# European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition
## Colonoscopic surveillance following adenoma removal

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Multidisciplinary, evidence-based guidelines for quality assurance in colorectal cancer screening and diagnosis have been developed by experts in a project coordinated by the International Agency for Research on Cancer. The full guideline document covers the entire process of population-based screening. It consists of 10 chapters and over 250 recommendations, graded according to the strength of the recommendation and the supporting evidence. The 450-page guidelines and the extensive evidence base have been published by the European Commission. The chapter on colonoscopic surveillance following adenoma removal includes 24 graded recommendations. The content of the chapter is presented here to promote international discussion and collaboration by making the principles and standards recommended in the new EU Guidelines known to a wider professional and scientific community. Following these recommendations has the potential to enhance the control of colorectal cancer through improvement in the quality and effectiveness of surveillance and other elements in the screening process, including multi-disciplinary diagnosis and management of the disease.

## Background

According to the most recent estimates by the International Agency for Research on Cancer [29] colorectal cancer (CRC) is the most common cancer in Europe with 432 000 new cases in men and women reported annually. It is the second most common cause of cancer deaths in Europe with 212 000 deaths reported in 2008. Worldwide CRC ranks third in incidence and fourth in mortality with an estimated 1.2 million cases and 0.6 million deaths annually. The European Union (EU) recommends population-based screening for breast, cervical and colorectal cancer using evidence-based tests with quality assurance of the entire screening process including diagnosis and management of patients with screen-detected lesions [25]. The EU policy takes into account the principles of cancer screening developed by the World Health Organization [93] and the extensive experience in the EU in piloting and implementing population-based cancer screening programmes [87]. Screening is an important tool in cancer control in countries with a significant burden of CRC, provided the screening services are high quality [88]. The presently reported multidisciplinary, evidence-based guidelines for quality assurance in colorectal cancer screening and diagnosis have been developed by experts and published by the EU [80].

## Methods

The methods used are described in detail elsewhere in this supplement [54]. Briefly, a multidisciplinary group of authors and editors experienced in programme implementation and quality assurance in colorectal cancer screening and in guideline development collaborated with a literature group consisting of epidemiologists with special expertise in the field of CRC and in performing systematic literature reviews. The literature group systematically retrieved, evaluated and synthesized relevant publications according to defined clinical questions (modified Patient-Intervention-Comparison-Outcome-Study method). Bibliographic searches for most clinical questions were limited to the years 2000 to 2008 and were performed on Medline, and in many cases also on Embase and The Cochrane Library. Additional searches were conducted without date restrictions or starting before 2000 if the authors or editors who were experts in the field knew that there were relevant articles published before 2000. Articles of adequate quality recommended

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

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

The methodological quality of the retrieved publications was assessed using the criteria obtained from published and validated check lists. Evidence tables were prepared for the selected studies. The evidence tables, clinical questions and bibliographic literature searches are documented elsewhere [53].

In the full guidelines document prepared by the authors and editors [80] over 250 recommendations were formulated according to the level of the evidence and the strength of the recommendation using the following grading scales.

### Level of evidence:

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

### Strength of recommendation:

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

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

## Results

A number of guiding principles and 24 graded recommendations are provided in Chapter 9.

## 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 **Fig. 9.1**)

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]

[1] **Sect** (superscript) after each recommendation in the list refers the reader to the section/s of the Guidelines dealing with the respective recommendation.*
**Rec** (superscript) throughout the chapter refers to the number of the recommendation dealt with in the preceding text.*
* The first digit of the section numbers and recommendation numbers refers to the respective chapter in the guidelines. For Chapters 1 to 8 see: [41, 50, 56, 31, 85, 84, 65, 83], respectively; and for Chapter 10 see [6].

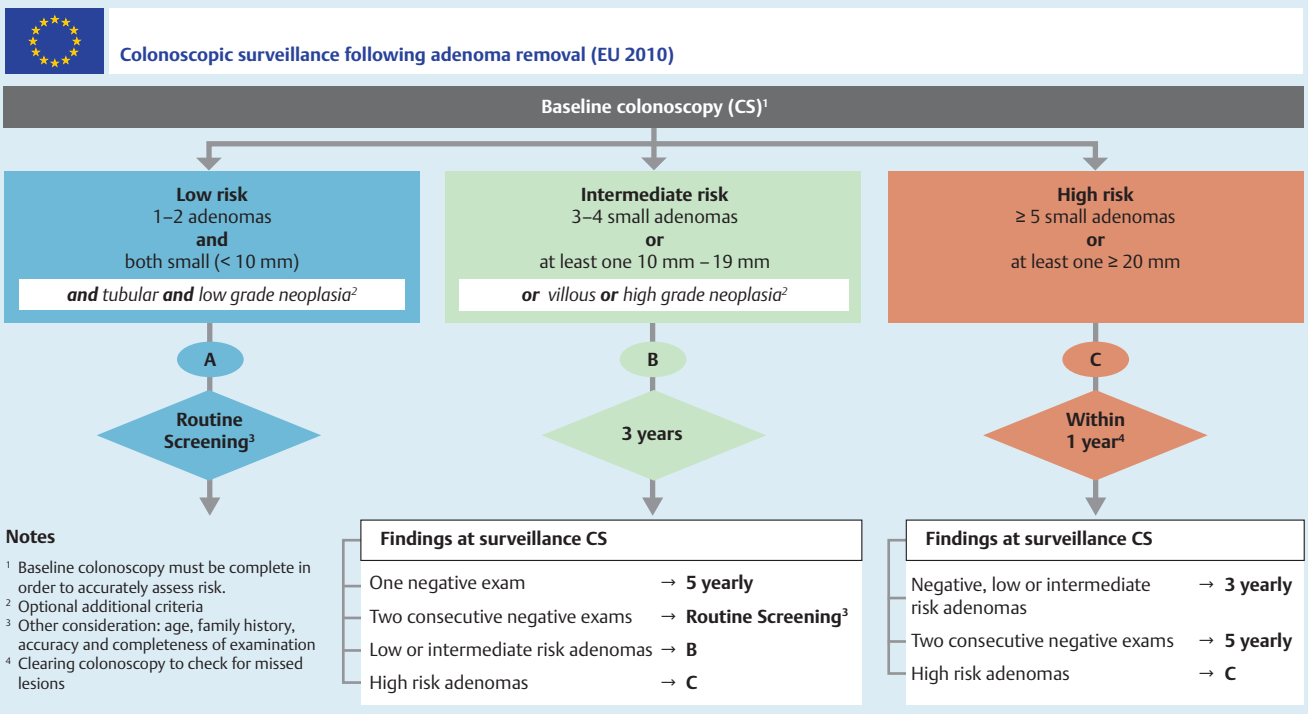


**Fig. 9.1 Recommended surveillance following adenoma removal.** (For explanation see Recommendations 9.1 – 9.20 and Sections 9.3 – 9.5)



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 [85], 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 [85], 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]

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]

[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.

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 [37,45,78]. Hyperplastic polyps are also frequently detected during endoscopic examinations, but most are of no clinical significance.

Chapter 8 [83] 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 [2,3,7,8,12,48,51,61,72,75]. Many of these adenomas and cancers represent lesions missed at baseline colonoscopy, emphasising the importance of high-quality examinations [68].

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 [19,72]. 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) [49,59,73,90]. 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 [44]. 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 [27,57]. Adenomas that are 10 mm or lar-

ger, 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 [95] (see Ch. 7 [65], 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 **Fig. 9.1** 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

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### 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 [67]. Miss rates for small adenomas at back-to-back colonoscopies are approximately 25%–50% [32,33,69], but the significance of this is as yet unclear. Of more concern is the observation that up to 6% of larger adenomas (≥10 mm) [11,32,69] and around 4% of cancers are missed at colonoscopy [19,28]. 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 [68] (Chapter 5 [85], Section 5.1.2). Most interval cancers in people undergoing surveillance are lesions that were missed or incompletely removed at the previous colonoscopy [63, 72].

**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 [85], 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 [85], 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 [85], 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 [95]. The NPS authors attribute the low subsequent risk of cancer seen in the NPS cohort compared with other studies [28,63,72] 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 [46,63].

The management of large, sessile lesions removed piecemeal, is described in Chapter 8 [83], 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 [74], patients with 3 or more adenomas at baseline were at an approximately two-fold increased risk of advanced neoplasia dur-

ing surveillance compared with those with only 1 – 2 adenomas. In a more recent pooled analysis [51] 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 [21].

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 [51, 74] but not all observational studies [86], increased adenoma size has been found to predict detection of advanced adenomas and cancer at follow-up. In the recent large US pooled study [51], 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 [55, 77], 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 [65], 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 [43]. 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 [24].

In a meta-analysis and systematic review [74] 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 [21]. However, in the large pooled US analysis [51], 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 [65] in Section 7.3.2 and Table 7.1. Some individual studies [16, 46] 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 [74], 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 [51]. 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 [43]; 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 [1, 2, 9, 30, 40, 51, 74].

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 [51, 96].

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 [51] but not all studies [96]. However, it is unclear how this finding should affect Guidelines.

[3] See Footnote 2

#### 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 [15,22,45,64]. Other studies have suggested that patients with a family history also have an increased risk of advanced or multiple adenomas [58,89].

The US National Polyp Study [97] 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 [62] 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 [52]. Similarly, in the recent US pooled analysis, the risk of developing advanced neoplasia during surveillance was not influenced by family history [51].

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 [5,13,34,76,94]. 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 **Fig. 9.1** 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) [66]. The US National Polyp Study [95] 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 [39] 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 [4] 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 [51] 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 [46, 52,60,86,97] in patients undergoing surveillance colonoscopies have identified a low risk group. All but one [52] 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 [46] 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 [82], most of which were unexamined histologically. A similar study from St Mark's Hospital [4], 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 [95]. This study identified a higher risk group which included patients with multiple (≥3) or large adenomas [92], 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 [66]. 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) [51,60].

In the US National Polyp Study [95], 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 [60] 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 [51].

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 [47]. While in the study from St Mark's Hospital [4], 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 advanceed adenomas and cancer and suggests that colonoscopic surveillance is warranted **(III–A)**.

The results of the US National Polyp Study [95] 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 provide information 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 [51], 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 [28, 46, 63, 72].

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. [38] 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 [14], 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 [91] 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. [10, 18, 51, 71, 81, 95] **(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 [70].

By their nature polyp cancers are high risk lesions [23,26,70]. 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 [83], 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 [65], 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 **Fig. 9.1** 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 [65], Sect. 7.1 and 7.2.4). They therefore preclude risk analysis stratified by the size and location of these lesions [36,42,79].

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 [20] 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 [17,35]. 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)

## Conclusions

In a multidisciplinary process, wide consensus has been achieved on a comprehensive package of evidence-based recommendations for quality assurance in colonoscopic surveillance following adenoma removal. Following these recommendations has the potential to enhance the control of colorectal cancer in Europe and elsewhere through improvement in the quality and effectiveness of the screening process that extends from systematic invitation to attend screening through to management of screen-detected cases, including surveillance of patients at elevated risk of recurrence of advanced adenomas and cancer.

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**Competing interests:** Dr Pox has received lecture honoraria and travel support of less than 7000 € 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 1500 € for attending an Advisory Board Meeting of the Abbot company, a broad-based health care manufacturer, and 2100 € 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 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 2000 € from Astra Zeneca and consultancy fees, lecture honoraria and travel support totalling less than 16000 € 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 165000 € from Roche and the pharmaceutical manufacturer Sanofi Aventis for studies in colorectal cancer screening and diagnosis.

Dr Schmiegel is the sole shareholder (25000 €) of Medmotive GmbH, a holding that until 2010 controlled 25% of the company Westdeutsches Darm-Centrum GmbH with a capital investment of 25000 €. 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.

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