and therefore likely to be innocuous hyperplastic polyps.

This chapter deals with decisions about the need for subsequent surveillance after removal of colorectal lesions once a pathological diagnosis has been made. The main focus of the chapter is on surveillance following adenoma removal but a small section has been devoted to other types of lesions including locally-removed pT1 cancers, serrated adenomas, hyperplastic polyps and other non-neoplastic serrated lesions.

Following initial detection and removal of adenomas, one third to one half of people will be found to have further adenomas within 3 years. In addition, cancer is detected in 0.3–0.9% within 5 years in patients undergoing surveillance (Nozaki et al. 1997; Alberts et al. 2000; Schatzkin et al. 2000; Lund et al. 2001; Baron et al. 2003; Robertson et al. 2005; Arber et al. 2006; Baron et al. 2006; Bertagnolli et al. 2006; Martinez et al. 2009). Many of these adenomas and cancers represent lesions missed at baseline colonoscopy, emphasising the importance of high quality examinations (Rex et al. 2002).

One of the primary purposes of colonoscopic surveillance is to prevent the development of colorectal cancer by removing new or missed adenomas before they have had a chance to progress to malignancy. Not all cancers are prevented by colonoscopy (Bressler et al. 2004; Robertson et al. 2005). Thus surveillance also aims to detect cancer at an earlier stage to increase the chance of survival.

Colonoscopy, with or without removal of a lesion, is an invasive procedure with a small but not insignificant risk of major complication, either from perforation (2% with, and 0.06% without excision), or from major post-excision haemorrhage (0.2%–2.7%, depending on size of lesion) (Macrae, Tan & Williams 1983; Nivatvongs 1986; Waye, Lewis & Yessayan 1992; Rosen et al. 1993). Surveillance colonoscopies also place an important burden on endoscopy services. In the USA, 22% of all colonoscopies in patients over 55 years are performed for surveillance purposes (Lieberman et al. 2005). For these reasons, surveillance colonoscopy should be targeted at those who are most likely to benefit, and at the minimum frequency required to provide adequate protection against the development of cancer.

The malignant potential of an adenoma - that is the chance that it harbours a focus of invasive cancer, or that it would progress to malignancy if not removed - varies according to its size, histology and grade of neoplasia (Muto, Bussey & Morson 1975; Eide 1986). Adenomas that are 10 mm or larger, have a villous component, or contain areas of high grade neoplasia have a higher malignant potential and are frequently described as “advanced”; however some studies, including the US National Polyp Study, include only large size (>10 mm) and high grade neoplasia in this definition (Winawer et al. 1993) (see Ch. 7, Sect. 7.2, 7.2.2, 7.3, and 7.3.2).

The future risk of diagnosing cancer or advanced adenomas following adenoma removal depends primarily on two major factors: the quality of the baseline colonoscopy and the characteristics of previously removed adenomas.

These Guidelines provide evidence that patients can be divided into low, intermediate, and high risk groups based on findings at baseline colonoscopy, and that the surveillance strategy can vary accordingly (see Figure 1 and Sections 9.3.1-3) **(III - A).**[Rec 9.1] The Guidelines also provide limited evidence that readjustment of the strategy can be made based on findings at the first and subsequent surveillance examinations (see Section 9.4.1) **(III - B).**[Rec 9.2]

9.2 Risk factors for advanced adenomas and cancer after baseline removal of adenomas

9.2.1 Procedural factors

9.2.1.1 Quality of colonoscopy

The efficacy and safety of the Guidelines in reducing risk of colorectal cancer depends on accurate detection and removal of baseline adenomas; otherwise risk status will be underestimated (see also Section 9.1) **(III - A).**[Rec 9.6]

Colonoscopy is not 100% sensitive even when intubation to the caecum is achieved. Adenomas, advanced adenomas and cancers can be missed, particularly by endoscopists using poor technique (Rex 2000). Miss rates for small adenomas at back-to-back colonoscopies are approximately 25%–50% (Hixson et al. 1990; Rex et al. 1997a; Heresbach et al. 2008), but the significance of this is as yet unclear. Of more concern is the observation that up to 6% of larger adenomas (≥10 mm) (Rex et al. 1997a; Bensen et al. 1999; Heresbach et al. 2008) and around 4% of cancers are missed at colonoscopy (Bressler et al. 2004; Farrar et al. 2006). These figures are remarkably similar to the detection rates of adenomas and advanced adenomas at first follow-up, suggesting that the majority of lesions detected at early follow-up were missed at baseline.

The risk stratification for surveillance is based partly on the assumption that patients with multiple or advanced adenomas are more likely to develop new important lesions. However, it also considers that these same subjects are more likely to harbour missed lesions that require early follow-up endoscopy. High quality baseline colonoscopy with adequate full assessment of the colon and complete removal of all adenomas is therefore essential and might have a similar magnitude of effect on colorectal cancer incidence as intensifying surveillance in most patients.

If colonoscopy surveillance is undertaken, it should also be done to the highest standard (Rex et al. 2002) (Chapter 5, Section 5.1.2). Most interval cancers in people undergoing surveillance are lesions that were missed or incompletely removed at the previous colonoscopy (Pabby et al. 2005; Robertson et al. 2005).

Infrequent high quality exams are probably more effective in preventing colorectal cancer than are frequent low quality exams.

Exams should be performed only after adequate bowel preparation i.e. without any residual stool or liquid in the lumen that could mask any suspicious area (see also Ch. 5, Rec. 5.22) **(VI – A)**. Exams should be complete to the caecum and there should be slow, careful inspection of the colonic mucosa during withdrawal of the scope (see Ch. 5, Rec. 5.35) **(I - A).**[Rec 9.7]

Higher detection rates are associated with adequate distension, suction and cleaning, position change, and slow and meticulous examination of the colonic mucosa, including behind folds (see also Chapter 5, Section 5.3.3 and 5.4.5.1).

When a small polyp is detected during insertion it is frequently difficult to relocate it on withdrawal. Where possible, consideration should be given to removing *small* lesions immediately on detection. Scanning the colonic mucosa during both insertion and withdrawal allows for essentially two examinations and potentially a reduction in the miss rate of small lesions. Removing larger lesions on insertion is not generally advisable because of the increased risk of bleeding and a possible increased risk of perforation.

9.2.1.2 Incomplete or inadequate colonoscopy

Patients with a failed colonoscopy should, if possible, undergo repeat colonoscopy or an alternative complete colonic examination, particularly if they are in the high risk group **(VI - B).**[Rec 9.8]

The decision may depend on patient factors such as age, risk group, the findings at the current examination, the difficulty of the examination, and the potential risks of repeating it, along with the general health and concerns of the patient. It also depends on local factors, such as waiting lists and whether the examination could be performed by a more experienced endoscopist.

In the US National Polyp Study (NPS), the examination was repeated if the baseline colonoscopy did not clear the colon with high confidence. Repeat examinations were required in 13% of exams (Winawer et al. 1993). The NPS authors attribute the low subsequent risk of cancer seen in the NPS cohort compared with other studies (Pabby et al. 2005; Robertson et al. 2005; Farrar et al. 2006) in which cancers were detected early in the surveillance programme to be the result of the careful baseline clearing of adenomas.

9.2.1.3 Management of incomplete adenoma excision

The safety and efficacy of the Guidelines depend on the complete and safe removal of all adenomas detected at colonoscopy.

Incompletely removed, large, flat lesions pose a high risk of cancer. At least one quarter of all cancers diagnosed within 3 years of a complete colonoscopy develop at the site of a previous excision (Pabby et al. 2005; Lieberman et al. 2007).

The management of large, sessile lesions removed piecemeal, is described in Chapter 8, Section 8.3.6. The site of excision should be re-examined after 2–3 months. Small areas of residual tissue can then be treated endoscopically, with a further check for complete eradication within 3 months. India ink tattooing aids recognition of the site of excision at follow-up. If extensive residual lesion is seen, surgical resection must be considered, or, alternatively, referral to a colonoscopist with special expertise in advanced polypectomy **(VI - B).**[Rec 9.9]

9.2.2 Characteristics of baseline adenomas

9.2.2.1 Number of adenomas

Multiplicity of adenomas is the most consistent predictor of the detection of advanced pathology or cancer at follow-up.

In a meta-analysis of several colonoscopic surveillance studies (Saini, Kim & Schoenfeld 2006), patients with 3 or more adenomas at baseline were at an approximately two-fold increased risk of advanced neoplasia during surveillance compared with those with only 1–2 adenomas. In a more recent pooled analysis (Martinez et al. 2009) that included eight US studies with a combined population of 9167 men and women with previously removed colorectal adenomas, advanced adenomas were detected at follow-up within 5 years in 12% (n=1082) and cancer in 0.6% (n=58). There was a highly significant linear trend of increasing frequency of advanced neoplasia (advanced adenomas and cancers) with increasing number of baseline adenomas detected. Compared with having a single baseline adenoma, risk was increased twofold in those with 3–4 adenomas and was increased fourfold in those with 5 or more adenomas. Another prospective study not included in the above analyses also confirmed these results (Cafferty et al. 2007).

The high detection rate of advanced neoplasia at follow-up after removal of multiple adenomas might result from a higher miss rate combined with a potential for such adenomas to be more advanced.

9.2.2.2 Size of adenomas

In several (Saini, Kim & Schoenfeld 2006; Martinez et al. 2009) but not all observational studies (Van Stolk et al. 1998), increased adenoma size has been found to predict detection of advanced adenomas and cancer at follow-up. In the recent large US pooled study (Martinez et al. 2009), risk was increased twofold for individuals who had at least one adenoma of size 10–<20 mm and threefold for size ≥20 mm, compared with those who only had adenomas <10 mm.

One reason for the inconsistent reporting of adenoma size as a risk factor for advanced adenoma recurrence is that current guidelines use 1 cm as a cut-off for identifying patients at higher risk and there are shorter intervals between surveillance exams for such patients in many studies, thereby attenuating risk. There are also inaccuracies in the endoscopic assessment of the size of adenomas, particularly around the 1 cm threshold (Morales et al. 1996; Schoen, Gerber & Margulies 1997), with frequent rounding up to 1 cm.

It is recommended that all measurements are reported in mm. When present, the pathologist's size should be used. If this is absent or if the lesion is fragmented, then the endoscopy size should be used (see Ch 7, Rec. 7.8 and 7.9, Sect. 7.2.1, 7.6.2 and 7.6.3).

9.2.2.3 Adenoma histology

The presence of tubulovillous or villous histology in a baseline adenoma is an inconsistent predictor of advanced neoplasia at subsequent surveillance colonoscopy. Correlations between size and histology of adenomas mean that the effects of the two factors are difficult to separate (Lieberman et al. 2008). Furthermore, sampling errors in small biopsies and large lesions exacerbate difficulties in interpretation, and classification of adenoma histology is subjective and prone to wide inter-observer variability (Costantini et al. 2003).

In a meta-analysis and systematic review (Saini, Kim & Schoenfeld 2006) on baseline risk factors for advanced adenomas, there was no significant difference between tubulovillous or villous vs. tubular adenomas in any of the individual studies. A subsequent prospective study found an increased risk of recurrence of villous adenomas among patients who had villous adenomas detected at baseline (Cafferty et al. 2007). However, in the large pooled US analysis (Martinez et al. 2009), the strong association between baseline villous histology (including tubulovillous and villous) seen in univariate analyses was almost completely attenuated in the multivariate analysis. Thus, considering that adenoma characteristics such as number and size represent stronger predictors of developing advanced pathology, and taking into account the low reproducibility of the histology classification, histology alone may not be considered a significant risk factor for neoplasia recurrence.

9.2.2.4 Grade of neoplasia[3]

Most studies compare risks for the subsequent development of advanced adenomas according to whether there are baseline adenomas with high grade dysplasia. This corresponds to high grade neoplasia as described in Chapter 7 in Section 7.3.2 and Table 7.1. Some individual studies (Bonithon-Kopp et al. 2004; Lieberman et al. 2007) have found risk to be higher in patients with high grade dysplasia in adenomas of any size. Similar results were reported by one meta-analysis (Saini, Kim & Schoenfeld 2006), although it included only two studies that evaluated the role of grade of neoplasia. The association was not confirmed, however in a large pooled analysis using individual-level data, in which neoplasia data were available from 6 studies, after adjusting for several risk factors (Martinez et al. 2009). Thus, available evidence suggests that high grade neoplasia may not have independent predictive value for the detection of advanced colorectal adenomas and cancer, and that after removal of small adenomas with high grade neoplasia, the risk of developing further advanced adenomas and cancer is not increased. Caution should be exercised with this interpretation of the evidence since high grade neoplasia is present in only 1% of adenomas smaller than 10 mm (Lieberman et al. 2008); therefore most studies suffer from small numbers and a lack of statistical power. It is therefore reasonable to be pragmatic and decide locally about whether to offer surveillance to individuals with small (<10 mm) adenomas demonstrating high grade neoplasia **(III - C).**[Rec 9.4]

9.2.2.5 Location

Several studies have found that having any proximal adenoma at baseline significantly increases risk for subsequent advanced neoplasia. Risks in individual studies vary from 1.5 to 2.5 fold compared with having adenomas only in the distal colon (Baron et al. 1995; Greenberg et al. 1994; Alberts et al. 2000; Alberts et al. 2005; Saini, Kim & Schoenfeld 2006; Laiyemo et al. 2009; Martinez et al. 2009).

It is as yet unclear how the finding of proximal adenomas should influence the Guidelines.

9.2.3 Patient characteristics

9.2.3.1 Age and sex

Older age has been found to be associated with an increased risk of advanced neoplasia in several studies (Yamaji et al. 2004; Martinez et al. 2009).

It is possible that the higher risk with older age is related to the increased difficulty of performing an accurate examination. Combined with a greater likelihood of older people having an advanced lesion, there is a greater chance of missing advanced neoplasia at older ages.

However, advanced age is not an indication for more intense surveillance. Colonoscopy is likely to be less successful and more risky at older ages. Furthermore, the lead time for progression of an adenoma to cancer is around 10 to 20 years, which is of the same order as the average life-expectancy of an individual aged 75 years or older, suggesting that most will not benefit from surveillance.

Male sex has been shown to be a moderate risk factor in some (Martinez et al. 2009) but not all studies (Yamaji et al. 2004). However, it is unclear how this finding should affect Guidelines.

[3] See Footnote 2 in this chapter (p. 276).

9.2.3.2 Family history

Several studies have found that the prevalence of adenomas on baseline colonoscopy is increased in patients with a family history of colorectal cancer (Bonelli et al. 1988; Cannon-Albright et al. 1988; Pariente et al. 1998; Lieberman et al. 2000). Other studies have suggested that patients with a family history also have an increased risk of advanced or multiple adenomas (Neklason et al. 2008; Wark et al. 2009).

The US National Polyp Study (Zauber et al. 1999) found that the subsequent risk of developing advanced adenomas in people undergoing surveillance was increased in people aged ≥60 years who had a parent affected by colorectal cancer. However, these data are published only in abstract form. One other study (Nusko et al. 2002) found that having a parent with a history of colorectal cancer conferred an increased risk, but this was based on small numbers, and other studies have not confirmed this finding. Detection rates of advanced adenomas among 1287 participants in a trial of wheat bran fibre were unaffected by inclusion of family history in a multivariate model after adjustment for adenoma characteristics at baseline (Martinez et al. 2001). Similarly, in the recent US pooled analysis, the risk of developing advanced neoplasia during surveillance was not influenced by family history (Martinez et al. 2009).

Thus there is no consistent evidence to suggest that recommendations on adenoma surveillance should differ for patients with a family history, unless it is suspected that they have one of the dominantly inherited conditions **(III - B).**[Rec 9.13]

9.3 Risk groups and surveillance intervals

Recommendations from several European countries and the USA have defined three risk groups: low, intermediate and high risk for the development of colorectal cancer and advanced adenomas, based on the number and characteristics of adenomas detected at baseline colonoscopy (Hoff et al. 1996; Atkin & Saunders 2002; Bjork et al. 2003; Winawer et al. 2006; Schmiegel et al. 2008). Stratifying patients with adenomas and adjusting intervals between exams can theoretically reduce the number of unnecessary procedures and thereby the burden and costs as well as the complication rate associated with adenoma surveillance, whilst protecting those at highest risk (see Figure 1 and Sections 9.3.1–3, 9.4 and 9.5).

Recommendations for surveillance intervals are based primarily on early trials and cohort studies. Because of the high recurrence rate of adenomas within 3 years after a baseline clearing examination, it was customary in the past to perform very frequent exams (even annually) (Ransohoff, Lang & Kuo 1991). The US National Polyp Study (Winawer et al. 1993) was a randomised comparison of two different surveillance intervals in 1418 patients with newly diagnosed adenomas removed at colonoscopy. In this study, the cumulative detection rate of advanced adenomas or cancer was 3% at 3 years, irrespective of whether 1 or 2 examinations were performed within the 3 year period. The Funen Adenoma Follow-up Study (Kronborg et al. 2006) was another randomised comparison of surveillance intervals. This study found that the incidence of advanced neoplasia was higher in patients examined at 4 compared with 2 years (8.6% vs. 5.2%), although the difference was not significant. However, on balance, the authors concluded that the more than 50% reduction in the number of examinations and the probable reduction in complications justified the longer interval.

These results suggested that the first follow-up colonoscopy should be delayed until at least 3 years after baseline polypectomy for most patients with adenomas. However, the data from these trials do not preclude the possibility that much longer intervals might offer adequate protection for most patients.

A long-term follow-up study of patients from St Mark's (Atkin, Morson & Cuzick 1992) showed that a proportion of patients with adenomas were at particularly low risk of developing colorectal cancer and may require no surveillance. Conversely, more recent studies (Martinez et al. 2009) have shown that 3-yearly screening may not be adequate to protect a small minority of patients who are at high risk of both advanced adenomas and cancer.

9.3.1 Low risk group

Five studies (Van Stolk et al. 1998; Zauber et al. 1999; Noshirwani et al. 2000; Martinez et al. 2001; Lieberman et al. 2007) in patients undergoing surveillance colonoscopies have identified a low risk group. All but one (Martinez et al. 2001) of these studies agreed that having only 1–2 adenomas confers a low risk of subsequent advanced adenomas, but disagreed on the importance of size and histology. As described in Section 9.2.2.3, size and histology are highly correlated and it is difficult to separate the effects of each variable.

The Veterans Affairs colonoscopy screening follow-up study in the USA (Lieberman et al. 2007) was the only study to have compared risk in people with low risk adenomas and those in whom no neoplasia was detected. They found that the cumulative risk of detecting advanced neoplasia at colonoscopy undertaken within 5 years in people with 1–2 small tubular adenomas was not significantly different from those with no neoplasia detected. However, the study was underpowered to observe any difference that might exist because there was poor attendance at follow-up among the no neoplasia group.

The longer term risk of developing colorectal cancer has been examined for patients from whom adenomas were removed from the distal sigmoid colon and rectum by sigmoidoscopy. No increased incidence of cancer was observed in comparison with the general population in 751 residents of Rochester, Minnesota, following removal of small (≤10 mm) colorectal polyps (Spencer et al. 1984), most of which were unexamined histologically. A similar study from St Mark's Hospital (Atkin, Morson & Cuzick 1992), in which all removed lesions were examined histologically, found that patients from whom only small (<10 mm) tubular adenomas were removed from the distal sigmoid colon or rectum had no long-term increased risk of developing colon cancer in comparison with the general population. Risk of rectal cancer was profoundly decreased compared with the unexamined population.

The US National Polyp Study found that the cumulative risk of colorectal cancer at 6 years following baseline colonoscopic removal of adenomas was 75% lower than the US population (Winawer et al. 1993). This study identified a higher risk group which included patients with multiple (≥3) or large adenomas (Weston & Campbell 1995), further emphasising the low risk among those with 1–2 small adenomas.

Thus it appears that whether the outcome is an advanced adenoma or cancer, future risk is low among patients with one to two small adenomas, whether or not histology is considered.

The benefits of surveillance colonoscopy are likely to be low in patients with 1–2 small adenomas and probably not cost-effective (Ransohoff, Lang & Kuo 1991). We recommend routine screening for this group **(III - A).**[Rec 9.3]

Some programmes may wish to include small (<10 mm) adenomas with a villous component or with high grade neoplasia in the intermediate risk group, although the available evidence is limited and inconsistent (see Section 9.2.2.3) **(III - C).**[Rec 9.4]

9.3.2 Intermediate risk group

It has been shown consistently that patients with 3 or more adenomas are a higher risk group for the development of advanced adenomas and cancer, particularly if one of the adenomas is also large (≥10 mm) (Noshirwani et al. 2000; Martinez et al. 2009).

In the US National Polyp Study (Winawer et al. 1993), 9% of patients with 3 or more adenomas and 5% of those with a large adenoma removed at baseline developed an advanced adenoma by their first follow-up examination, compared with only 1% in those with a single adenoma. An analysis of 697 patients in the Cleveland Clinic Foundation Adenoma Registry (Noshirwani et al. 2000) showed that, compared with 1–2 small adenomas, risk is increased fivefold following removal of multiple (4 or more) small adenomas and tenfold following removal of multiple adenomas at least one of which is larger than 10 mm. In the pooled analysis of US studies, having 3–4 adenomas or an adenoma of size ≥10 mm was associated with an approximately twofold increased risk of advanced adenomas and cancer (Martinez et al. 2009).

There have been two studies of the long-term risk of colorectal cancer following removal of large distal colorectal lesions. Risk was increased threefold (compared with the general population) in Rochester, Minnesota residents from whom large lesions (≥10 mm and mostly adenomas) were removed (Lotfi et al. 1986). While in the study from St Mark's Hospital (Atkin, Morson & Cuzick 1992), risk of colon cancer was increased fourfold following removal of large (≥10 mm) distal adenomas or those with a villous component and sevenfold if there were also multiple adenomas.

Therefore having 3 or more adenomas or an adenoma ≥10 mm confers an increased risk of advanced adenomas and cancer and suggests that colonoscopic surveillance is warranted **(III - A)**. The results of the US National Polyp Study (Winawer et al. 1993) suggest that a 3-year interval to the first surveillance colonoscopy is adequate for most patients in this group **(II - A).**[Rec 9.4]

There are few data to inform on intervals after the first examination (see Section 9.4).

9.3.3 High risk group

Recent studies have reported that a proportion of patients remain at increased risk of developing advanced neoplasia despite 3-yearly surveillance**.** In the pooled analysis of US studies (Martinez et al. 2009), having 5 or more adenomas conferred a fourfold increased risk, and having an adenoma of size ≥20 mm conferred a threefold increased risk. Missed and incompletely removed lesions may be an explanation for the high detection rate of advanced neoplasia (Pabby et al. 2005; Robertson et al. 2005; Farrar et al. 2006; Lieberman et al. 2007)**.**

Thus, although not entirely consistent, the data suggest that an additional clearing colonoscopy at 12 months may be warranted in people found at a single colonoscopy to have 5 or more adenomas or an adenoma of size 20 mm or larger. These patients require careful surveillance colonoscopy because of the substantial risk of missing adenomas with high malignant potential **(III - B).**[Rec 9.5]

The aim of a single early surveillance colonoscopy in this group is to remove synchronous lesions not detected at an examination at which ≥5 adenomas or at least one adenoma of size ≥20 mm is

removed. This complete colonoscopy examination should be distinguished from polypectomy site surveillance exams undertaken following piecemeal removal of sessile lesions (refer to 9.2.13).

9.4 Adjusting surveillance during follow-up

9.4.1 Significance of a normal surveillance colonoscopy

Khoury et al. (1996) undertook a retrospective examination of 389 patients who had undergone follow-up colonoscopy at 1-year intervals after resection of colorectal cancer. The adenoma detection rate at follow-up was 10% if the prior colonoscopy was negative and 40% if the prior colonoscopy was positive. If multiple adenomas were found at the prior examination, 70% of colonoscopies were positive. In another series (Blumberg et al. 2000), a normal follow-up colonoscopy was associated with a lower incidence of subsequent adenomas at the next colonoscopy compared with those with adenomas detected (15% vs. 40%).

None of the studies to date has provided evidence to inform Guidelines on the degree of protection afforded by a single negative follow-up examination in patients with intermediate or high risk adenomas at baseline. One study (Wegener, Borsch & Schmidt 1986) has shown that a negative result at first follow-up examination in patients with multiple adenomas initially does not preclude the subsequent development of new adenomas. Thus, until data to the contrary are available, it must be assumed that patients in the intermediate or high risk groups remain at increased risk despite a single negative follow-up examination. Following two consecutive negative examinations there can be greater confidence that adenomas have not been missed and that subsequent risk is therefore decreased.

Given the limited available evidence, we recommend extending the interval after the first negative surveillance colonoscopy to five years in the intermediate risk group **(V - C)**. For the high risk group, we recommend a 2-year extension of the interval after two consecutive negative surveillance colonoscopies **(V - C).**

Following two complete, negative surveillance colonoscopies we assume that patients in the intermediate risk group are probably at low risk, and surveillance can cease **(VI - C).**[Rec 9.4; 9.5]

In the absence of evidence on the safety of stopping surveillance in the high risk group we recommend continuing surveillance in this group, taking into account the issues discussed in the following section **(VI - C).**[Rec 9.5]

9.4.2 Stopping surveillance

The risks and benefits of adenoma surveillance must be balanced at all ages, particularly in patients who have significant co-morbidity. The decision to undertake each colonoscopy examination at follow-up should depend not only on the number and type of adenomas, but also on the patient's age and wishes, and the presence of significant co-morbidity. Patient status should therefore be established prior to attendance for each examination **(VI - A).**[Rec 9.10; 9.11]

Following cessation of surveillance, individuals of appropriate age should be returned to the population screening programme **(VI - C).**[Rec 9.12]

The cut-off age for stopping surveillance is usually 75 years, but this should also depend upon patient wishes, co-morbidity and findings at surveillance exams **(VI - A).**[Rec 9.11] Older patients should be advised that adenomas generally take many years to become malignant, and newly detected adenomas are likely to remain benign for the remaining lifespan of most people aged over 75 years. This should not preclude further surveillance in a fit and motivated individual who has a tendency to produce multiple or advanced adenomas at follow-up.

9.4.3 Symptoms developing between surveillance exams

New symptoms should be assessed on the basis that a recent colonoscopy reduces the chance of advanced adenomas and cancers but does not eliminate the risk altogether. (Winawer et al. 1993; Rex et al. 1997b; Brenner et al. 2006; Singh et al. 2006; Baxter et al. 2009; Martinez et al. 2009) **(III - A).**[Rec 9.14]

9.4.4 Role of faecal occult blood testing

The potential benefit of supplementing colonoscopy exams with faecal occult blood testing is presumed to be too small to warrant double testing; therefore it is recommended to stop faecal occult blood testing in individuals who are undergoing surveillance **(VI - C).** [Rec 9.15]

9.5 Colonoscopic surveillance guidelines following removal of other colorectal lesions

9.5.1 Locally removed pT1 cancers

There are two reasons for performing colonoscopic surveillance after local removal of a low risk pT1 cancer. One is to examine the remaining colon and rectum to detect intraluminal recurrence; the other is to detect metachronous cancer or adenomas (Rex et al. 2006).

By their nature polyp cancers are high risk lesions (Chu et al. 2003; Di Gregorio et al. 2005; Rex et al. 2006). They therefore should undergo a surveillance strategy similar to the high risk adenoma group **(III - B).**[Rec 9.16]

It is assumed that there has been a high quality baseline clearing examination to detect and remove all synchronous lesions. It is also assumed that the cancer has been completely removed and the site re-examined as described in Chapter 8, Section 8.4.

This policy should also apply to locally-removed pT1 cancers detected during surveillance exams in any risk group.

9.5.2 Serrated adenomas

For surveillance purposes, serrated adenomas (i.e., traditional serrated adenomas and mixed polyps with at least one adenomatous component; see Chapter 7, Section 7.2.4.4 and 7.2.4.5) should be dealt with like any other adenoma; there are no data to suggest that surveillance intervals different from those in Figure 1 are required **(VI - C).**[Rec 9.17]

9.5.3 Hyperplastic polyps and other non-neoplastic serrated lesions

There is evidence that patients in whom only small, distally located hyperplastic polyps are detected are not at increased risk for colorectal cancer. These patients should therefore be offered routine screening **(III - A).**[Rec 9.18]

Recent publications dealing with hyperplastic polyps and other serrated non-neoplastic lesions are limited by methodological issues such as small sample size and diagnostic accuracy (see also Ch. 7, Sect. 7.1 and 7.2.4). They therefore preclude risk analysis stratified by the size and location of these lesions (Imperiale et al. 2008; Li et al. 2009; Schreiner, Weiss & Lieberman 2010).

Patients found to have a large (≥10 mm) hyperplastic polyp or other non-neoplastic serrated lesion anywhere in the colon or multiple lesions of these types in the proximal colon may be at increased risk, but there are no data available to indicate appropriate surveillance intervals **(VI - B).**[Rec 9.19]

Hyperplastic polyposis was defined by Burt & Jass (2000) for the WHO Classification of Tumours as:

- at least 5 histologically diagnosed hyperplastic polyps proximal to the sigmoid colon, of which 2 are greater than 10 mm in diameter; or
- any number of hyperplastic polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with hyperplastic polyposis; or
- more than 30 hyperplastic polyps of any size distributed throughout the colon.

Studies have found an increased risk for colorectal cancer in patients with hyperplastic polyposis defined less stringently than the WHO criteria (Hyman, Anderson & Blasyk 2004; Boparai et al. 2010). However, the available information is insufficient to inform appropriate surveillance intervals in this group **(III - B).**[Rec 9.19]

9.6 Opportunity costs

Surveillance colonoscopy consumes considerable endoscopic resource and may, as a result, prevent a country from sustaining reasonable waiting times. This may adversely affect the symptomatic service and tarnish the reputation of screening. Thus a country may, as a result of limited endoscopic resources, choose to adopt the guidance for surveillance, but only of the high risk group until it has created the capacity to adopt the full guidance. The stratification of risk proposed by this, and most other guidelines on surveillance, enables a country to implement what it can afford (see Section 9.7).

9.7 Quality standards and auditable outcomes

The aim of this chapter on colonoscopic surveillance is to define the minimum requirements for protecting individuals in whom colorectal adenomas are detected at screening from subsequently developing fatal colorectal cancer. The degree of protection depends on the quality of colonoscopic examinations and the appropriate frequency of surveillance colonoscopies. Data on the effects of increasing intervals between exams is limited; however, these Guidelines are based on the best available evidence.

Every screening programme should have a policy on surveillance. The policy may limit surveillance to the high risk group, if sufficient resources are not available to include people at lower risk (see Section 9.6) **(VI - B).**[Rec 9.20]

The responsibility of programme management to assure the quality of screening services includes quality assurance of surveillance. For surveillance the same principles, methods and standards of quality assurance apply that are elucidated elsewhere in the first edition of the European Guidelines **(VI - B).**[Rec 9.21]

9.7.1 Adherence to the guideline

Adherence to the EU Surveillance Guidelines should protect patients from low quality exams and from inappropriately frequent or infrequent exams. Setting targets based on the Guidelines, monitoring performance, and acting on the results should help, among other things, to lower miss rates of important lesions at baseline. This, in turn, is likely to avoid misclassification of risk and to thereby improve surveillance results.

Adherence to the Guidelines should therefore be monitored **(VI - A).**[Rec 9.22]

Auditable outcomes:

- Percentage of people screened or already under surveillance who are assigned to the respective risk groups by the programme and the proportion of people allocated to each risk group who fulfil the Guidelines criteria for that group.
- In each risk group, the percentage in which the interval assigned in practice agrees with the interval recommended in the Guidelines.[4]

Patient choice and clinical factors should be removed from the denominator. The above data should be broken down and analysed by relevant subgroups, such as age, sex and region.

[4] Not applicable to low risk category because persons with low risk are recommended to return to screening according to the EU Guidelines.

9.7.2 Timeliness of surveillance procedures

The programme should monitor whether the recommended surveillance procedures are happening and whether they are undertaken on time.

Therefore, surveillance histories should be documented and the results should be available for quality assurance **(VI - A).**[Rec 9. 23]

Auditable outcomes:

- Percentage of allocated procedures performed
- Of those that are performed, what percentage is performed within 6 months of the due date?

Patient choice and clinical factors should be removed from the denominator.

The above data should be broken down and analysed by relevant subgroups, such as risk category, age-group, sex and region.

9.7.3 Incident cancers

The occurrence of colorectal cancer in any individual in whom adenomas or pT1 cancers have been detected at a previous exam is a key auditable outcome for any surveillance programme **(VI - B).** **Rec 9.24**

Collecting this information will require linkage of data on the occurrence of cancer in the target population with the screening and surveillance histories of all people attending respective programmes.

The above data should be broken down and analysed by relevant subgroups, such as risk category, age-group, sex and region.

The data should also be subdivided into cancers detected at surveillance examinations; cancers diagnosed in the intervals between scheduled surveillance examinations; and cancers diagnosed after stopping surveillance (post surveillance cancers) which might inform on the safety of stopping surveillance in a specific patient.

Auditable outcomes in subgroups of individuals with histories of adenomas or pT1 cancers detected in screening or surveillance:

- Rate of cancers detected at a surveillance exam (surveillance detected cancers)
- Rate of cancers diagnosed before a scheduled surveillance exam (surveillance interval cancers)
- Rates of cancers diagnosed after stopping surveillance, and intervals to cancer diagnosis (post-surveillance cancers)

9.8 References

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10

Communication

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Recommendations[1]

10.1 Developing communication strategies for an organised CRC screening programme is important to ensure that as many of the target population as possible receive the relevant information to be able to make informed decisions about whether or not they wish to attend for CRC screening **(VI - A).**[Sect 10.2.2.2]

10.2 Any framework developed to communicate CRC screening information must enable individuals to make an informed decision, and should be underpinned by the four ethical principles of autonomy, non-malfeasance, beneficence and justice **(VI - A).**[Sect 10.2.2.2]

10.3 CRC screening programmes should provide balanced, quantified and unbiased information about CRC (e.g. incidence, risk factors and symptoms) and CRC screening (benefits, harms and risk factors). Scientific evidence should be used to develop patient information materials and should be easily accessible for public consultation **(VI - A).**[Sect 10.2.2.2]

10.4 CRC screening programmes should identify the barriers, needs and facilitators to informed decision-making (IDM) of their target population (including specific groups) **(VI - A)**. The information materials produced, including written instructions on how to use the FOBT kit or perform the bowel cleansing procedure, and the intervention(s) used must conform to these identified information needs and facilitators. The public should be involved in the entire process, from identifying barriers, needs and facilitators to developing information materials **(VI - A).**[Sect 10.2.2.2]

10.5 To communicate CRC screening information, including written instructions on how to use the FOBT kit or perform the bowel cleansing procedure, the language and text format used should be easy to understand and illustrations may be used. Ideally, written information (including written instructions) should not be the only source of information and should be complemented by visual communication instruments and/or oral interventions **(VI - A).**[Sect 10.2.2.2]

10.6 Primary health care providers should be involved in the process of conveying information to people invited for screening (see Ch. 2, Rec. 2.11) **(II - A).**[Sect 10.4.1.1; 2.4.3.4; 2.4.3.4.1]

10.7 In the context of an organised programme, personal invitation letters, preferably signed by the GP, should be used. A reminder letter should be mailed to all non-attenders to the initial invitation (see Ch. 2, Rec. 2.8) **(I - A).**[Sect 10.4.1.2; 2.4.3.4.1, 2.4.3.2]

10.8 Although more effective than other modalities, phone reminders may not be cost-effective (see Ch. 2, Rec. 2.9) **(II - B).**[Sect 10.4.1.2; 2.4.3.2]

10.9 Mailing of the FOBT kit may be a good option, taking into account feasibility issues (such as reliability of the mailing system and test characteristics) as well as factors (such as the expected impact on participation rate) that might influence cost-effectiveness (see Ch. 2, Rec. 2.15) **(II - B).**[Sect 10.4.1.3; 2.5.1.1]

10.10 Clear and simple instruction sheets should be provided with the kit (see Ch. 2, Rec. 2.16) **(V - A).**[Sect 10.4.1.3; 2.5.1.1]

10.11 Use of a non-tailored leaflet for the general population is advised; the leaflet should be included with the invitation letter. Information about CRC screening risks and benefits, CRC risks (incidence and risks factor), meaning of test results, potential diagnostic tests and potential treatment options should be included **(VI - A)**. Illustrations may be used, which would be particularly useful for minorities, the elderly or low-literacy participants **(II - A).**[Sect 10.4.2.1]

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

10.12 A tailored leaflet for "harder to reach" groups could be used if these groups can be identified **(II - B).**[Sect 10.4.2.1]

10.13 Although there is good evidence that leaflets can increase knowledge of CRC screening, there is inconclusive evidence on the impact of leaflets on informed decision making (IDM). As a consequence, other interventions should be used in addition to leaflets **(VI - A).**[Sect 10.4.2.1]

10.14 Video/DVD may be a useful component in a multi-modal intervention in addition to written information, and would be particularly useful for the elderly, minorities and low literacy participants **(I - B)**. For the elderly, increasing the number of components of the multi-modal intervention and the period over which these components are provided may be more effective **(I - B).**[Sect 10.4.2.2.1]

10.15 A computer-based decision aid could be used to help both the general population and specific groups to make informed decisions about CRC screening **(I - B)**. The computer-based decision aid should be "user-friendly" and designed to fit with the computer abilities of the target population (general or specific groups)**.**[Sect 10.4.2.2.2]

10.16 ICT-generated reminders[2] to physicians could be used as an opportunity to provide counselling to patients on CRC and CRC screening, if primary care or other health practitioners are involved, and if patient medical records are electronic and give screening status **(I - A).**[Sect 10.4.2.2.3]

10.17 If possible, all information provided by the screening programme should be available on a specific web site. This information should be regularly updated **(VI - A).**[Sect 10.4.2.2.4]

10.18 It is not cost-effective or feasible to implement a tailored reminder telephone call in the general population. It may be possible for CRC screening programmes to use such an intervention for "harder to reach" groups if these groups can be identified **(II - B)**. For example peer telephone support could be used.[Sect 10.4.2.3.1]

10.19 Patient navigation could be used within CRC screening programmes, particularly to reach subgroups of the population such as the elderly, those with low literacy, and medically underserved patients. When used with minorities, the patient navigator should be from a similar ethnic background and/or live in the same community as the participant **(I - B).**[Sect 10.4.2.3.2]

10.20 Verbal face-to-face interventions with a nurse or physician could be used to improve knowledge and participation. They would be useful to reach subgroups of the population such as the elderly, minorities and those with low literacy **(I - A).**[Sect 10.4.2.3.3]

10.21 Nurses and primary care practitioners (GPs) should receive adequate training to be able to help people make informed decisions about CRC screening **(VI - A).**[Sect 10.4.2.3.3]

10.22 Community-based verbal face-to-face interventions such as church-based sessions or in-person interviews could be used to reach minorities, in the case where the providers of such interventions received adequate training **(II - B).**[Sect 10.4.2.3.3]

10.23 Mass media campaigns using celebrities may be used to increase the awareness of CRC and CRC screening programmes. However these should be complemented by other measures as the effects are only temporary **(V - C).**[Sect 10.4.2.4]

10.24 When addressed to minority groups, information provided by mass media campaigns should emphasise positive progress made by the minority group instead of emphasising racial disparities **(VI - C).**[Sect 10.4.2.4]

10.25 CRC screening programmes should work closely with advocacy groups and the media and provide them with up-to-date, accurate and comprehensive information about CRC and CRC screening **(VI - A).**[Sect 10.4.2.4; 10.4.2.5]

10.26 A telephone or ideally a verbal face-to-face intervention, e.g. nurse or physician intervention, should be used to inform a patient of a positive screening test result, as obtaining such a result

[2] ICT-generated reminders are produced electronically using information and communication technologies.

could be a source of psychological distress for the patient. A letter informing the patient should not be used as the only way of notifying a positive result **(VI - A).**[Sect 10.4.3]

10.27 To increase endoscopy follow-up after a positive FOBT and facilitate communication, CRC screening programmes should, where possible:

- Use a reminder-feedback and an educational outreach intervention targeted to the primary care physician **(II - A)**;
- Provide patients with a written copy of their screening report **(II - A)**;
- Facilitate patient consultation with a gastroenterologist **(V - B)**;
- Describe the follow-up procedure, make the follow-up testing more convenient and accessible **(VI - A)**; and
- Use direct contact intervention to address psychological distress and other specific barriers. **(V - B).**[Sect 10.4.3]

10.28 Each endoscopy service must have a policy for pre-assessment that includes a minimum data set relevant to the procedure. There should be documentation and processes in place to support and monitor the policy (see Ch. 5, Rec. 5.20) **(III - B).**[Sect 10.4.3; 5.3.2]

10.29 The endoscopy service must have policies that guide the consent process, including a policy on withdrawal of consent before or during the endoscopic procedure (see Ch. 5, Rec. 5.25) **(VI - B).**[Sect 10.4.3; 5.3.1]

10.30 Before leaving the endoscopy unit, patients should be informed about the outcome of their procedure and given written information that supports a verbal explanation (see Ch. 5, Rec. 5.26) **(VI - A).**[Sect 10.4.3; 5.5.3]

10.31 The outcome of screening examinations should be communicated to the primary care doctor (or equivalent) so that it becomes part of the core patient record (see Ch. 5, Rec. 5.27) **(VI - B).**[Sect 10.4.3; 5.5.5]

10.32 Ideally, the invitation letter and the letter used for notification of a positive result should be sent with a leaflet and should encourage participants to read it **(VI - A).**[Sect 10.5.1]

10.33 Certain basic information, e.g. logistic/organisational information, description of the screening test, harms and benefits of screening, information about the FOBT kit and the bowel cleansing procedure, must be included in the invitation/result letter in case a person reads only the letter and not the leaflet **(VI - A).**[Sect 10.5.1]

10.34 Recommendations when FOBT is used for screening: FOBT invitation letter, FOBT invitation leaflet, FOBT result/follow-up letter, see Section 10.5.2.

10.35 Recommendations when FS or colonoscopy (CS) is used for screening, either as primary screening test (FS or CS) or to follow-up a positive FOBT result (only CS): Endoscopy invitation letter, Colonoscopy leaflet, Endoscopy result/follow-up letter, see Section 10.5.3.

10.1 Introduction

10.1.1 Using communication strategies for a colorectal cancer screening programme: goals and challenges

The essential goal of colorectal cancer (CRC) screening programmes is to reduce illness and death due to colorectal cancer. This requires the need to ensure that as many of the target population as possible receive the relevant information to be able to make informed decisions about whether or not they wish to attend CRC screening. As adverse effects are intrinsic to screening practice, participants should understand that a balance exists between benefits and harms associated with CRC screening. In the policy brief *Screening in Europe*, Holland, Stewart & Masseria (2006) state that there is "above all, an imperative to involve participating individuals in decisions on screening and to give them clear and understandable information about what it involves". A key component of CRC screening programmes, therefore, is the information and education provided about CRC and CRC screening tests and procedures: people who use CRC screening services should receive accurate and accessible information that reflects the most current evidence about the CRC screening test and its potential contributions to reducing illness as well as information about its risks and limitations.

Providing effective information is particularly challenging in CRC screening. In contrast to other type of cancer screening, e.g. cervical or breast, CRC screening is indeed far more complex:

- There are multiple tests (FOBT, FS and Colonoscopy), which could be used for CRC screening, and information that should be given to the patient related to each of these tests is different;
- Some CRC screening tests (e.g. Colonoscopy or FS) are invasive and have known adverse effects; and
- Some CRC screening procedures (FOBT screening test and preparation for endoscopy screening (bowel cleansing procedure)) are generally undertaken without supervision from a healthcare professional; therefore specific instructions on how to use the FOBT kit or perform the bowel cleansing procedure need to be communicated to the patient.

This complexity may generate an additional source of anxiety for patients. Communication strategies that are used in other types of cancer screening programmes may not be suitable and/or sufficient to address both CRC screening complexity and this additional source of anxiety. Moreover the success of FOBT and endoscopy screening may rely on patient's understanding of the written instructions to perform the FOBT test or the bowel cleansing procedure; how this is communicated and then acted upon is crucial. Barriers that influence comprehension of written instructions (e.g. low literacy) could be a major issue in CRC screening.

10.1.2 Purpose of this chapter

There are two primary objectives of this chapter: First, to give people involved in providing and/or managing CRC screening (e.g. managers, decision-makers, health professionals etc.) an insight into the complexity of communication in CRC screening and its related critical issues; and second, to provide them with pragmatic recommendations on information strategies/tools/interventions that could be used. These recommendations mainly refer to an organised (and centralised) CRC screening programme, as this represents the gold standard to achieve (see Chapters 1 and 2). In this communication chapter, we specifically provide guidance for FOBT screening programmes. Indeed, most of the EU countries are using FOBT as the primary screening test and more may adopt this test

based on these EU guidelines recommendations (see Chapter 4). Most of the recommendations can be applied to endoscopy programmes as well.

10.2 General principles

10.2.1 Informed decision-making, ethical principles

In the past few years, the autonomy of patients and their right to make informed decisions has become a central issue in medical interventions. Informed decision-making is a decision process in which individuals are supposed to make a rational and autonomous choice concerning their own health in order to protect themselves from risks and harms. It implies that these patients know the pros (benefits) and cons (harms) of screening and are aware not only of all the risks and benefits of participation in screening but also of non-participation (Raffle 1997; Austoker 1999; Goyder, Barratt & Irwig 2000). Receiving information about the cancer itself seems also important in the informed decision-making process (Jepson et al. 2005). As a consequence, any framework developed to communicate health information about CRC screening needs to be underpinned by the following ethical principles (Beauchamp & Childress 1979):

- Autonomy: the obligation to respect the decision-making capacities of autonomous persons. This obligation emphasises that patients should normally be in a position to choose whether to accept an intervention or not as part of their general right to determine their own lives;
- Non-malfeasance: the obligation to avoid causing harm intentionally or directly (the principle is not necessarily violated if a proper balance of benefits exists; that is, if the harm is not directly intended, but is an unfortunate side-effect of attempts to improve a person's health);
- Beneficence: the obligation to provide benefits, balancing them against risks; and
- Justice: the obligation of fairness in the distribution of benefits and risks.

Provision of balanced, unbiased and quantified information about CRC (e.g. incidence, risk factors and symptoms) and CRC screening (benefits, harms and risk factors) is crucial for helping patients in making informed decisions. It is important that scientific evidence is used to develop patient information materials, and that this evidence is easily accessible for public consultation. For example, in the UK, the summary of the evidence used in the development of the NHS National Bowel Cancer Screening Programmes patient information materials (Bowel Cancer Screening: The Facts and Bowel Cancer Screening: The Colonoscopy Investigation) is available on the NHS Cancer Screening Programme Website: http://www.cancerscreening.nhs.uk/bowel/publications/nhsbcsp04.html.

10.2.2 Identifying and reducing barriers/obstacles to informed decision making

Informed decision-making (IDM) is a complex process. Receiving balanced, unbiased and quantified information related to CRC and CRC screening may be not sufficient for patients to make informed decisions; patients need also to be able to understand the information provided, to make a decision and to carry out their decision (O'Connor et al. 2009). Barriers/obstacles to IDM may exist and may be related to:

- The setting and the organisation of the CRC screening programme, such as the access and the availability of the screening service and the access and the availability of the screening information (see Chapter 2);
- The knowledge, attitudes and practice of the CRC screening provider(s) (see Chapter 2 and 10.4.2.3.3); or
- The patient themselves: age, gender (Friedemann-Sanchez, Griffin & Partin 2007), physical or mental health problems, occupation, education or abilities to read or understand information (see below) may be barriers to IDM. In some cases, risk information can be also a barrier (Steckelberg et al. 2004; Woodrow et al. 2008).

It is important to understand what these barriers are so that measures can be taken to overcome them.

10.2.2.1 Barriers related to the patients themselves

Population heterogeneity

Health professionals offering screening to the population have to deal with individuals of different ages and with different cultures, values and beliefs. For these reasons, the information provided may be viewed differently and what is best for one recipient may not be the best for another (Rimer et al. 2004; Giordano et al. 2008). In addition, contextual and personal factors may directly influence the way an individual processes health information and may therefore affect the motivations to attend screening. Educational status can also have an impact on how the presented information is understood (Aro et al. 1999; Lagerlund et al. 2000; Davis et al. 2002).

Ethnic minorities

Providers of screening programmes frequently have to cater to multicultural and multi-linguistic populations with all the related communication problems. Overcoming these problems requires more than just translating the information material. An understanding should be gained of ethno-cultural values, beliefs, health practices and communication styles of these varied groups, and the information materials produced must conform to these identified needs (van Wieringen, Harmsen & Bruijnzeels 2002).

Low health literacy

Inadequate or low health literacy is defined as the inability to read and comprehend basic health-related information. Health literacy requires a complex group of reading, listening, analytical, and decision-making skills, and the ability to apply these skills to health situations. Low health literacy is independently linked to mortality and a range of poor health outcomes (Baker et al. 2002; Dewalt et al. 2004; Sudore et al. 2006a; Sudore et al. 2006b). Poverty, ethnicity and age are also considered predictors of limited literacy (Davis et al. 2002). In most countries, low literacy is a widespread problem as is low numeracy. In the UK 16% of the population (5.2 million adults) are classified as having lower literacy (Skills for life survey 2003) and 47% (15 million adults) as having low numeracy. In a screening context, low health literacy can represent a major obstacle in understanding cancer screening information, diagnosis, treatments options, etc. This is particularly true in CRC screening as the demands of written information are perhaps greatest (see 10.1.1). In a group of US male veterans, those with low literacy were 3.5 times as likely not to have heard about colorectal cancer, 1.5 times as likely not to know about the FOBT screening test, and more likely to have negative attitudes about the FOBT (Dolan et al. 2004). Specifically, they were 2 times as likely to be worried that FOBT was “messy”, and 4 times as likely to state that they would not use an FOBT kit if their physician recommended it.

In order to achieve health literacy, it is important that health and screening operators ascertain people’s needs by using appropriate communication strategies, promoting access, identifying and

removing barriers/obstacles within systems, and continuously evaluating the efforts to ensure improvement.

10.2.2.2 Reducing barriers

As there are many communication interventions that could be used (Figure 10.1 and section 10.4), CRC screening programmes should identify what would be the most appropriate communication strategy(ies) to use for their target population (including specific groups); CRC screening programmes should take into account their population barriers, needs and facilitators to IDM. The information materials produced must conform to these identified information needs and facilitators. The public perspective is important for appropriate understanding of these barriers, needs and facilitators. The public should be involved when communication tools are developed.

To reduce individuals' barriers, especially related to language and ways of processing information, CRC screening should provide information in a practical and concise way, using a simple and clear language, avoiding jargon and technical terms, such as incomprehensible mathematical or statistical concepts for expressing risk, and illustrations should be used (see also 10.4.2.1). This is particularly true for written instructions on how to use the FOBT kit or perform the bowel cleansing procedure.

Ideally, written information (including written instructions) should not be the only source of information and should be complemented by visual communication instruments and/or verbal interventions.

Summary of evidence

- Developing communication strategies in CRC screening programmes is important to ensure that as many of the target population as possible receive the relevant information to be able to make informed decisions about whether or not they wish to attend for CRC screening.
- Providing effective communication is particularly challenging in CRC screening as CRC screening is far more complex than other types of cancer screening. Communication strategies adopted/used in other types of cancer screening may not be suitable and/or sufficient to address CRC screening complexity and the additional source of anxiety generated for patients. Some screening procedures (e.g. FOBT) may rely on patient's understanding of the written instructions; how this is communicated and then acted upon is essential.
- Any framework developed to communicate CRC screening information must enable individuals to make an informed choice and should be underpinned by the four ethical principles of autonomy, non-maleficence, beneficence and justice. Informed decision making (IDM) in screening supposes that people make a rational and autonomous decision to participate, knowing the pros and cons of screening and being aware of all risks and benefits of their participation **(VI)**.
- CRC programmes should provide balanced, unbiased and quantified information about CRC (e.g. incidence, risks factors and symptoms) and CRC screening (benefits, harms and risks). Scientific evidence should be used to develop patient information materials and should be easily accessible for public consultation.
- Barriers/obstacles to IDM may exist and may be related to the setting and the organisation of the CRC screening programme, the knowledge, attitudes and practice of the CRC screening provider(s) or the patient themselves.
- CRC screening programmes should identify the barriers, needs and facilitators to IDM of their target population (including specific groups) **(VI)**. An understanding should be gained of ethno-cultural values, beliefs, health practices and communication styles of the varied groups of the target population. Research should be carried out to identify how to better communicate information to low literacy groups in the population. The information materials produced (including the written instructions on how to use the FOBT kit or perform the bowel cleansing procedure) and the intervention(s) used must conform to these identified information needs and

facilitators. The public should be involved in the entire process, from identifying barriers, needs and facilitators to developing information materials.

- To reduce individuals' barriers, especially related to language and ways of processing information, the language and text format should be easy to understand and illustrations should be used. Ideally, written information should not be the only source of information and should be complemented by visual communication instruments and/or oral interventions. This is particularly true for written instructions on how to use the FOBT kit or perform the bowel cleansing procedure **(VI)**.

Recommendations

10.1 Developing communication strategies for an organised CRC screening programme is important to ensure that as many of the target population as possible receive the relevant information to be able to make informed decisions about whether or not they wish to attend for CRC screening **(VI - A)**.

10.2 Any framework developed to communicate CRC screening information must enable subjects to make an informed decision and should be underpinned by the four ethical principles of autonomy, non-maleficence, beneficence and justice **(VI - A)**.

10.3 CRC screening programmes should provide balanced, quantified and unbiased information about CRC (e.g. incidence, risk factors and symptoms) and CRC screening (benefits, harms and risks). Scientific evidence should be used to develop patient information materials and should be easily accessible for public consultation **(VI - A)**.

10.4 CRC screening programmes should identify the barriers, needs and facilitators to informed decision making (IDM) of their target population (including specific groups) **(VI - A)**. The information materials produced, including written instructions on how to use the FOBT kit or perform the bowel cleansing procedure, and the intervention(s) used must conform to these identified information needs and facilitators. The public should be involved in the entire process; from identifying barriers, needs and facilitators to developing information materials **(VI - A)**.

10.5 To communicate CRC screening information, including written instructions on how to use the FOBT kit or perform the bowel cleansing procedure, the language and text format used should be easy to understand and illustrations may be used. Ideally, written information (including written instructions) should not be the only source of information and should be complemented by visual communication instruments and/or oral interventions **(VI - A)**.

10.3 Communication tools/interventions used in CRC screening programmes

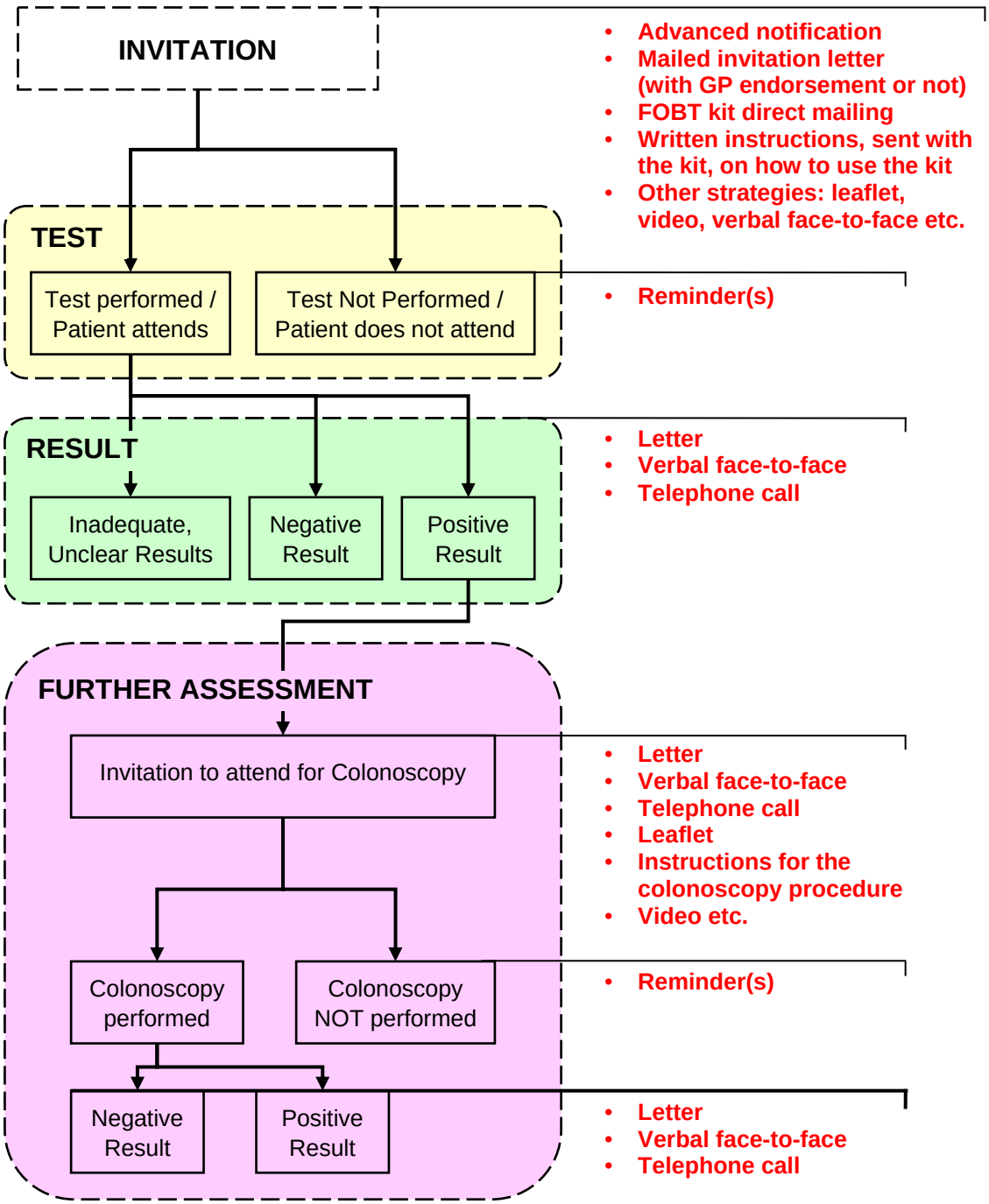
Organised screening programmes generally have three distinct "communication" phases throughout the CRC screening process, where information (general or person-specific information) can be provided to participants. For a CRC FOBT screening programme, Figure 10.1 illustrates these three phases and the corresponding communication tools:

i. The invitation phase: people are invited to participate in screening. Information for this screening phase is generally provided through invitation letters and leaflets. Written instructions on how to use the FOBT kit are usually provided with the kit;

ii. The reporting results phase: people are notified of the results of their screening test. Information conveyed during this phase may be very sensitive and the communication tools must be carefully crafted to address the people's information needs;

iii. The follow-up phase: only for people with a positive FOBT result who require further assessment (colonoscopy). Usually information about colonoscopy is notified at the same time as positive results. This phase also involves information about management of the colonoscopy procedure.

Figure 10.1: Communication tools in FOBT-CRC screening



10.4 Effectiveness of communication interventions in CRC screening

In this chapter, we review all the principal communication interventions that have been used or are being used in CRC screening and assess their effectiveness and limitations. Even though it would be useful to evaluate the effectiveness of an intervention in facilitating IDM, it would be very difficult: there is a lack of agreement about the definition of IDM, and validated measures do not exist (Jepson et al. 2005; Fox 2006). As a result, the majority of studies use participation or uptake as the main outcome of interest to assess the effectiveness of a communication intervention.

10.4.1 Interventions used to invite a person undergo the test

The interventions listed in this section (10.4.1) are closely associated with the organisation of the screening programme. Therefore, they have already been discussed in detail in Chapter 2 and this discussion will not be repeated here. The Summary of evidence and Recommendations sections are the same as in Chapter 2.

10.4.1.1 Physician/GP endorsement

Summary of evidence

- The impact of information conveyed with the invitation is greater if the invitation is signed by an individual's physician. Involvement of GPs also shows a positive influence on the impact of more tailored and structured information methods **(II)**.

Recommendations

10.6 Primary health care providers should be involved in the process of conveying information to people invited for screening (see Ch. 2; Rec. 2.11; Sect. 2.4.3.4 and 2.4.3.4.1) **(II - A)**.

10.4.1.2 Letters

Summary of evidence

- A personalised letter signed by a general practitioner or by another trusted primary health care providers is more effective than an impersonal letter sent by a central screening centre **(I)**.
- An advance notification letter may increase participation **(II)**.
- Any kind of reminder is effective in increasing adherence, with telephone reminders being the most effective option, but also the most expensive **(I)**.

Recommendations

10.7 In the context of an organised programme, personal invitation letters, preferably signed by a GP, should be used. A reminder letter should be mailed to all non-attenders to the initial invitation (see Ch. 2; Rec. 2.8; Sect. 2.4.3.4.1 and 2.4.3.2) **(I - A)**.

10.8 Although more effective than other modalities, phone reminders may not be cost-effective (see Ch. 2; Rec. 2.9; Sect. 2.4.3.2) **(II - B)**.

10.4.1.3 FOBT: delivery of the kit and instruction sheet

Summary of evidence

- There is no evidence that the proportion of inadequate samples may be affected by the provider used to deliver the kit, as long as clear and simple instruction sheets are provided with the kit **(II - V)**.
- The time required to reach the test provider represents a strong determinant of compliance **(II)**.
- Sending the FOBT kit together with the invitation letter may be more effective than letter alone, but the cost-effectiveness of such strategy might be low **(II)**.

Recommendations

10.9 Mailing of the FOBT kit could be a good option, but feasibility issues (such as reliability of the mailing system and test characteristics), as well as factors (such as the expected impact on participation rate) that may influence cost-effectiveness must be taken into account (see Ch. 2; Rec. 2.15; Sect 2.5.1.1) **(II - B)**.

10.10 Clear and simple instruction sheets should be provided with the kit (see Ch. 2; Rec. 2.16; Sect 2.5.1.1) **(V - A)**.

10.4.2 Other interventions which can be used with the invitation: written, visual, face-to-face interventions

10.4.2.1 Leaflets and booklets

Leaflets are a key way for the organisers of screening programmes to communicate with the target population. The results of a recently published study, in which an information leaflet was provided in addition to the invitation letter, showed that CRC participation was significantly higher among patients who read both the leaflet and the letter compared to those who read just the letter (Senore et al. 2010).

Two RCTs have investigated the effectiveness of leaflets in increasing participation in CRC screening either by FOBT (Hart et al. 1997) or colonoscopy (Denberg et al. 2006):

i. Hart et al. (1997) showed that leaflets significantly increased participation in men but not in women. According to the authors, one possible explanation was that women are generally better informed that men about the benefits of screening as they are targeted by breast and cervical screening programmes. Hence the participation rate for women is higher than for men.

ii. Denberg et al. (2006) showed that a leaflet mailed before a scheduled appointment increased adherence to screening colonoscopy among patients receiving referrals for the procedure.

Five studies assessed the content of leaflet:

i. One survey (van Rijn et al. 2008) was conducted to qualify the level of knowledge obtained by using a leaflet that provided information similar to that used in leaflets designed for other European screening trials. Although the leaflet was reported to be clear and readable, the information provided in it was not always well understood. The authors concluded that other educational options should be investigated in order to improve general knowledge of CRC screening in patients.

ii. In another RCT, Trevena, Irwig & Barratt (2008) assessed the relative effectiveness of using a comprehensive “decision-aid (DA) booklet” (20-page leaflet) and a 2-page leaflet that contained minimal information about false-positives and follow-up, no quantification of outcomes, no graphs or pictures, and no personal worksheet or examples. The results showed that providing more

information about FOBT screening contributed to increasing informed choice, defined by the authors as: knowledge, clear values and screening intention (decision). There was no noticeable effect on the screening uptake.

iii. Adding explanatory illustrations to written material about the polyp-cancer process and the removal of polyps during FS, significantly increased knowledge and understanding (Brotherstone et al. 2006).

iv. Robb et al.'s RCT (Robb et al. 2006) showed that using leaflets that gave information on CRC risk factors with or without information on colorectal screening by FOBT and FS was effective in increasing knowledge about the risk factors for CRC without increasing anxiety.

v. In an experimental pilot study, Lipkus et al. (Lipkus, Green & Marcus 2003) assessed the effect of adding information about CRC risks (CRC incidence and risk factors) and CRC severity (treatment modalities for CRC and two testimonials of patients living with advanced CRC) in a leaflet for FOBT screening. Whereas perception of CRC risks had no apparent effect, perception of CRC severity significantly increased intention to be screened.

Four studies have assessed the effect of using tailored/targeted leaflets/booklets:

i. Myers et al. (2007) investigated the impact of targeted and tailored interventions in an RCT by testing the effect of a leaflet addressing personal barriers to screening in one urban primary care practice. The barriers to screening were identified through a baseline telephone survey involving the entire test population. The impact of the telephone contact on the survey results is not known. The authors reported no significant difference between the interventions.

ii. Lipkus et al. (2005) assessed the effect of adding tailored information about CRC risks to a leaflet aimed at members of a specific occupational group (carpenters) by adding a section highlighting occupational risk factors that increased their personal CRC risk. The study showed that adding tailored risk factor information affected neither risk perception nor screening uptake.

iii. Marcus et al.'s RCT (Marcus et al. 2005) investigated the impact of targeted and tailored interventions on CRC screening participation outside of a primary care setting. Tailored messages were derived from a baseline telephone survey. Three tailored conditions were tested and compared to a non-tailored intervention (a booklet): a single-tailored intervention (a 16-page tailored booklet), a multiple-tailored intervention (the tailored booklet plus tailored leaflets mailed out over a 12-month period) and a multiple-re-tailored intervention (as the latter except that subsequent leaflets were "re-tailored" based on follow-up interviews). Over a 14-month period, the multiple-tailored intervention was more effective than the non-tailored one, which could be explained by the "multiple" nature of the intervention. When comparing the two multiple interventions, there was no effect of using "re-tailored" material. When age stratification was used, a significant effect of the single-tailored intervention compared to the non-tailored booklet was observed for the younger participants (ages 50-59). The impact of the baseline telephone survey is not known.

iv. Wardle et al. (2003) evaluated the effect of a leaflet specially designed for a "harder-to-reach" group of people identified in the screening arm of a FS trial. In addition to presenting basic information on CRC and screening, the booklet addressed psychological barriers to the FS test. The booklet was shown to decrease negative attitudes toward FS screening and increased screening attendance.

According to these studies, there is good evidence that leaflets can increase knowledge of CRC screening, but the evidence that leaflets facilitate the exercise of informed choice is less obvious. Fox's systematic review (Fox 2006) came to the same conclusions. As there is a lack of agreement about the definition of "informed choice" and validated measures (Jepson et al. 2005; Fox 2006), it is indeed difficult to evaluate the impact of leaflets use on patients' informed choice about CRC screening. Therefore, other interventions should be used in addition to leaflets.

Summary of evidence

- Non-tailored leaflets are effective in increasing screening participation and/or knowledge. Leaflets in addition to the invitation letter are valuable tools **(I)**.

- Including more detailed information in a leaflet (e.g. information about false-positive and follow-up, quantification of outcomes, graphs and pictures, personal worksheets or examples) contributed to an increase in knowledge, clear values and screening intention (decision) but not uptake **(I)**.
- Providing information about risk factors for CRC was effective in increasing knowledge about the risk factors for CRC without increasing anxiety. Perception of CRC risks did not affect the uptake rate for FOBT screening **(I)**.
- Adding illustrations to written material about the polyp-cancer process and the removal of the polyps during FS significantly increased knowledge and understanding **(II)**.
- Tailored leaflets for "harder-to-reach" groups seem to be effective in increasing screening participation and knowledge **(II)**.
- A tailored booklet compared to a non-tailored proved more effective in increasing participation of younger participants. A multiple-tailored intervention over a period of time was more effective than using a non-tailored booklet **(II)**. However, the impact of the baseline telephone survey to tailor the materials in this study cannot be evaluated.
- When using multiple-tailored interventions, there was no effect of using "re-tailored" material **(II)**.
- It is difficult to prove that leaflets facilitate the exercise of IDM **(I)**.

Recommendations

10.11 Use of a non-tailored leaflet for the general population is advised; the leaflet should be included with the invitation letter. Information about CRC screening risks and benefits, CRC risks (incidence and risk factors), meaning of test results, potential diagnostic tests and potential treatment options should be included **(VI - A)**. Illustrations may be used, which would be particularly useful for minorities, elderly or low-literacy participants **(II - A)**.

10.12 A tailored leaflet for "harder-to-reach" groups could be used if these groups can be identified. **(II - B)**.

10.13 Although there is good evidence that leaflets can increase knowledge of CRC screening, there is inconclusive evidence on the impact of leaflets on informed decision making (IDM). As a consequence, other interventions should be used in addition to leaflets **(VI - A)**.

10.4.2.2 Videotapes/DVDs, interactive computer-based decision aids, ICTs (information & communication technologies) and Internet

10.4.2.2.1 Videotapes/DVDs

a. Non multi-modal intervention

Two US studies (Friedman et al. 2001; Zapka et al. 2004) showed that using a videotape had no effect on the overall rate of CRC screening. In the second study the video, mailed before a scheduled examination, only modestly improved sigmoidoscopy screening rates.

Two studies by Griffith et al. (2008) investigated the effect of introducing differential content in a DVD. In the first study, the DVD presented to both groups differed only in the inclusion of a segment where an individual discussed why he did not participate in screening. In the second study, two forms of a DVD were evaluated: one included two screening test options, and the other five screening test options. Participants' interest in CRC screening was investigated; neither study found a difference between the interventions.

Meade, McKinney & Barnas (1994) investigated whether a booklet or a videotape, both tailored to the target population of participants, was more effective for improving CRC knowledge, which was evaluated just after the intervention. Results indicated that both booklet and videotape significantly increased knowledge and there were no statistically significant differences between the 2 interventions, regardless of the patients' literacy levels. The "tailored" aspect of both of the interventions was one hypothesis to explain the absence of discrepancy between the two interventions.

b. Multi-modal intervention including videotape/DVD and print material

Four studies (Pignone, Harris & Kinsinger 2000; Campbell et al. 2004; Powe, Ntekop & Barron 2004; Lewis et al. 2008) assessed the effect of using a multi-modal intervention, which included a videotape and print material:

i. Pignone et al.'s (Pignone, Harris & Kinsinger 2000) RCT trial used an educational videotape, targeted brochure and chart marker. The study showed that the intervention, compared to no intervention, increased CRC screening participation.

ii. In Lewis et al.'s (Lewis et al. 2008) controlled trial the intervention consisted of a mailed package containing an educational videotape, a reminder letter from their physician, surveys to be completed before and after the video watching, and system changes allowing patients direct access to schedule screening tests. The study showed that the intervention, compared to no intervention, increased CRC screening participation.

iii. Campbell et al.'s (Campbell et al. 2004) randomised trial compared the effect of a tailored print and video intervention (4 personalised computer-tailored newsletters and videotapes), designed to target a rural minority (African-American) community, to a lay health advisor (a trained member of the community) intervention. The study showed that the tailored print and video intervention was more effective in increasing FOBT screening than no intervention. The authors reported suboptimal advisor reach and diffusion.

iv. Powe, Ntekop & Barron (2004) showed that a 5-phase culturally relevant intervention (video, calendar, poster, brochure, flier) among community elders and delivered over a 12-month period, significantly increased knowledge and screening participation compared to either a 6-month and 3-phase intervention or a single intervention (video or usual care). However, it is not possible to determine which aspects of the multi-modal intervention were most effective.

Summary of evidence

- A DVD alone had no effect on screening rates or interest in screening. Changing the video content did not affect this result. No difference was found between a tailored booklet and a tailored DVD regardless of the patients' literacy levels **(I)**.
- When a video/DVD was used in a multi-modal intervention, an improvement in knowledge and increase in screening rates was observed. When the components of the multi-modal interventions were provided successively over a period of time, increasing the number of components and the period over which they were provided, there was an increased in knowledge and in participation of elderly people **(I)**.

Recommendations

10.14 Video/DVD may be a useful component in a multi-modal intervention in addition to written information and would be particularly useful for the elderly, minorities and low literacy participants **(I - B)**. For the elderly, increasing the number of components of the multi-modal intervention and the period over which these components are provided may be more effective **(I - B)**.

10.4.2.2.2 Interactive computer-based decision aids

Four studies (Dolan & Frisina 2002; Kim et al. 2005; Miller Jr. et al. 2005; Menon et al. 2008) showed that a computer-based decision aid improved patients' knowledge about screening and was useful to most in making decisions about screening (increased intention to be screened and increased interest in screening). The same results were obtained in rural primary care practices (Geller et al. 2008) and in a Hispano/Latino community (Makoul et al. 2009) for which the decision aid was specifically designed.

Three studies have assessed the effect of a computer-based decision aid on screening participation:

i. An RCT by Ruffin et al. (Ruffin, Fetters & Jimbo 2007) showed that an interactive programme to help to establish a preference among the CRC screening tests options was more effective than an existing CRC website selected to represent the standard, state-of-the art and non interactive website.

ii. In an uncontrolled trial, Kim et al. (2005) tested the effect of an interactive computer-based decision aid including an audio track playing during the entire programme and explaining all of the figures that were presented, making the content accessible to users with varying levels of literacy. The intervention improved screening uptake.

iii. Dolan and Frisina's (Dolan & Frisina 2002) RCT showed that a computer-based decision aid designed to help patients choose between different strategies for CRC screening and including the option of 'no screening', when added to a simple educational interview intervention, had no effect on CRC screening uptake.

Jerant et al. (2007) conducted an RCT comparing the effects of using a tailored versus a non-tailored interactive multimedia program. Besides a tailored component (e.g. specific screening recommendation tailored to the individual), the tailored programme also contained brief patients and physician video clips that were not in the non-tailored intervention. The study showed that the tailored programme was significantly more effective in bolstering CRC screening readiness and self-efficacy than the non-tailored intervention. It is not clear to what extent the video clips component of the tailored computer-based decision aid contributed to the result.

Summary of evidence

- Interactive computer-based decision aids improved knowledge and were useful in helping people decide whether or not to be screened. The same results were obtained in rural primary care practices and in an ethnic community for which the decision aid was specifically designed **(I)**.
- Interactive computer-based decision aids increased screening participation, but had no effect if added to an interview intervention. A tailored computer-based intervention affected knowledge and intention to be screened more than a non-tailored intervention, but it is not clear to what extent the video clips component of the tailored computer-based decision aid contributed to the result **(II)**.

Recommendations

10.15 A computer-based decision aid could be used to help both the general population and specific groups to make informed decisions about CRC screening **(I - B)**. The computer-based decision aid should be "user-friendly" and designed to fit with the computer abilities of the target population (general or specific groups).

10.4.2.2.3 Information and communication technologies: future promises and challenges for enhancing CRC screening delivery

Information and communication technologies (ICTs) are a diverse set of technological tools and resources used to communicate, create, disseminate, store, and manage information. ICT is sometimes referred to as simply Information Technologies (IT). ICTs include computers, the Internet,

broadcasting technologies (radio and television), and telephones. They are typically used in combination rather than singly.

The European Union's Commission for Information Society and Media has defined eHealth as ICT-based tools covering "the interaction between patients and health-service providers, institution-to-institution transmission of data, or peer-to-peer communication between patients and/or health professionals" (http://ec.europa.eu/information_society/activities/health/whatis_ehealth/index_en.htm). Examples include health information networks, electronic health records, telemedicine services, wearable and portable systems which communicate, health portals, and many other ICT-based tools assisting disease prevention, diagnosis, treatment, health monitoring and lifestyle management.

According to a recent systematic review (Jimbo et al. 2006), the published research using ICT in the context of cancer screening in general and CRC screening in particular almost exclusively tested the impact of ICT-generated reminders to either the provider alone or to both the patient and the provider. Dexheimer et al.'s review (Dexheimer et al. 2008), found that ICT tools used to generate reminders, were either "computer-generated" (ICT tools were used to identify eligible patients and were integrated with electronic appointment systems so that reminders were automatically printed in advance of patient appointments and placed in the patient's chart) or "computerized" (ICT were used to identify eligible patient and generate electronic prompt).

There is ample evidence that patient- and provider-directed computerised reminder systems increase adherence in other cancer screening fields e.g. mammography. For CRC screening, three out of four recent studies showed that ICT-generated reminders to physicians increased CRC screening:

i. Sequist et al. (2009) used computerized reminders, in both a passive and active form, added within each patient's electronic medical record, and thus visible by their physician during the appointment. Results showed that electronic reminders tended to increase screening rates among patients with 3 or more primary care visits.

ii. Chan & Vernon (2008) tested the feasibility of using the NetLET website interface to provide patients with a personalised reminder from their physician to undergo CRC screening. The study concluded that it was not feasible to implement the NetLET. For the authors the lack of success was essentially due to the e-mail access barrier (patients without email at home or work) and the ICT system barrier itself, i.e. the complexity of accessing the NetLET website.

iii. Nease et al. (2008) investigated the effect of a computer-generated reminder placed in the patient's chart. The study showed that 11 out of 12 practices significantly increased their CRC screening rates and there was no significant difference between sending reminders either to clinician alone or to both patient and clinician.

iv. Jimbo et al.'s review (Jimbo et al. 2006) identified 13 studies evaluating the effect on ICT-generated reminders in FOBT CRC screening: 8 out of 13 studies showed that reminders increased FOBT screening participation.

According to the EU commission (Information Society and Media), the widespread implementation of ICT in health will increase the quality of healthcare services and will provide:

- Better information for patients and healthcare professionals;
- More efficient organisation of resources; and
- More "patient-friendly" healthcare services by helping healthcare providers to be more flexible and better able to address the differing needs of individual patients.

Still "poverty and illiteracy in developing nations are major barriers to the adoption and sustainability of information technologies" (Abbott & Coenen 2008). Nevertheless, the existence of many successful implementations of ICT-enabled health communications and electronic health record systems in less industrialised countries in Africa (Abbott & Coenen 2008), suggests that it is possible to bypass these barriers.

For Vernon & Meissner (2008), ICT is one of the "Six elements of a New Model of Primary healthcare delivery" in colorectal cancer screening. ICT use for interventions in screening in general, and in CRC screening more specifically, has the potential to go beyond simple reminder systems (Jimbo et al. 2006; Vernon & Meissner 2008). But to widely realise the potential of the use of IT in screening, patients' charts must provide the infrastructure to do this. Patients' charts must be organized enough to determine patient screening status and ideally physicians and clinics should use electronic medical records. According to Vernon & Meissner (2008) and Dexheimer et al. (2008), these are areas that clearly need to be improved.

Summary of evidence

- ICT-generated reminders to physicians increased CRC screening rates **(I)**. ICT has an important role to play in increasing efficiency of CRC screening and has the potential to go beyond simple reminder systems, and will provide better information for patients and healthcare professionals, more efficient organisation of resources and more "patient-friendly" healthcare services by providing a more flexible and personalised approach **(I)**.
- To widely realise the potential of the use of IT in screening, patients' medical records should be improved to easily determine patient screening status, and ideally should be electronic **(I)**.

Recommendations

10.16 ICT-generated reminders to physicians could be used as an opportunity to provide counselling to patients on CRC and CRC screening, if primary care or other health practitioners are involved, and if patient medical records are electronic and give screening status **(I - A)**.

10.4.2.2.4 Internet

There is no evidence of the impact of the internet on screening in general and more specifically on CRC screening. Based on Della et al's review (Della et al. 2008), the popularity of the internet as a conduit for health information is increasing. Still, not everyone is online; research indicates that higher usage of the internet is associated with younger age, more education and higher income (Fox & Rainie 2000; Pereira et al. 2000; Brodie et al. 2001; Della et al. 2008). As the variety of health information on the internet is expanding, source credibility continues to be a pivotal factor in determining the quality of information (Della et al. 2008). James et al. (2007) performed a study of information seeking by cancer patients and their caregivers. This study has shown that "those who accessed Internet information, either directly or indirectly, reported high levels of satisfaction with it and generally rated it more highly than booklets or leaflets". The authors concluded that "the internet is an effective means of information provision in those who use it. Facilitated internet access and directed use by health professionals would be effective way of broadening access to this medium."

Summary of evidence

- There is no evidence of the impact of the Internet on CRC screening **(VI)**.
- The popularity of the Internet as a conduit for health information is increasing **(VI)**.
- People with younger age, more education and higher income have higher usage of the Internet **(V)**.
- Source credibility continues to be a pivotal factor in determining the quality of information **(V)**.
- Generally, using the internet as a source of information about cancer is more satisfying than leaflets or booklets **(VI)**.

Recommendations

10.17 If possible, all information provided by the screening programme should be available on a specific web site. This information should be regularly updated **(VI - A)**.

10.4.2.3 Telephone intervention, patient navigator (PN) intervention, and verbal face-to-face intervention other than PN

10.4.2.3.1 Telephone intervention

The majority of the studies assessed the impact of a reminder tailored telephone call added to printed materials (the "usual care"), which were incrementally added. In some studies, the intervention also included a booklet/leaftlet/brochure sent before the call.

We retrieved seven studies:

i. Turner et al.'s RCT (Turner et al. 2008) compared a phone call by a trained peer coach with a mailed colonoscopy brochure about CRC screening in improving adherence to a first scheduled colonoscopy. Seven trained older patients who had had a colonoscopy served as peer coaches. The calls (1 per patient) were scheduled within two weeks of the colonoscopy appointment to address barriers to attendance. In this study peer coach telephone support significantly increased colonoscopy attendance. The fact that coaches received payment for each completed patient call might have introduced a bias in the study.

ii. In Braun et al.'s RCT (Braun et al. 2005), the number of telephone calls has been suggested to have a negative effect on screening. The authors compared an intervention (one culturally targeted educational presentation) delivered by a nurse to an intervention delivered by physician and a peer, both of the same community background as the participants. The first intervention also included one reminder call, whereas the second intervention included multiple reminder telephone calls to encourage screening and address barriers. The two interventions realized similar gains in CRC knowledge but the education provided by the nurse was more effective in increasing uptake of CRC screening; one hypothesis to explain this result was that the multiple reminder phone calls made the intervention too invasive and burdensome.

iii. Lairson's RCT (Lairson et al. 2008) compared a usual care intervention (invitation letter, FOBT test, booklet and reminder letter) to tailored interventions, which incrementally added a tailored leaflet (two message pages) and a reminder telephone call to the usual care intervention. The most effective intervention was the intervention that used the tailored leaflet and the tailored telephone call reminder. An economic analysis showed that it was also the most costly.

iv. Three RCTs were performed either in a primary care population (Costanza et al. 2007), at worksites for automobile industry employees (Tilley et al. 1999), or in an HMO association (Myers et al. 1994). These studies compared standard intervention to an intervention including printed materials along with tailored telephone outreach. In Costanza's RCT, the intervention did not increase colorectal cancer screening compared to control. In Tilley's RCT, the authors concluded that the tailored intervention (mailed invitation, tailored booklet followed by a tailored telephone call) produced a modest but higher screening participation compared to standard intervention (personal letters and flyers at the worksites). In Myers et al.'s survey (1994), adding to the control intervention (a FOBT kit and a reminder letter) a brochure followed by a phone call increased participation comparing to the control intervention.

v. Myers et al. (1991) tested the effect of using usual care (i.e. mailing an advance letter, FOBT kit and a reminder letter) followed either by one telephone call intervention or by two calls plus a brochure intervention. The telephone outreach was used to resolve patient's barriers to non adherence or answer patient-specific questions. The study showed that one call significantly increased the participation compared to usual care. Moreover two calls seemed to have more impact than one on the participation rate.

Even if a tailored telephone call intervention seemed to be effective, it could certainly not be applicable as part of the normal invitation process in CRC screening for reasons of cost-effectiveness and the high volume of calls to be processed. It may be possible to implement tailored telephone calls for harder-to-reach groups if these groups can be identified.

Summary of evidence

- The majority of the studies assessed the impact of tailored reminder telephone call on CRC screening participation.
- A tailored telephone intervention seemed to be effective in increasing screening participation when used as a reminder to mailed invitation materials (usually booklet, FOBT kit, and mailed letter). The most effective but also the most costly intervention was to add to usual care a tailored leaflet and a tailored telephone call reminder.

Tailored telephone calls could certainly not be applicable as part of the normal invitation process for CRC screening for reasons of cost-effectiveness and the high volume of calls to be processed. It may be possible to implement tailored telephone call for "harder-to-reach" groups if these groups can be identified **(II - B)**. For example, peer coach telephone support for explaining colonoscopy procedure seemed to improve attendance for colonoscopy **(II)**. It has been suggested that multiple reminder phone calls could make the intervention too invasive and burdensome.

Recommendations

10.18 It is not cost-effective or feasible to implement a tailored reminder telephone call in the general population. It may be possible for CRC screening programmes to use such an intervention for harder-to-reach groups if these groups can be identified **(II - B)**. For example peer telephone support could be used especially to decrease the attendance barrier to colonoscopy **(II - B)**. Multiple telephone calls seem to have more effect, but it is important to avoid coercion **(I - C)**.

10.4.2.3.2 Patient navigation/patient navigator

A patient navigator (PN) is an individual whose role has been described as providing individualized assistance (by telephone and/or by direct contact) to a patient to both educate and help them overcome healthcare system barriers related to, for example, doctors' offices, clinics, hospitals, out-patient centres, payment systems. In cancer screening, patient navigation should be considered as a method for guiding individuals through the cancer screening process (Myers et al. 2008). "The client navigator approach included the traditional method (i.e. educated patients about cancer screening) along with a social worker who 'navigated' the health care system" (Jandorf et al. 2005). By being able to provide social and logistical services, PN intervention should be differentiated from the usual "telephone intervention" (above section) or "verbal face-to-face intervention" (next section). Social and logistical services provided by patient navigators could be for example facilitating communication among patients/family members/survivors/healthcare providers, coordinating care among providers, facilitating appointments and follow-up appointments, and facilitating access and transportation to services facilities. Patient navigators could be trained community health workers/advisors who have close ties to the local community or trained social workers/health professional/volunteers or belong to a specific organization. The American Cancer Society (ACS) Patient Navigator Program, launched in 2005, currently operates in 60 sites across the USA. The ACS navigators are concentrated in hospitals and clinics that treat a large number of medically underserved patients.

Summary of evidence

- We retrieved eight recent US studies that examined the impact of involving PN in CRC screening in either urban public hospitals setting (Myers et al. 2008) or minority/ethnic urban community health centres (Jandorf et al. 2005; Basch et al. 2006; Dietrich et al. 2006; Nash et al. 2006; Christie et al. 2008; Lasser et al. 2008; Percac-Lima et al. 2009). In the minority/ethnic community, the PN was from a similar ethnic background and/or lived in the community from which the participants were recruited. Patient navigator intervention significantly increased the screening participation. The results of Myers et al.'s pilot study (Myers et al. 2008) are currently being tested in two RCTs.

Recommendations

10.19 Patient navigation could be used within CRC screening programmes, particularly to reach subgroups of the population such as the elderly, those with low literacy, and medically underserved patients. When used with minorities, the PN should be from a similar ethnic background and/or live in the same community as the participant **(I - B)**.

10.4.2.3.3 Verbal face-to-face intervention other than PN: verbal face-to-face with GP, nurse or other health or trained non-health professional

As assessed by Wee et al.'s study (Wee, McCarthy & Phillips 2005), and other studies detailed in Chapter 2, primary care physician (GP) counselling of patients has been positively associated with increasing CRC screening participation rates.

We retrieved eight studies that assessed the impact of direct interaction other than GP (e.g. face-to-face with nurse or other health or trained non-health professional) with participants either in the general population or in some specific subgroups of the general population, such as the socio-economically disadvantaged and/or belonging to racial/ethnic minority groups.

a. In the general population

Two studies (Thompson et al. 2000; Stokamer et al. 2005) evaluated the effect of one-to-one/face-to-face education about the FOBT screening process (purpose/technique of obtaining samples/further testing) provided by a nurse and showed that the intervention increased the return rate of FOBT kits. Stokamer et al. (2005) also reported that participants in the intervention group were significantly less likely to contact the clinic with additional questions. In Thompson et al. study, the nurse was also allowed to order FOBT kits that were given to patients before they left the clinic. This study showed an increased number of ordered kits.

Courtier et al. (2002), evaluated the impact of a trained, non-healthcare professional who provided in-home information and a FOBT kit and personally collected the specimens from the participant's home. The study showed that CRC screening participation was higher in the intervention group.

In Hudson's study (Hudson et al. 2007), practices that reported using nursing or health educator staff to provide behavioural counselling to patients on topics such as diet, exercise or tobacco also resulted in significantly increased CRC screening rates.

b. In some specific sub groups of the general population

Ford et al.'s RCT (Ford, Havstad & Davis 2004) tested different combinations of mail, reminder mail and call, phone call and in person church-based recruitment to invite older (55–74 years) African-American men in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial. They concluded that the most intensive intervention increased significantly the participation compared with the control or the other interventions. The most intensive intervention was the one that besides mail, telephone call, and reminder telephone call, added a face-to-face contact with participants (one session held at church).

Katz et al. (2007) showed in a non-randomised trial that a community-based intervention (a face-to-face interview delivered by trained volunteers from the communities) performed among low-income women (78% African-American) led to a significant increase in positive beliefs about CRC screening and in the intention to complete CRC screening in the next 12 months after the intervention. However CRC screening rates were not significantly increased 1 year after the intervention.

Based on Gren et al.'s paper (Gren et al. 2009), the American PLCO (The Prostate, Lung, Colorectal and Ovarian Cancer) screening trial of centres with enhanced minority recruitment programmes, relied

extensively on community outreach, particularly church-based recruitment and in-person information sessions, to meet their goals.

c. Quality of counselling

In an observational study Ling et al. (2008) evaluated a provider's (physician and nurse practitioner) intervention about CRC screening. They coded each intervention for nine elements of communication (Informed Decision-Making (IDM) Model) that have been shown to be important for IDM. The study showed that 6 of the 9 elements occurred in ≤20% of the visits with none addressed in ≥50%. In this study, compared to patients whose understanding was not assessed, patients whose understanding was assessed during the visit had a higher rate of completing CRC screening. On the contrary, CRC screening participation was less when "patient's screening test preference" or "pros and cons of the alternatives" was discussed.

Ferreira et al.'s RCT (Ferreira et al. 2005) assessed the effect of trying to improve healthcare providers' (nurse practitioner and residents) counselling by using an intervention directed to the health-care provider. The intervention was a series of workshops on rationale and guidelines for CRC screening, and on strategies for improving communication with patients with low literacy skills. During the study, the healthcare providers received confidential information on their individual recommendation and adherence rates. The intervention significantly increased both recommendations and CRC screening completion (FOBT, endoscopy) among patients. The intervention also increased the screening rates among patients with low literacy skills.

Summary of evidence

- Verbal face-to-face intervention and education (nurse and GP) were clearly useful in improving knowledge and participation in CRC screening **(I)**.
- A trained non-health professional, who provided in-home information and a FOBT kit and personally collected the specimens from the participant's home, was effective in increasing CRC screening **(II)**.
- Practices, that reported using nursing or health educator staff to provide behavioural counselling to patients on topics such as diet, exercise or tobacco, also resulted in significantly increased CRC screening rates **(V)**.
- All the elements that should be discussed by GP/nurse to help patients in making informed decisions seemed not to be used **(V)**. Some of these elements seemed to influence patient participation in CRC screening.
- Nurse practitioner/resident training (about CRC screening and communication strategies) and performance communication significantly increased both CRC screening recommendations and completion among patients in general and patients with low literacy skills **(VI)**.
- Community-based interventions such as church-based sessions or in-person interviews significantly increased CRC participation or the intention to be screened in minority subgroups of the US population, especially in the elderly **(II)**.

Recommendations

10.20 Verbal face-to-face interventions with a nurse or physician could be used to improve knowledge and participation. They would be useful to reach subgroups of the population such as the elderly, minorities and those with low literacy **(I - A)**.

10.21 Nurses and primary care practitioners (GPs) should receive adequate training to be able to help patients in making informed decisions about CRC screening **(VI - A)**.

10.22 Community-based verbal face-to-face interventions such as church-based sessions or in-person interviews could be used to reach minorities, in the case where the providers of such interventions received adequate training **(II - B)**.

10.4.2.4 Mass media campaigns

A Cochrane systematic review (Grilli, Ramsay & Minozzi 2002) supports the view that mass media campaigns may have a positive influence upon the way health services are utilised, while the effect on promoting cancer screening is less clear.

Two studies conducted in the late 1980s combined the free distribution of FOBT kits through pharmacies with repeated educational reports on a local television station (McGarrity et al. 1989; McGarrity, Long & Peiffer 1990). However, neither study included any outcomes addressing the effect advertisements may have had on participation rates or decision-making. A cross-sectional survey (Schroy III, et al. 2008) aimed at assessing the extent to which mass media campaigns launched since the year 2000 in the USA have achieved the goal of educating the public about CRC and screening. Although the authors concluded that media campaigns can be effective in increasing public awareness about CRC risk, the study was not designed to support this assertion.

Two studies were identified that reported the effect on CRC screening rates after extensive media coverage involving celebrities:

i. In the first study, Brown & Potosky (1990) reported various outcomes related to media coverage of US President Ronald Reagan's CRC episode in July 1985. The authors reported that there was a transitory increase in public interest in CRC, with a corresponding increase in early detection tests following media coverage of the President's CRC surgery. However, as stated by the authors, the evidence is only suggestive and the methodology of the study quite poor.
ii. The second study assessed the impact of a CRC awareness campaign on colonoscopy investigations by a well-known television celebrity (Cram et al. 2003). The study found that the awareness campaign was temporally associated with an increase in colonoscopy rates. The authors concluded that a celebrity spokesperson can have a substantial impact on public participation in screening programmes.

Nicholson et al.'s RCT (Nicholson et al. 2008) has shown that the way information about colorectal cancer was reported in a medium could influence the motivation to be screened in minority groups: information emphasising the progress African-Americans were making in increasing CRC screening and decreasing CRC mortality led to significantly increase intention to be screened, and counteracted the negative effects of medical mistrust, compared to information emphasising racial disparities.

As media can be a source of information for patients, those in charge of CRC screening programmes should work closely with the media and provide them with up-to-date, accurate and comprehensive information to prevent contradictory, false messages or false expectations being sent to the public.

Summary of evidence

Several studies have investigated the role that the mass media may have in increasing participation in CRC screening. Unfortunately, the quality of the published studies is quite poor, with the majority failing to include any outcomes assessing the role or effect that advertisements or mass media may have either on the decision-making process or the decision to participate or not in CRC screening.

- Celebrity campaigns were useful to increase participation but the increase was only temporary **(V)**.
- Information emphasising the progress a minority group was making in increasing CRC screening and decreasing CRC mortality led to significantly increase intention to be screened, and counteracted the negative effects of medical mistrust, compared to information emphasising racial disparities **(II)**.

As the media can be a source of information for patients, those in charge of CRC screening programmes should work closely with the media and provide them with up-to-date, accurate and comprehensive information.

Recommendations

10.23 Mass media campaigns using celebrities may be used to increase the awareness of CRC and CRC screening programmes. However, they should be complemented by other measures as the effects are only temporary **(V - C)**.

10.24 When addressed to minority groups, information provided by mass media campaigns should emphasise positive progress made by the minority group instead of emphasising racial disparities **(VI - C)**.

10.25 (See below).

10.4.2.5 Advocacy groups

Advocacy groups are playing an increasing role in promoting cancer screening (Ganz 1995). In colorectal cancer screening, for example, we can refer to the role played by the European Cancer Patient Coalition in the generation of CRC awareness and lobbying for effective CRC screening programmes in Europe. However, there are at present no studies showing the impact of such groups on CRC screening. The role of advocacy groups should be investigated. However, as advocacy groups can be a source of information for patients, e.g. by disseminating education messages to the target audience and providing supportive care during and after treatment patient, screening organisations should share information with advocacy groups to prevent contradictory messages being sent to the public.

Recommendations

10.25 CRC screening programmes should work closely with advocacy groups and the media and provide them with up-to-date, accurate and comprehensive information about CRC and CRC screening **(VI - A)**.

10.4.3 Communication tools/interventions used to inform a person of a screening test result and facilitate follow-up of a positive result

In CRC screening, positive results are usually accompanied by information about follow-up. Miglioretti et al. (2008) reported that 16% of patients refused follow-up after a positive FOBT test. A similar figure is reported in many countries worldwide. This result emphasises the need for vigilance and continued effort at patient-centred communication and counselling (Zapka 2008).

Very little is known regarding which interventions should be used to ensure follow-up of patients with abnormal findings in CRC screening. Based on a 2004 systematic review (Bastani et al. 2004), it seems that various interventions such as mail and telephone reminders, telephone counselling, and print educational interventions are effective in increasing follow-up rates of abnormal cancer screening findings. In this review, just four studies were retrieved related to CRC screening. Among these studies, Myers et al.'s RCT (2004) has shown that a reminder-feedback and an educational outreach intervention targeted to the primary care physician were effective in improving follow-up.

A retrospective chart review study (Rao, Schilling & Sequist 2009) has shown that one factor associated with higher rates of colonoscopy after positive FOBT results was the patient having a consultation with a gastroenterologist.

Rubin et al.'s RCT (Rubin et al. 2007) has shown that providing patients with a written copy of their standard colonoscopy screening report at the conclusion of their procedure enhanced recall of the findings and recommendations.

Zheng et al. (2006) investigated the factors relating to adherence to follow-up after an abnormal screening FOBT result. The results of this survey suggest that future interventions should focus on:

- Clarifying misperceptions about follow-up (e.g. understanding the benefits and meanings of follow-up);
- Promoting the acceptance of colonoscopy, as for example patients could perceive unpleasantness regarding preparation for colonoscopy and discomfort of the procedure. Turner et al.'s (Turner et al. 2008) result supports this finding: a peer coach telephone support, in which former patients who had had a colonoscopy served as peer coaches, scheduled within 2 weeks of the colonoscopy appointment significantly increased screening colonoscopy attendance; and
- Addressing psychological distress (e.g. being afraid of finding cancer), and making follow-up testing more convenient and accessible.

Regarding patient consent, verbal face-to-face intervention before (pre-assessment) and after the endoscopic procedure for programmes undergoing endoscopy (FS or colonoscopy) either for primary screening, or more specifically, as recommended by the EU, for assessment of abnormalities detected in FOBT screening (follow-up): see summary below and Chapter 5 for more details.

Summary of evidence

- A reminder-feedback and an educational outreach intervention targeted to the primary care physician can be effective in improving follow-up. Providing patients with a written copy of their standard screening report enhanced recall of the findings and recommendations **(II)**.
- Using peer coach telephone support increases colonoscopy attendance: interventions should focus on clarifying misperceptions about follow-up, promoting the acceptance of the follow-up procedure, addressing psychological distress and making follow-up testing more convenient and accessible **(II)**.
- Obtaining a consultation with a gastroenterologist increases the rates of follow-up colonoscopy **(V)**.

The patient should give consent to the endoscopy procedure and should have the opportunity to withdraw consent at any stage before or during the procedure. Patients should be informed about the outcome of their procedure both orally and with written information before leaving the endoscopy unit. The outcome of screening examinations should be communicated to the primary care doctor or equivalent (see Chapter 5 for more details).

Recommendations

10.26 A telephone or ideally a verbal face-to-face intervention, e.g. nurse or physician intervention, should be used to inform a patient of a positive screening test result, as obtaining such a result could be a source of psychological distress for the patient. A letter informing the patient should not be used as the only way of notifying a positive result **(VI - A)**.

10.27 To increase endoscopy follow-up after a positive FOBT and facilitate communication, CRC screening programmes should, where possible:

- Use a reminder-feedback and an educational outreach intervention targeted to the primary care physician **(II - A)**;
- Provide patients with a written copy of their screening report **(II - A)**;
- Facilitate patient consultation with a gastroenterologist **(V - B)**;
- Describe the follow-up procedure, make the follow-up testing more convenient and accessible **(VI - A)**; and

- o Use direct contact intervention to address psychological distress and other specific barriers **(V - B)**.

From Chapter 5 (see Chapter 5 for more details):

10.28 Each endoscopy service must have a policy for pre-assessment that includes a minimum data set relevant to the procedure. There should be documentation and processes in place to support and monitor the policy (see Ch. 5, Rec. 5.20, Sect 5.3.2) **(III - B)**.

10.29 The endoscopy service must have policies that guide the consent process, including a policy on withdrawal of consent before or during the endoscopic procedure (see Ch. 5, Rec. 5.25, Sect 5.3.1) **(VI - B)**.

10.30 Patients should be informed about the outcome of their procedure before leaving the endoscopy unit and given written information that supports a verbal explanation (see Ch. 5, Rec. 5.26, Sect 5.4.3) **(VI - A)**.

10.31 The outcome of screening examinations should be communicated to the primary care doctor (or equivalent) so that it becomes part of the core patient record (see Ch. 5, Rec. 5.27, Sect 5.5.5) **(VI - B)**.

10.5 Content that should be included in: the invitation letter and leaflet, the letter and leaflet used to notify results, and the instructions

10.5.1 General recommendations

Summary of evidence

In organised CRC screening programmes, letters and leaflets are the two most disseminated communication instruments used by health organisations. Letters are generally used to invite people to participate in CRC screening, to notify them of the result of the test and provide information on follow-up. Written materials have advantages such as flexibility of delivery, portability, reusability and can be produced relatively quickly and inexpensively. But they have some obvious limitations: information must be concise, addressed to a general readership and is not effective for individuals who do not read. Leaflets should be used to support and detail the information provided in the letters. Some basic information must be included in the letter in case a person reads only the invitation letter and not the leaflet. Screening programmes should ensure that participants understand the instructions on how to use the FOBT kit and perform the bowel cleansing. Letters, leaflets and written instructions should be developed taking into account all the recommendations given previously.

Currently there is no consensus on what should be said in the letter/leaflet even if the majority of experts agree that individuals must be given information about the pros and the cons of screening to enable IDM. The material listed below could be used as guidelines/examples:

- The recent EU guidelines for cervix cancer screening;

- The IPDAS (an international group of more than 100 researchers, practitioners and stakeholders, see following chapter) recommendations for information content (Elwyn et al. 2006);
- The ICSN publication, 2007: "Designing Print Materials: A Communications Guide for Breast Cancer Screening", (National Cancer Institute (NCI) 2007);
- The invitation leaflet developed and used for the UK CRC screening programme (The NHS Bowel Cancer Screening Programme: "Bowel Cancer Screening: the Facts", http://www.cancerscreening.nhs.uk/bowel/publications/bowel-cancer-the-facts.pdf, and the Evidence Summary: patient information for the NHS Bowel cancer screening programme);
- The colonoscopy leaflet developed and used for the UK CRC screening programme (The NHS Bowel Cancer Screening Programme, "Bowel Cancer Screening: The colonoscopy; investigation", http://www.cancerscreening.nhs.uk/bowel/publications/colonoscopy-investigation.pdf); and/or
- The invitation and colonoscopy leaflets developed and used for the UK CRC screening programme for those with disabilities: http://www.cancerscreening.nhs.uk/bowel/publications/nhsbcsp-learning-disabilities-leaflet.pdf and http://www.cancerscreening.nhs.uk/bowel/publications/nhsbcsp-colonoscopy-learning-disabilities-leaflet.pdf

Recommendations

Letters, leaflets and written instructions (on how to use the FOBT kit and perform the bowel cleansing) should be developed by taking into account all the recommendations below, some of which are either taken from previous relevant sections of Chapter 10 as indicated:

- General principles (Paragraph 10.2): recommendations 10.1–10.5.
- Physician/GP endorsement, Letters, FOBT delivery and instructions (Paragraph 10.4.1): recommendations 10.6, 10.7, 10.10.
- Leaflets/booklets (Paragraph 10.4.2.1): recommendations 10.11–10.13.
- Result and follow-up (Paragraph 10.4.3 and Chapter 5): 10.27–10.31.

New recommendations

10.32 Ideally, the invitation letter and the letter used for notification of a positive result should be sent with a leaflet and participants should be encouraged to read it **(VI - A)**.

10.33 Certain basic information e.g. logistic/organisational information, a description of the screening test, the harms and benefits of screening, information about the FOBT kit and the bowel cleansing procedure, must be included in the letter in case a person reads only the invitation/result letter and not the leaflet **(VI - A)**.

10.5.2 When FOBT is used for screening: content of letters and leaflets

10.5.2.1 FOBT invitation letter

The letter inviting patients to perform FOBT screening should contain the following information:

- **Screening information:**
  - The purpose of screening (describe the natural course taken by the disease if not detected and explain the aim of early detection, mention the different prospects depending on whether the disease is found with screening or not, specifically mention the option of not participating);
  - Who the test is for (target population, age group); and

  - The screening interval.
- **Organisational information:**
  - How to make and change the appointment when an appointment is required to pick-up the test;
  - Cost of the test (free or not); and
  - Where further information can be obtained (information services, telephone hotlines, patient groups, websites, etc.).
- **Information about the the screening test:**
  - Details of the screening test that will be performed (including who performs the test, how long it will take, what the test is designed to measure);
  - How to obtain the result (mentioning the approximate waiting times); and
  - The proportion of people who may require further testing.
- **Information about the benefits of screening:** Emphasise that early detection can save lives.
- **Information about the harms/side effects/disadvantages of screening:**
  - Meaning of a FOBT positive result in terms of follow-up: what is colonoscopy, benefits and possible harms of the colonoscopy (see Chapter 5 for details), referring to colonoscopy leaflet; and
  - Fear/anxiety about cancer and screening results.
- **Information about the FOBT kit:**
  - Where to collect it; and
  - If the FOBT kit is sent with the letter, the letter should refer to the instruction leaflet and encourage participants to read it.
- **Referral to the invitation leaflet:** encouraging participants to read it.

10.5.2.2 FOBT invitation leaflet

The leaflet inviting patients to perform FOBT screening should contain the following information:

- **Screening information:**
  - The purpose of screening (describe the natural course taken by the disease if not detected and explain the aim of early detection, mention the different prospects depending on whether the disease is found with screening or not, specifically mention the option of not participating)
  - Who the test is for (target population, age group);
  - The screening interval;
  - Quality standards and quality assurance;
  - Other types of screening; and
  - Comments on people outside the recommended age group, including those at risk of colorectal cancer.
- **Colorectal cancer:**
  - Incidence;
  - Lifetime morbidity and mortality; and
  - Risk factors.

- **Screening test:**
  - Nature (what is it?);
  - Purpose (what the test is designed to measure);
  - Details of the screening test that will be performed (including who performs the test, how long it will take, what the test is designed to measure);
  - Informed consent;
  - How to obtain the result (mentioning the approximate waiting times);
  - Meaning of the test results (What "negative", "positive" and "unclear" mean);
  - Meaning of a FOBT positive result in terms of follow-up: what is colonoscopy, benefits and possible harms of the colonoscopy (see Chapter 5 for details), referring to colonoscopy leaflet;
  - Mention the proportion of people who may require further testing; and
  - Reassurance about follow-up.
- **Test characteristics:**
  - False positive and false negative results (including chances of true positive, true negative, false positive, and false negative tests);
  - Positive predictive value;
  - Number needed to screen to prevent one death; and
  - Reasons why FOBT sometimes need to be repeated.
- **Benefits of screening:**
  - Mention that early detection can save lives;
  - Cancer can be found earlier/be prevented; and
  - Screening relieves fear and anxiety about cancer; peace of mind.
- **Harms/side effects/disadvantages of screening:**
  - Harms/side effects/disadvantages of colonoscopy if follow-up is required: sedation, cleansing procedure, possible complications, discomfort and pain during the colonoscopy procedure;
  - Identification and treatment of clinically unimportant tumours: the possibility of over-diagnosis; and
  - Fear/anxiety about cancer and screening results.
- **Options:**
  - Include deciding on having a colonoscopy or not (describe the natural course taken by the disease if not detected) or being not clear about what to decide (methods for clarifying and expressing values); and
  - The opportunity to request to withdraw from the programme.

Guidelines on presenting probabilities of outcomes in an unbiased and understandable way (IPDAS, NHSBSP no. 65, p. 5):

- Use event rates specifying the population and time period;
- Compare outcome probabilities using the same denominator, time period, scale;
- Describe uncertainty around probabilities;
- Absolute risk should be used in preference to relative risk;
- Use visual diagrams;
- Use multiple methods to give probabilities (words, numbers, diagrams);

- Allow the patient to select a way of viewing probabilities (words, numbers, diagrams);
- Allow patient to view probabilities based on their own situation (e.g. age); and
- Place probabilities in context of other events.

10.5.2.3 FOBT result/follow-up letter

The letter to inform patients about FOBT screening result should contain the following information:

- The letter should be personalised with the name of the patient and give the FOBT screening test result.
- If the result is negative, its meaning should be explained in terms of the likelihood of having CRC and the possibility of false negatives. The screening interval should be also specified.
- If the test is unclear, its meaning should be explained. If the directives of the screening programme are to repeat the FOBT, the letter should mention it and the patient should be invited to perform a repeat test.
- If the test is positive, its meaning should be explained in terms of the likelihood of having CRC and possibility of false positive. The letter should refer to the colonoscopy leaflet sent with the letter that describes in detail the colonoscopy procedure and should encourage participants to read it. However, certain basic and practical information about the colonoscopy procedure, its harms and benefits, and logistic/organisational information relating to the colonoscopy appointment must be included in the letter in case a person reads just the letter and not the colonoscopy leaflet.

10.5.2.4 Colonoscopy leaflet (see Section 10.5.3.2)

10.5.3 When flexible sigmoidoscopy (FS) or colonoscopy is used for screening, either as primary screening test (FS or CS) or to follow-up a positive FOBT result (only CS): content of letters and leaflets

10.5.3.1 Endoscopy invitation letter

The letter inviting patients to perform endoscopy screening should contain the following information:

- **Screening information:**
  - The purpose of screening (describe the natural course taken by the disease if not detected and explain the aim of early detection, mention the different prospects depending on whether the disease is found with screening or not, specifically mention the option of not participating);
  - Who the test is for (target population, age group); and
  - The screening interval.
- **Organisational information:**
  - How to make and change the appointment;
  - Cost of the test (free or not); and
  - Where further information can be obtained (information services, telephone hotlines, patient groups, web sites, etc...).

- **Information about the screening test:**
  - Details of the screening test that will be performed (including who performs the test, how long it will take, what the test is designed to measure);
  - How to obtain the result (mentioning the approximate waiting times); and
  - Mention the proportion of people who may require further testing.
- **Information about benefits of screening:** Early detection can save lives.
- **Information about harms/side effects/disadvantages of endoscopy screening (see Chapter 5 for details):**
  - For both FS (if colonoscopy is used as follow-up procedure) and colonoscopy: The possible complications of colonoscopy and discomfort and pain during the procedure;
  - The meaning of a positive FS result in terms of follow-up: what is colonoscopy, benefits and possible harms of the colonoscopy, referring to colonoscopy leaflet; and
  - Identification and treatment of clinically unimportant tumours: the possibility of over-diagnosis.
- **Information about the cleansing procedure.**
- **Referral to the endoscopy leaflet** encouraging participants to read it.
- **Options:**
  - Include deciding whether to have an endoscopy (describe the natural course without having the endoscopy), or being not clear about what to decide (methods for clarifying and expressing values); and
  - The possibility to withdraw consent at any stage (Chapter 5 recommendation).

10.5.3.2 Endoscopy invitation leaflet: example for colonoscopy

The leaflet to inform patients about a colonoscopy screening, either for primary screening or as follow-up after a positive FOBT or FS, should contain the following information:

- **Colorectal cancer and colorectal screening:**
  - The purpose and the importance of screening; what early detection means;
  - A description of colorectal cancer disease; and
  - General information about the CRC screening programme.
- **In cases where colonoscopy is used as follow-up after a positive FOBT result or FS:**
  - Explain why colonoscopy is required;
  - How to interpret a FS positive result; and
  - How to interpret a FOBT positive result: What “positive FOBT” result means: including chances of true positive, true negative, false positive and false negative test.
- **Colonoscopy procedure:**
  - Nature (what is it?);
  - Who the test is for; validity;
  - Purpose (what the test is designed to measure, why it is being done);
  - How to make and change an appointment;
  - How the test is carried out;
  - How to prepare for the colonoscopy (including bowel cleansing and options for sedation);

- Who performs the test, where it is performed;
- How long it takes;
- What to do when the test is done;
- Cost of the procedure: free or not;
- How to obtain the result (approximate waiting times);
- Meaning of colonoscopy results (normal, polyps, cancer);
- Quality control of the colonoscopy procedure; and
- What to do if people have symptoms after colonoscopy.

- **Positive outcomes:** Cancers can be found earlier/be prevented.
- **Harms/side effects/disadvantages of colonoscopy (see Chapter 5 for details):**
  - Associated restrictions on travelling or making important decisions due to sedation;
  - Cleansing procedure;
  - Possible adverse events including discomfort, pain and complications;
  - Identification and treatment of clinically unimportant tumours: the possibility of over-diagnosis;
  - Fear/anxiety about cancer and colonoscopy results; and
  - What support may be needed after the procedure, particularly if the patient is sedated.
- **Options:**
  - Include deciding on having a colonoscopy or not (describe the natural course without having the colonoscopy), or being not clear about what to decide (methods for clarifying and expressing values)
  - The opportunity to withdraw consent at any stage (Chapter 5 recommendation)

Guidelines on how to present probabilities of outcomes in an unbiased and understandable way (IPDAS, NHSBSP no65 p5) as described above for the invitation leaflet.

10.5.3.3 Endoscopy results/follow-up letter

The letter should be personalised with the name of the patient and give the endoscopy screening test result:

- If the result is negative, its meaning should be explained in terms of the likelihood of having CRC and possibility of false negatives. The screening interval should be also specified;
- If the test is positive, the letter should describe in detail what following steps to take.

10.6 Stylistic advice

The way information is presented plays an important role in determining its comprehension and acceptance. For this reason, it is essential that written information be guided by good communication principles in order to be easy to read and understood by the users.

Written information material should be clear, visually appealing and motivating to the intended audience.

Some recommendations on language, on text style and wording, and formatting are provided hereafter, based on the recent EU guidelines for quality assurance in cervical cancer screening (European Cancer Network 2008). They should be carefully considered by the screening staff to make the communication more effective and easily understandable to participants.

Recommendations

The language, text style, wording and formatting used in written information should follow these suggestions:

- **Language:**
  - Clear (about the topic: clarify points with examples);
  - Honest, respectful, polite;
  - Simple everyday language (no technical terms, jargon, abbreviations and acronyms);
  - Informal (use of pronouns like “we” and “you” to personalise the text);
  - Impartial;
  - Not top-down (no prescriptive style or paternalistic tone); and
  - Written in the active voice.
- **Text style and wording:**
  - Credible, reliable (indicating the source of information);
  - Up-to-date and contemporary;
  - Friendly and sympathetic;
  - Positively framed (e.g. 9 out of 10 recalled patients are found to be normal rather than 1 out of 10 recalled women will have cancer); and
  - Positive tone (alarming statements should be avoided).
- **Text format:**
  - Preferably plain layout;
  - Short sentences and brief paragraphs;
  - Use of diagrams and pictures;
  - Use of titles and subtitles (to distinguish different areas);
  - Bold or capital letters (to underline important points);
  - Larger print (essential for older target populations);
  - Use of white spaces (to facilitate reading);
  - Preferably question/answer and paragraph formats;
  - Appropriate colours (as some colours are difficult for colour-blind people to read); and
  - Logo.

10.7 Evaluating the quality of public information materials: are these materials meeting the required standard for quality?

There are currently different guides to assess the quality of communications tools. The International Patient Decision Aid Standard (IPDAS) collaboration group (an international group of more than 100 researchers, practitioners and stakeholders) has provided a framework of quality criteria for patient decisions aids used for screening or health decisions (Elwyn et al. 2006). Even if the IPDAS checklist does not address CRC screening specifically, it is a good guideline for evaluating the quality of communication tools produced by CRC screening programmes. This is the reason why we recommend using it.

The IPDAS framework, a list of 80 items, was produced as a consensus of the IPDAS group and developed based on evidence where it exists and the view of IPDAS experts. These criteria "might be considered to represent an ideal construction that may be difficult to attain. ....The criteria are not meant to be prescriptive." (Elwyn et al. 2006). The criteria (in *Developing a quality criteria framework for patient decision aids: online international Delphi consensus process* and IPDAS criteria checklist) address 3 domains of quality: the content (specific to the health condition and therapeutic/screening options), the development process (referring to the way the decision aid should be developed and relevant to any decision aid) and the effectiveness (relevant to any decision aid, to evaluate the effectiveness of the decision aid). Based on these criteria, a new instrument has been developed to assess the quality of decision support materials: the IPDASi assessment service (http://www.ipdasi.org/) which is currently undertaking a validation study assessing 30 decision support technologies.

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Appendix 1

Systematic evidence review:

Summary documents and evidence tables for key clinical questions compiled for the European guidelines for quality assurance in colorectal cancer screening and diagnosis - First edition

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For users of the printed Guidelines version, the full contents of Appendix 1 are available on the attached CD.

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Appendix 2

Council Recommendation of 2 December 2003 on cancer screening (2003/878/EC)

L 327/34 EN Official Journal of the European Union 16.12.2003

COUNCIL RECOMMENDATION
of 2 December 2003
on cancer screening

(2003/878/EC)

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 152(4), second subparagraph, thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the European Parliament,

Whereas:

(1) Article 152 of the Treaty provides that Community action is to complement national policies and be directed towards improving public health, preventing human illness and diseases, and obviating sources of danger to human health. Such action shall cover the fight against the major health scourges, by promoting research into their causes, their transmission and their prevention, as well as health information and education. Community action in the field of public health shall fully respect the responsibilities of the Member States for the organisation and delivery of health services and medical care.

(2) Further development of cancer screening programmes should be implemented in accordance with national law and national and regional responsibilities for the organisation and delivery of health services and medical care.

(3) Cancer is a major disease and cause of death throughout Europe, including the future Member States. An estimated number of 1 580 096 new cancer cases, excluding non-melanoma skin cancer, occurred in the European Union in 1998. Of these, 1,4 % were cervical cancers, 13 % breast cancers, 14 % colorectal cancers and 9 % prostate cancers. Cervical and breast cancer constituted 3 % and 29 %, respectively, of new cancers in women. Prostate cancer constituted 17 % of new cancers in men.

(4) Principles for screening as a tool for the prevention of chronic non-communicable diseases were published by the World Health Organisation in 1968 and by the Council of Europe in 1994. These two documents form, together with the current best practice in each of the cancer screening fields, the basis for the present recommendations.

(5) Additionally, these recommendations are based on the 'Recommendations on cancer screening' of the Advisory Committee on Cancer Prevention together with the experience gathered under the different actions sustained under the Europe against Cancer programme where European collaboration has helped, for example, high quality cancer screening programmes to provide efficient European guidelines of best practice and to protect the population from poor quality screening.

(6) Important factors which have to be assessed before a population-wide implementation is decided upon include, *inter alia*, the frequency and interval of the application of the screening test as well as other national or regional epidemiological specificities.

(7) Screening allows detection of cancers at an early stage of invasiveness or possibly even before they become invasive. Some lesions can then be treated more effectively and the patients can expect to be cured. The main indicator for the effectiveness of screening is a decrease in disease-specific mortality. As in the case of cervical cancer, cancer precursors are detected, a reduction in cervical cancer incidence can be considered a very helpful indicator.

(8) Evidence exists concerning the efficacy of screening for breast cancer and colorectal cancer, derived from randomised trials, and for cervical cancer, derived from observational studies.

(9) Screening is, however, the testing for diseases of people for which no symptoms have been detected. In addition to its beneficial effect on the disease-specific mortality, screening can also have negative side effects for the screened population. Healthcare providers should be aware of all the potential benefits and risks of screening for a given cancer site before embarking on new population-based cancer screening programmes. Furthermore, for the informed public of today, these benefits and risks need to be presented in a way that allows individual citizens to decide on participation in the screening programmes for themselves.

(10) Ethical, legal, social, medical, organisational and economic aspects have to be considered before decisions can be made on the implementation of cancer screening programmes.

(11) Due account should be taken of specific needs of persons who may be at higher cancer risk for particular reasons (e.g. biological, genetic, lifestyle and environmental, including occupational).

(12) The public health benefits and cost efficiency of a screening programme are achieved if the programme is implemented systematically, covering the whole target population and following best-practice guidelines.

(13) The cost-effectiveness of cancer screening depends on several factors such as epidemiology, and healthcare organisation and delivery.

(14) Systematic implementation requires an organisation with a call/recall system and with quality assurance at all levels, and an effective and appropriate diagnostic, treatment and after-care service following evidence-based guidelines.

(15) Centralised data systems, including a list of all categories of persons to be targeted by the screening programme and data on all screening tests, assessment and final diagnoses, are needed to run organised screening programmes.

(16) All procedures for collecting, storing, transmitting and analysing data in the medical registers involved must be in full compliance with the level of protection referred to in Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data [1], as well as in full compliance with the relevant provisions of Member States on the management and processing of health data in accordance with Article 8 of the Directive.

(17) Quality screening includes analysis of the process and outcome of the screening and rapid reporting of these results to the population and screening providers.

(18) This analysis is facilitated if the screening database can be linked to cancer registries and mortality databases.

(19) Adequate training of personnel is a prerequisite for high quality screening.

(20) Specific performance indicators have been established for cancer screening tests. These should be monitored regularly.

(21) Adequate human and financial resources should be available in order to assure the appropriate organisation and quality control in all the Member States.

(22) Action should be taken to ensure equal access to screening taking due account of the possible need to target particular socioeconomic groups.

(23) It is an ethical, legal and social prerequisite that cancer screening should only be offered to fully informed people with no symptoms if the screening is proved to decrease disease-specific mortality, if the benefits and risks are well known, and if the cost-effectiveness of the screening is acceptable.

(24) The screening methods which presently meet these strict prerequisites are listed in the Annex.

(25) No screening test other than those listed in the Annex is scientifically justified to be offered to people with no symptoms in an organised population-based programme before it has been shown in randomised controlled trials to decrease disease-specific mortality in particular.

(26) The screening tests listed in the Annex can only be offered on a population basis in organised screening programmes with quality assurance at all levels, if good information about benefits and risks, adequate resources for screening, follow-up with complementary diagnostic procedures and, if necessary, treatment of those with a positive screening test are available.

(27) The introduction of the recommended screening tests in the Annex, which have demonstrated their efficacy, should be seriously considered, the decision being based on available professional expertise and priority-setting for healthcare resources in each Member State.

(28) Once there is evidence that a new screening test is effective, evaluation of modified tests may be possible using other epidemiologically validated surrogate endpoints if the predictive value of these endpoints is established.

(29) Screening methodologies are subject to ongoing development. The application of recommended screening methodologies should therefore be accompanied by simultaneous assessments of the quality, applicability and cost-effectiveness of new methods if available epidemiological data justify this. In fact, the ongoing work may lead to new methods, which could ultimately replace or complement the tests listed in the Annex or be applicable to other types of cancer,

[1] OJ L 281, 23.11.1995, p. 31.

HEREBY RECOMMENDS THAT MEMBER STATES:

1. Implementation of cancer screening programmes

(a) offer evidence-based cancer screening through a systematic population-based approach with quality assurance at all appropriate levels. The tests which should be considered in this context are listed in the Annex;

(b) implement screening programmes in accordance with European guidelines on best practice where they exist and facilitate the further development of best practice for high quality cancer screening programmes on a national and, where appropriate, regional level;

(c) ensure that the people participating in a screening programme are fully informed about the benefits and risks;

(d) ensure that adequate complementary diagnostic procedures, treatment, psychological support and after-care following evidence-based guidelines of those with a positive screening test are provided for;

(e) make available human and financial resources in order to assure appropriate organisation and quality control;

(f) assess and take decisions on the implementation of a cancer screening programme nationally or regionally depending on the disease burden and the healthcare resources available, the side effects and cost effects of cancer screening, and experience from scientific trials and pilot projects;

(g) set up a systematic call/recall system and quality assurance at all appropriate levels, together with an effective and appropriate diagnostic and treatment and after-care service following evidence-based guidelines;

(h) ensure that due regard is paid to data protection legislation, particularly as it applies to personal health data, prior to implementing cancer screening programmes.

2. Registration and management of screening data

(a) make available centralised data systems needed to run organised screening programmes;

(b) ensure by appropriate means that all persons targeted by the screening programme are invited, by means of a call/recall system, to take part in the programme;

(c) collect, manage and evaluate data on all screening tests, assessment and final diagnoses;

(d) collect, manage and evaluate the data in full accordance with relevant legislation on personal data protection.

3. Monitoring

(a) regularly monitor the process and outcome of organised screening and report these results quickly to the public and the personnel providing the screening;

(b) adhere to the standards defined by the European Network of Cancer Registries in establishing and maintaining the screening databases in full accordance with relevant legislation on personal data protection;

(c) monitor the screening programmes at adequate intervals.

4. Training

adequately train personnel at all levels to ensure that they are able to deliver high quality screening.

5. Compliance

(a) seek a high level of compliance, based on fully informed consent, when organised screening is offered;

(b) take action to ensure equal access to screening taking due account of the possible need to target particular socioeconomic groups.

6. Introduction of novel screening tests taking into account international research results

(a) implement new cancer screening tests in routine healthcare only after they have been evaluated in randomised controlled trials;

(b) run trials, in addition to those on screening-specific parameters and mortality, on subsequent treatment procedures, clinical outcome, side effects, morbidity and quality of life;

(c) assess level of evidence concerning effects of new methods by pooling of trial results from representative settings;

(d) consider the introduction into routine healthcare of potentially promising new screening tests, which are currently being evaluated in randomised controlled trials, once the evidence is conclusive and other relevant aspects, such as cost-effectiveness in the different healthcare systems, have been taken into account;

(e) consider the introduction into routine healthcare of potentially promising new modifications of established screening tests, once the effectiveness of the modification has been successfully evaluated, possibly using other epidemiologically validated surrogate endpoints.

7. Implementation report and follow-up

report to the Commission on the implementation of this Recommendation within three years of its adoption and subsequently at the request of the Commission with a view to contributing to the follow-up of this Recommendation at Community level.

HEREBY INVITES THE COMMISSION:

1. To report on the implementation of cancer screening programmes, on the basis of the information provided by Member States, not later than the end of the fourth year after the date of adoption of this Recommendation, to consider the extent to which the proposed measures are working effectively, and to consider the need for further action.
2. To encourage cooperation between Member States in research and exchange of best practices as regards cancer screening with a view to developing and evaluating new screening methods or improving existing ones.
3. To support European research on cancer screening including the development of new guidelines and the updating of existing guidelines for cancer screening.

Done at Brussels, 2 December 2003.

For the Council

The President

R. MARONI

ANNEX

SCREENING TESTS WHICH FULFIL THE REQUIREMENTS OF THE RECOMMENDATION (*):

— pap smear screening for cervical cancer precursors starting not before the age of 20 and not later than the age of 30;

— mammography screening for breast cancer in women aged 50 to 69 in accordance with European guidelines on quality assurance in mammography;

— faecal occult blood screening for colorectal cancer in men and women aged 50 to 74.

(*) The indicated age ranges are to be understood as maximum ranges; subject to national epidemiological evidence and prioritisation, smaller age ranges may be appropriate.

Appendix 3

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)

COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 22.12.2008
COM(2008) 882 final

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)

EN EN

1. PREFACE

1.1. Introduction

On 2 December 2003 the Health Ministers of the European Union unanimously adopted a Recommendation on cancer screening[1]. The Recommendation on cancer screening of the Council of the European Union acknowledges both the significance of the burden of cancer in the European population and the evidence for effectiveness of breast, cervical and colorectal cancer screening in reducing the burden of disease.

The Council Recommendation spells out fundamental principles of best practice in early detection of cancer and invites Member States to take common action to implement national cancer screening programmes with a population-based approach and with appropriate quality assurance at all levels, taking into account European Quality Assurance Guidelines for Cancer Screening, where they exist. Updated and expanded EU guidelines for breast[2] and cervical[3] cancer screening have recently been published by the Commission; comprehensive European guidelines for quality assurance of colorectal cancer screening are currently in preparation.

The development of new guidelines on cancer screening as a means to foster good health in an ageing Europe, has also been highlighted in the EU Health Strategy[4]. Implementation of the Recommendation has also been supported by the European Parliament through resolutions adopted in 2003[5], 2006[6] and 2008[7].

The Recommendation invites the European Commission to report on the implementation of cancer screening programmes, to consider the extent to which the proposed measures are working effectively, and to consider the need for further action. This is the first such report.

1.2. Basis of the report

In preparing this report, the Commission invited Member States to reply to a written survey in the second half of 2007. 22 of the 27 Member States (82%) returned the questionnaire as of May 2008 (Austria, Belgium, Cyprus, Czech Republic, Estonia, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, United Kingdom).

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1 Council Recommendation of 2 December 2003 on Cancer Screening (2003/878/EC): OJ L327/34-38.

2 EU guidelines for quality assurance in breast cancer screening and diagnosis – 4th edition: Luxembourg: Office for Official Publications of the European Communities; ISBN: 92–79–01258–4, catalogue number: ND-73–06–954-EN-C © European Communities, 2006.

3 EU guidelines for quality assurance in cervical screening – 2nd edition: Luxembourg: Office for Official Publications of the European Communities; ISBN 978-92-79-07698-5, catalogue number: ND-70-07-117-EN-C © European Communities, 2008.

4 Together for Health: A Strategic Approach for the EU 2008-2013, COM(2007) 630 final of 23.10.2007.

5 European Parliament resolution of 05 June 2003 on breast cancer in the European Union (P5_TA(2003)0270): OJ C 68 E, 18.3.2004, p. 611.

6 European Parliament resolution of 25 October 2006 on breast cancer in the enlarged European Union (P6_TA(2006)0449 B6-0528/2006): OJ C 313 E, 20.12.2006, p.273.

7 European Parliament resolution of 10 April 2008 on combating cancer in the enlarged European Union (P6_TA(2008)0121).

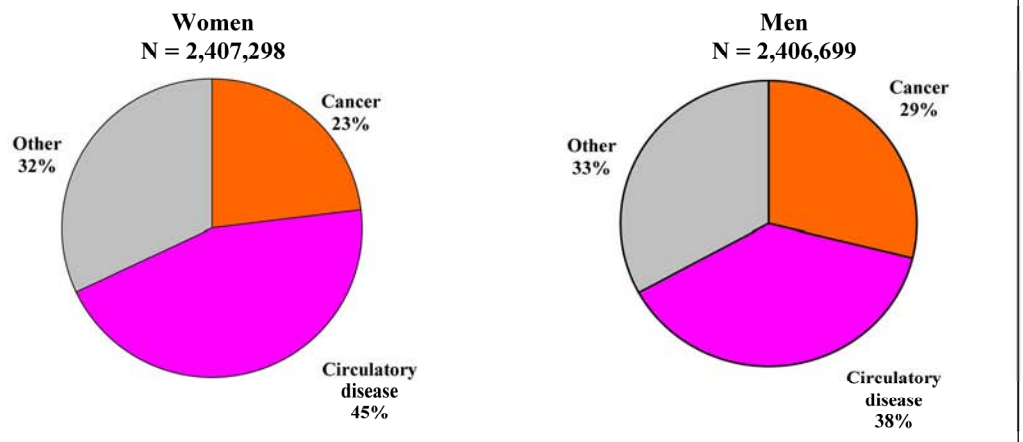
This survey was supplemented by information obtained in two ongoing European projects supported by the EU Public Health programme (2003-2008[8]) dealing with monitoring, evaluation and quality assurance of cancer screening: the European Cancer Network (ECN); and the European Network for Information on Cancer (EUNICE).

Population statistics were obtained from the European Statistical System, or from national sources if more recent data was available. Preliminary findings were also discussed with health ministers at the informal health council under the Slovenian Presidency in April 2008, following which several Member States provided further information. This has enabled reporting on programme implementation status for 27 of the 27 Member States. The detailed findings collated and analysed by the European Cancer Network have also been published separately (ECN Report[9]).

1.3. The relative burden of cancer as part of the overall burden of disease

After circulatory disease, cancer is the second most common cause of death in the European Union in 2006, accounting for two out of ten deaths in women, which amounts to a total number of 554,000 women, and three out of ten deaths in men, which amounts to 698,000 men (Figure 1a). Due to the ageing population this number is expected to rise further every year, if no preventive action is taken by the EC and the Member States.

Figure 1a. Total number of deaths in the EU in 2006 and proportions of two major causes of death



Source: EUROSTAT 2006

As regards cancer cases, every year, 3.2 million Europeans are diagnosed with cancer, most of whom are suffering from breast, colorectal or lung cancers. But the

[8] Decision No 1786/2002/EC of the European Parliament and of the Council of 23 September 2002 adopting a programme of Community action in the field of public health (2003-2008): OJ L271/1-11 of 09.10.2002.

[9] First report on the implementation of the Council Recommendation on Cancer Screening by the European Cancer Network and the European Network for Information on Cancer: Luxembourg (http://ec.europa.eu/health/ph_determinants/genetics/documents/cancer_screening.pdf).

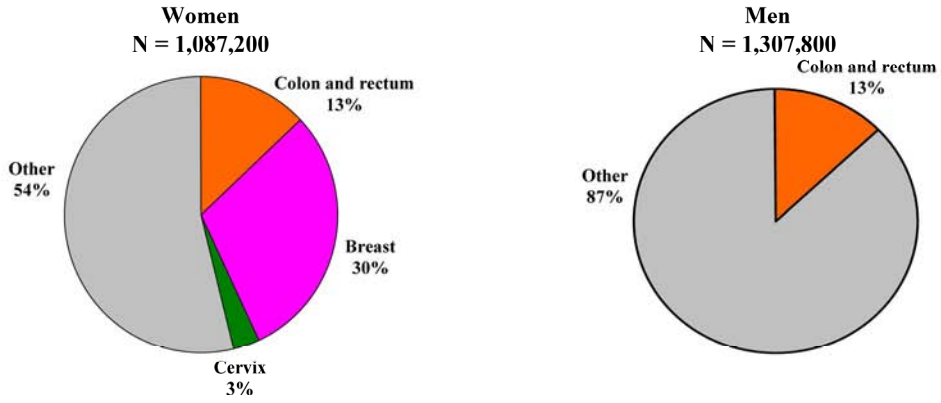
burden of cancer is far from being equally distributed across the European Union (for details see 1.5 below)[10].

As illustrated by national differences in cancer mortality, there is considerable scope to reduce deaths from cancer across the Community by sharing information and exchange of best practice in cancer prevention and control on an EU level. EU cooperation can thus provide significant added value, as developed under "Europe against Cancer" since 1987 for the area of screening for cancer in particular.

1.4. Specific burden of breast, cervical and colorectal cancer

Breast, cervical and colorectal cancer are a major cause of suffering and death in the Member States of the European Union[10]. According to estimates of incidence and mortality by the International Agency for Research on Cancer (IARC), there were 331,000 new cases and 90,000 deaths due to breast cancer, and 36,500 new cases and 15,000 deaths due to cervical cancer[11] among women in the EU in 2006. At the same time new cases of colorectal cancer were estimated at 140,000 in women and 170,000 in men. Colorectal cancer deaths were estimated at 68,000 for women and 78,000 for men in the EU. Together, these cancers account for almost one out of two (47%) new cases and one out of three (32%) cancer deaths in women in the EU. In men, colorectal cancer currently accounts for one out of eight (13%) new cases and one out of nine (11%) cancer deaths (Figures 1b and 1c).

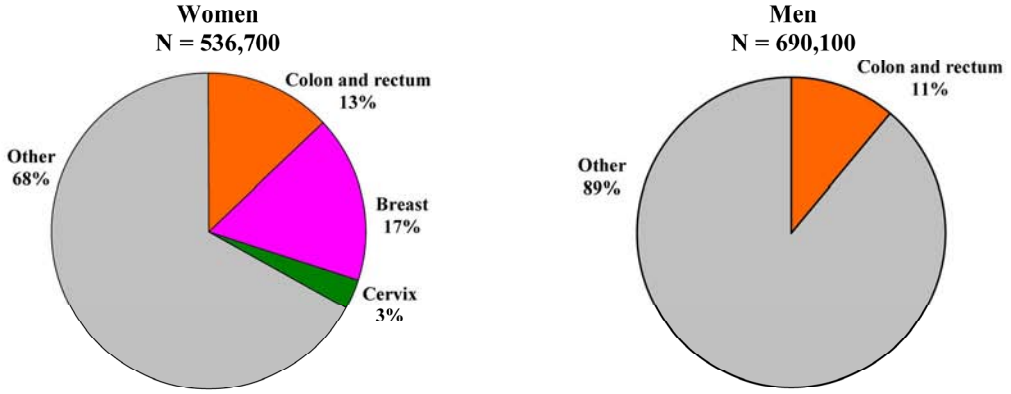
Figure 1b. Total number of cancer cases in the EU in 2006 and proportion of breast, cervical and colorectal cancer[9,10]



10 Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P (2007) Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 18: 581-592.

11 IARC mortality estimates for cervical cancer include a proportion of deaths attributed to "unspecified uterine cancer".

Figure 1c. Total number of cancer deaths in the EU in 2006 and proportion of deaths due to breast, cervical and colorectal cancer. Percentages for women do not add up due to rounding[9,10]



1.5. Diversity of cancer rates in the EU27[10]

Incidence and mortality rates of these cancers vary widely across the EU, reflecting a major health burden in various Member States.

According to IARC estimates the highest incidence rate of breast cancer is 137.8[12] for Belgium, with a mortality rate of 33.5, while the highest mortality rate is 34.5 for Denmark, with an incidence rate of 122.6. The lowest estimated incidence rate for breast cancer is 61.2 for Romania with a mortality rate of 23.9 and the lowest mortality rate is 19.2 for Spain with an incidence rate of 93.6.

The burden of disease is particularly unevenly distributed in the case of cervical cancer. For cervical cancer IARC estimates the highest incidence rate as 24.5 for Romania with the highest mortality rate of 17.0. The lowest incidence rate is 4.9 for Finland and at the same time Finland enjoys the lowest mortality rate of 1.6. The proportion of cancer cases and deaths attributed to this cancer is markedly elevated in all but one of the Member States which acceded to the EU in 2004 and 2007.

For colorectal cancer the highest incidence rate is 106.0 for Hungary, which in addition suffers from the highest mortality rate of 54.4. The lowest incidence rate for colorectal cancer is 31.0 for Greece, which at the same time enjoys the lowest mortality rate of 15.5.

2. RESULTS

2.1. Overview of results

The maps below show the current coverage of population-based screening programmes across the EU.

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12 Reflecting standard practice, incidence and mortality rates given in this Report are per 100,000 of the population.

Distribution of Breast Cancer Screening Programmes Based on Mammography in the EU in 2007

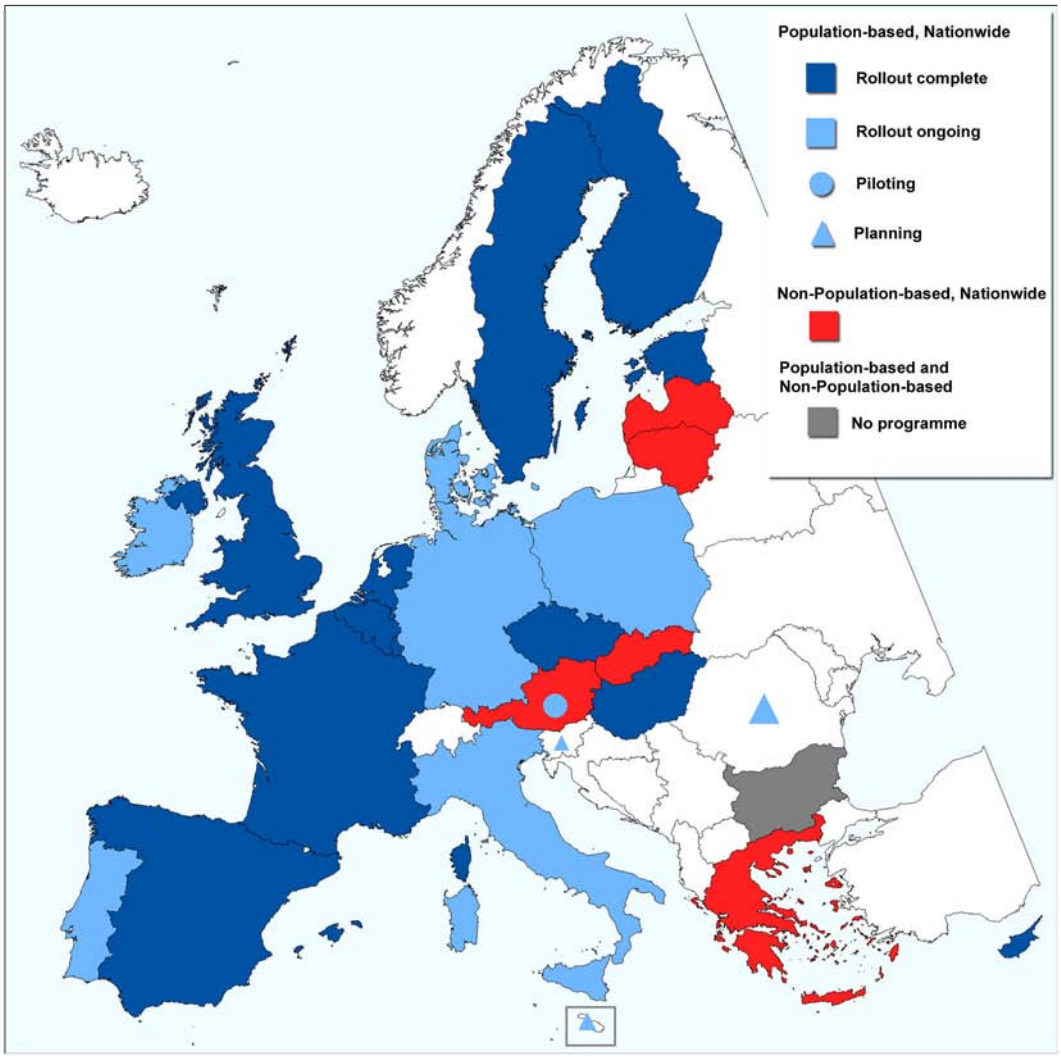

Figure 2. Breast screening programmes in the European Union in 2007, by programme type (population-based; non-population-based; no programme) and country implementation status (population-based: nationwide or regional, rollout complete or ongoing, piloting and/or planning; non-population-based: nationwide or regional). Programmes shown use screening test (mammography) recommended by the Council of the European Union in 2003[1].

Source: ECN[9]

Distribution of Cervical Screening Programmes based on Cervical Cytology in the EU in 2007

Figure 3. Cervical cancer screening programmes in the European Union in 2007, by programme type (population-based; non-population-based; no programme) and country implementation status (population-based: nationwide or regional, rollout complete or ongoing, piloting and/or planning; non-population-based: nationwide or regional). Programmes shown use screening test (PAP smear) recommended by the Council of the European Union in 2003[1].

Source: ECN[9]

Distribution of Colorectal Cancer Screening Programmes based on the Faecal occult Blood Test in the EU in 2007

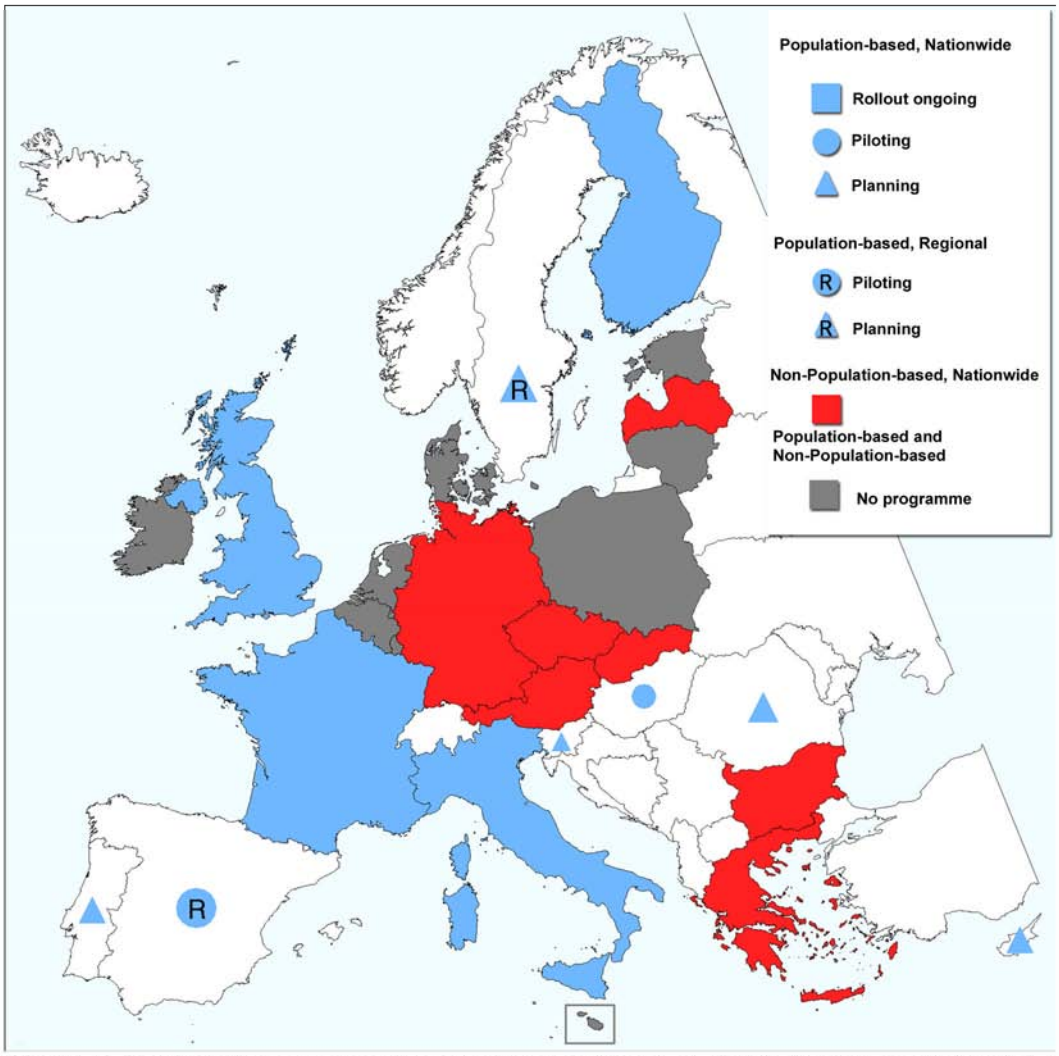

Figure 4. Colorectal cancer screening programmes based on FOBT (faecal occult blood test) in the European Union in 2007, by programme type (population-based; non-population-based; no programme) and country implementation status (population-based: nationwide or regional, rollout complete or ongoing, piloting and/or planning; non-population-based: nationwide or regional). Programmes shown use screening test recommended by the Council of the European Union in 2003[1].

Source: ECN[9]

As the three maps above indicate, although much progress has been made, more is still required:

- For breast cancer, only 22 Member States are running or establishing population-based screening programmes;
- For cervical cancer, only 15 Member States;
- For colorectal cancer, only 12 Member States.

The current annual volume of screening examinations in the EU is considerable; however, this volume is less than one-half of the minimum annual number of examinations that would be expected if the screening tests specified in the Council Recommendation on cancer screening were available to all EU citizens of appropriate age (approximately 125 million examinations per year). Furthermore, less than one-half of the current volume of examinations (41%) is performed in population-based programmes which provide the organisational framework for implementing comprehensive quality assurance as required by the Council Recommendation.

2.2. Implementation of the Council Recommendation by the Member States

2.2.1. Implementation of cancer screening programmes

Section one of the Council Recommendation comprises a set of safeguards, technical, ethical and legal standards to be followed when implementing screening programmes in the Member States. It covers a set of eight recommendations ensuring a strict evidence base for implementing screening programmes, the recognition of EU guidelines on best practice, the observation of ethical standards in informing on benefits and risks and to be able to adequately follow-up any screen-detected lesion, and last but not least the necessary level of data protection. Most of these eight recommendations, dealing specifically with establishing screening programmes, are reported to be followed by at least two out of three of the Member States (67%).

2.2.2. Registration and management of screening data

Section two comprises a set of four recommendations ensuring the proper functioning of any quality assured screening programme requesting an electronic call/recall system and the collection, management and evaluation of all data from screening tests.

These points are reported to be followed by a very large proportion of the responding Member States. Eighteen out of 22 (82%) use centralized data systems and call/recall systems for running programmes and for inviting all targeted persons, respectively. Twenty out of 22 (91%) Member States report that data is collected, managed and evaluated not just on screening results, but also on assessment of persons with positive screening results and on diagnosis. The same high conformity is reported for data handling in full accordance with European data protection legislation, particularly as it applies to personal health data, prior to implementing cancer screening programmes.

2.2.3. Monitoring

Section three comprises three recommendations aiming to establish the necessary basis for quality insurance by regular monitoring of screening programmes.

Although a majority of the Member States indicate that they comply with two of the three specific items in this section dealing with monitoring screening programmes,

compliance was substantially lower than for most items in all other sections (except section six).

With regard to item 3 (a) in the Council Recommendation, only 55% of the responding Member States report that the process and outcome of organised screening is monitored regularly by an independent peer review and 59% indicate that the results are reported quickly to the general public and to screening staff. The lower proportions of responding Member States performing such monitoring reflect the limited applicability of the respective questions in the EU survey to Member States in which population-based cancer screening programmes have not been initiated. The comparatively very low proportion of Member States which report that national cancer registries monitor screening programmes (45%) will have to be further explored.

2.2.4. Training

Section four contains one recommendation highlighting the importance of training for all health professionals involved in screening programmes.

Very high compliance is reported for section four of the Council Recommendation dealing with training. Twenty out of 22 Member States (91%) report that screening programme personnel is adequately trained at all levels to ensure that they are able to deliver high quality screening.

2.2.5. Compliance

Section five comprises two recommendations seeking high compliance for the population including special action to insure equal access for particular vulnerable social economic population groups.

A high proportion of the Member States indicate that they adhere to these recommendations. Twenty out of 22 Member States (91%) report that a high level of compliance is sought from the eligible population when organised screening is offered. Eighteen out of 22 Member States (82%) report that action is taken to ensure equal access to screening, taking due account of the possible need to target particular socio-economic groups.

2.2.6. Introduction of novel screening tests

Section six comprises a set of five recommendations how to deal with and implement new screening methods for two distinct situations: Novel screening tests and variations or improvements of the recommended screening tests listed in the annex of the Council Recommendation on cancer screening.

Approximately 11 out of the 22 Member States (50%) report adherence to the respective items in section six of the Council Recommendation dealing with introduction of novel screening tests taking into account international research results.

3. CONCLUSIONS

Four years after the Council of Ministers of the European Union adopted a Recommendation on Cancer Screening, most Member States have acted on the Recommendation and intend to undertake further action where implementation is not yet complete. Thus, the formulation of joint priorities and principles of health policy at the European level has been followed up by actions at the level of the Member States to implement the shared policies and priorities.

Nevertheless, and despite these substantial efforts, overall the EU is still only around half-way towards implementing the Recommendation. Slightly less than half the population who should be covered by screening according to the Recommendation actually are; and less than half of those examinations are performed as part of screening programmes meeting the stipulations of the Recommendation.

This illustrates the need for greater efforts within Member States, supported by collaboration between Member States and professional, organisational and scientific support for Member States seeking to implement or improve population-based screening programmes. Substantial added value may be expected from such support and from additional efforts to improve and maintain high quality of screening programmes.

Work continues to help support the implementation of the Recommendation. For example, development and piloting of EU-wide accreditation/certification schemes[13] for screening services based on EU guidelines for quality assurance of cancer screening would enable programmes to focus efforts on achieving the EU standards. This, in turn, would enable Member States to reap the potential of population-based screening to lower the burden of cancer in the population.

Even though the current volume of activities is still far from the level which can be expected in the future, the current expenditure in human and financial resources is already considerable. A sustained effort is therefore necessary at Community level and within Member States in identifying appropriate and effective measures to assure the quality, effectiveness and cost-effectiveness of current and future screening activities, taking into account scientific developments. Regular, systematic investigation, monitoring, evaluation and EU-wide status reporting on implementation of cancer screening programmes will continue to support exchange of information on successful developments and to identify weak points requiring improvement.

Cancer continues to represent one of the greatest burdens of ill-health within the European Union. The Recommendation on cancer screening represents a shared EU-wide commitment to taking practical steps to minimise that burden in practice, to the benefit of individual citizens and their families as well as to society as a whole. As this Report shows, putting in place these screening measures is a challenging task, and more work is needed to fully implement the Recommendation.

This effort only addresses one aspect of action against cancer. Actions to better monitor and prevent cancer at Community and Member States' level can help to reduce the number of cases arising at all; application of best-practice treatment can help to ensure better outcomes for people with cancer, as can European cooperation on cancer research for the future. The Commission will also consider whether and what further support can be provided to Member States to address other specific issues related to cancer challenges for the future.

In 2009 the Commission intends to launch a partnership for action against cancer. This partnership intends to put in place EU-wide commitments on concrete action to prevent and control cancer and thus contribute to reducing inequalities in tackling cancer. It will aim to support the Member States by providing a framework for

[13] Regulation (EC) No 765/2008 of the European Parliament and of the Council of 9 July 2008 setting out the requirements for accreditation and market surveillance relating to the marketing of products and repealing Regulation (EEC) No 339/93: OJ L218/30-47 of 13.08.2008.

identifying and sharing information, capacity and expertise in cancer prevention and control, and by engaging relevant stakeholders across the European Union in a collective effort to reduce the burden of ill health that cancer represents.

Appendix 4

List of websites

COUNTRY	WEB SITES
CZECH REPUBLIC	www.kolorektum.cz
DENMARK	www.cancer.dk/international/english/Bowel+cancer+screening.htm
ENGLAND	www.cancerscreening.nhs.uk/bowel/
FINLAND	www.cancer.fi/joukkotarkastusrekisteri/english/
FRANCE InVS InCa	 www.invs.sante.fr/surveillance/cancers/default.htm www.e-cancer.fr/depistage/cancer-colorectal/
GERMANY	www.g-ba.de/institution/themenschwerpunkte/frueherkennung/krebsfrueherkennung/ www.kbv.de/rechtsquellen/2500.html www.zi-berlin.de/cms/projekte/studien/darmkrebs-frueherkennung/
ICELAND	www.krabb.is
IRELAND	www.cancerscreening.ie/colorectal.html
ITALY	www.osservatorionazionalescreening.it www.giscor.it
NORTHERN IRELAND	www.cancerscreening.n-i.nhs.uk
POLAND	www.coi.pl/jelito.htm
PORTUGAL	www.ligacontracancro.pt
SLOVENIA	www.program-svit.si
SPAIN	ppc.cesga.es www.cribadocancer.es (in preparation*)
SWEDEN	www.swedish.org/Services/Cancer-Institute/Services/Cancer-Prevention-Screening#Colorectal
SWITZERLAND	www.colon-cancer.ch
SCOTLAND	www.nsd.scot.nhs.uk/services/screening/bowelscreening/

* Announced for December 2010

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List of abbreviations

ACS	American Cancer Society
AJCC	American Joint Committee on Cancer
AO	Auditable Outcome/s
ASA	American Society of Anaesthesiologists
BMI	Body Mass Index
BSA	Bovine Serum Albumin
CCD	Charge Coupled Device
CE	Conformité Européenne (European conformity)
CEP	Centre for Evidence-based Purchasing
CI	Confidence Interval
CITES	Convention on International Trade in Endangered Species
CJD	Creutzfeldt-Jakob Disease
CMI	Circumferential Margin Involvement
COGS	Conference on Guideline Standardisation
COPD	Chronic Obstructive Pulmonary Disease
CRC	Colorectal Cancer
CRM	Circumferential Margin Involvement
CRT	Chemoradiation Therapy
CS	Colonoscopy
CT	Computerised Tomography
CTC	Computerised Tomography Colonography
DG SANCO	Directorate General for Health and Consumers
DNA	Deoxyribonucleic Acid
DR	Detection Rate
EC	European Commission
EMR	Endoscopic Mucosal Resection
EQAS	External Quality Assessment Scheme
ESD	Endoscopic Submucosal Dissection
ESGE-ESGENA	European Society of Gastrointestinal Endoscopy - European Society of Gastroenterology and Endoscopy Nurses and Associates
EU	European Union
FAP	Familial Adenomatosis Polyposis
FDA	Food and Drug Administration
FICE	Fuji Intelligent Chromo Endoscopy
FIT	Faecal Immunochemical Test

FlexiSig	Flexible Sigmoidoscopy
FOB	Faecal Occult Blood
FOBT	Faecal Occult Blood Test
FS	Flexible Sigmoidoscopy
GCHP	Goblet-cell-rich type of Hyperplastic Polyp
gFOBT	Guaiac Faecal Occult Blood Test
GI	Gastrointestinal
GIST	Gastrointestinal Stromal Tumour
GP	General Practitioner
Hb	Haemoglobin
HGIEN	High Grade Intraepithelial Neoplasia
HGMN	High Grade Mucosal Neoplasia
HMO	Health Maintenance Organisation
HNPCC	Hereditary Non-Polyposis Colorectal Cancer
HP	Hyperplastic Polyp
IARC	International Agency for Research on Cancer
ICRCSN	International Colorectal Cancer Screening Network
ICSN	International Cancer Screening Network
ICT	Information and Communication Technology
IDM	Informed Decision-Making
IEC	International Electrotechnical Commission
iFOBT	Immunochemical Faecal Occult Blood Test
IFU	Instructions For Use
IPDAS	International Patient Decision Aid Standard
IQC	Internal Quality Control
ISO	International Organisation for Standardisation
IT	Information Technology
JP	Juvenile Polyposis
LGMN	Low-Grade Mucosal Neoplasia
LMWH	Low-Molecular-Weight-Heparin
LR	Likelihood Ratio
LST	Laterally Spreading Type
MDT	Multidisciplinary Team
MEI	Magnetic Endoscopic Imaging

MHRA	Medicines and Healthcare products Regulatory Agency
MP	Mixed Polyp
MPHP	Mucin-poor type of Hyperplastic Polyp
MRI	Magnetic Resonance Imaging
MVHP	Microvesicular type of Hyperplastic Polyp
NBI	Narrow Band Imaging
NCCN	National Comprehensive Cancer Network
NHIS	(US) National Health Interview Survey
NHS	National Health Service
NHSBSP	NHS Breast Screening Program
NORCCAP	Norwegian Colorectal Cancer Prevention study
NPS	(US) National Polyp Study
NSAID	Non-Steroidal Anti-Inflammatory Drug
NZHTA	New Zealand Health Technology Assessment
OR	Odds Ratio
PLCO	Prostrate, Lung, Colorectal and Ovarian
PN	Patient Navigation
PNI	Perineural Invasion
PPV	Positive Predictive Value
QA	Quality Assurance
QC	Quality Control
QI	Quality Indicator
QUADAS	Quality Assessment of Diagnosis Accuracy Studies
RCT	Randomised Controlled Trial
RR	Relative Risk
RRR	Relative Risk Reduction
SES	Socioeconomic Status
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic Review
SSA	Sessile Serrated Adenoma
SSL	Sessile Serrated Lesion
SSP	Sessile Serrated Polyp
TC	Total Colonoscopy
TEM	Transanal Endoscopic Microsurgery

TNM	Tumour Node Metastasis (classification system)
TSA	Traditional Serrated Adenoma
UICC	Union for International Cancer Control
UKFSS	UK Flexible Sigmoidoscopy Study
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization

Glossary of terms

Adenoma	A colorectal adenoma is a lesion in the colon or rectum containing unequivocal epithelial neoplasia (see Chapter 7).
Advanced adenoma	In screening programmes the use of the term advanced adenoma has developed and is sometimes used to categorise adenomas for management. In this context an advanced adenoma is one that is either ≥10 mm or contains high-grade mucosal neoplasia or a villous component (see Chapters 3 and 7).
Background incidence rate	The CRC incidence rate expected in the absence of screening. It is not directly observable but can be estimated.
Cancers	Colorectal cancer diagnosed by the screening programme, or diagnosed as a direct result of participating in the screening programme (see Chapter. 3). Pathologists working in CRC screening programmes define colorectal cancer as adenocarcinoma, i.e. an invasion of neoplastic cells through the muscularis mucosae into the submucosa (see Chapter 7).
Colonoscopy	See *Endoscopic colorectal examination.*
Coverage by examination	Coverage of the screening programme by examination is the extent to which screening examinations have actually been delivered to the eligible population.
Coverage by invitation	Coverage of the screening programme by invitation is the extent to which the invitations sent out by the screening programme within the defined screening interval include the eligible population.
Effectiveness	The reduction in CRC cancer mortality and/or incidence in screening in the target population, under real conditions.
Efficacy	The reduction in CRC mortality and/or incidence in randomised trials; i.e., under ideal conditions. Sometimes used also to describe the effect among those screened.
Eligible population	The eligible population are those people in the target population who fulfil the eligibility criteria specified in the programme policy.
Endoscopic colorectal examination	Endoscopic colorectal examinations visualise the inside of the colon (large intestine and rectum) using flexible optical instruments. Full colonoscopy permits examination of the entire colon. Flexible sigmoidoscopy permits examination of the rectum and the sigmoid colon.
Faecal occult blood test (FOBT)	In vitro stool test which detects hidden blood in stools. The guaiac faecal occult blood test (gFOBT) detects the haem component of haemoglobin, which is identical across

	human and animal species and is chemically robust and only partially degraded during its passage through the gastrointestinal tract (see Chapter 4). The immunochemical faecal occult blood test (iFOBT) detects human globin making the test specific for human blood (see Chapter 4).
Fail safe system	System aimed to maximise follow-up compliance or adherence to standard procedures, by sending reminders or applying computer based or other automated checks.
Flexible sigmoidoscopy	See *Endoscopic colorectal examination.*
Follow-up colonoscopy	Included in this group are the participants with a positive screening FS or CS who require a medical appointment for follow-up colonoscopy
Inadequate test	An inadequate FOBT is a test returned by a participant, the results of which cannot be reliably determined (see Chapter 3). The quality is insufficient for processing and the test cannot be used for recording a result according to the programme policy. The group of participants with an inadequate FS or CS examination are those, the results of which could not be interpreted because of inadequate preparation, and who do not have an adequate screening FS or CS in the reporting period. In such cases a new screening examination should be performed (see Chapter 3).
Interval cancer	A primary CRC cancer, which is diagnosed in a participant who had a screening, test, with/without follow up, which was negative for malignancy, either: · before the next invitation to screening; or · within a time period equal to a screening interval for a former participant who has reached the upper age limit for screening.
Invited	The invited are those members of the eligible population who have received an invitation for screening according to the programme policy/process; e.g. invited by mail, by primary care practitioner. NB not all invitations sent may be received.
Lesion	Any abnormality removed or biopsied at endoscopy or surgery.
Opportunistic screening	Screening outside an organised programme, as a result of e.g. a recommendation made during a routine medical consultation, consultation for an unrelated condition, on the basis of a possibly increased risk for developing cervical cancer, or by self-referral.

Organised screening

Screening programmes organised at national or regional level, targeting the whole population at risk and with an explicit policy, a team responsible for organisation of screening and management of screen-positives, including quality assurance and evaluation.

Over-diagnosis with screening

Detection of colorectal cancers or pre-cancerous lesions in screening that might never have progressed to a clinically recognisable cancer during an individual's lifetime.

Participation rate

See *Uptake.*

Positive predictive value (PPV)

The positive predictive value (PPV) for detection of a lesion/ adenoma/ advanced adenoma/ cancer through an FOBT screening programme is defined as the percentage of people with detection of at least one lesion/ adenoma/ advanced adenoma/ cancer at follow-up CS among those with positive tests who have attended follow-up CS.

Positive test

A positive i.e. abnormal FOBT result is a result based on the last adequate test that according to the programme policy leads directly to referral to follow-up colonoscopy.
A positive i.e. abnormal FS or CS screening examination is one resulting either directly in diagnosis of cancer or removal of an adenoma or other lesion, or in referral for further investigation according to the programme policy (see Chapters 2 and 5).

Screened / tested

The group of screened or tested participants are those who have used and returned an FOBT or have attended the FS or CS screening examination irrespective of the result. This includes people with inadequate/incomplete results. Note that each person is counted once regardless of the number of tests performed.

Screening episode

The screening test and follow-up based on the test.

Screening interval

Fixed interval between routine screenings decided upon in each programme.

Screening policy

Policy of the screening programme that defines the targeted age group, the geographical area, the screening interval and the screening method.

Sigmoidoscopy

See *Endoscopic colorectal examination.*

Subsequent screening

All screening examinations of individuals within the screening programme following an initial screening examination, regardless of the organisational screening round in which individuals are screened (see Chapters 2 and 3).

Surveillance	Continuous monitoring of disease occurrence within a population. The primary aims of colonoscopic surveillance are to reduce the morbidity and mortality from colorectal cancer by removing high risk adenomas before they have had a chance to become malignant, and by detecting invasive cancers at an early, curable, stage (see Chapter 9).
Target population	The target population are those people of eligible age according to the programme policy residing in the area designated to be served by the screening programme.
Tertiary endoscopy	This group of participants includes those who require an appointment for surgery, or endoscopy performed by a highly qualified expert for removal of challenging lesions following a positive screening FS or CS (or as a consequence of follow-up colonoscopy after primary screening with FS or CS).
Uptake (participation rate)	The number of people who have been screened, within a defined time frame following an invitation, as a proportion of all people who are invited to attend for screening.

European Commission

European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis - First Edition

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Colorectal cancer (CRC) is the most common newly-diagnosed cancer in Europe and the second most common cause of cancer deaths. In the 27 Member States of the EU approximately 330 000 new cases and 150 000 deaths occur each year. Many of these deaths could be avoided through early detection, by making effective use of screening tests followed by appropriate treatment.

In its Recommendation on Cancer Screening of 2 December 2003 the Council of the EU pointed out the need for appropriate quality assurance at all levels when performing CRC screening. That is the aim of the new *European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis.*

The multidisciplinary Guidelines are evidence based and build on the positive experience gained from producing the EU Guidelines for breast and cervical cancer screening. They focus on elements essential to screening but also include principles which are equally important in diagnosis such as training, multi-disciplinary teamwork, monitoring and evaluation, cost-effectiveness, minimising adverse effects, and timeliness of further investigations.

The Guidelines include 10 chapters each of which begins with a list of key recommendations. These are graded according to the strength of the recommendation and the supporting evidence. The respective evidence is summarised in the body of the chapters, with explicit citation of over 750 references. In total, more than 250 recommendations are provided.

According to the European Commissioner for Health and Consumer Policy, John Dalli, the new EU Guidelines represent a major achievement with the potential to add substantial value to the efforts of the Member States to improve control of colorectal cancer. Like the previous EU Guidelines for breast and cervical cancer screening, the new EU Guidelines are expected to become an indispensable guide for colorectal cancer screening in the coming years. This, in turn, will save lives and help improve the quality of life of millions of EU citizens, their families and friends.

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