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Review

Screening of colorectal cancer: present and future

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Abstract

Introduction: Colorectal cancer (CRC) is the third most common cancer in males and second in females, and the fourth most common cause of cancer death worldwide. Currently, about 60-70% of diagnosed cases in symptomatic patients are detected at an advanced stage of disease. Earlier stage detection through the use of screening strategies would allow for better outcomes in terms of reducing the disease burden.

Areas covered: The aim of this paper is to review the current published evidence from literature which assesses the performance and effectiveness of different screening tests for the early detection of CRC.

Expert commentary: Adequate screening strategies can reduce CRC incidence and mortality. In the last few decades, several tests have been proposed for CRC screening. To date, there is still insufficient evidence to identify which approach is definitively superior, and no screening strategy for CRC can therefore be defined as universally ideal. The best strategy would be the one that can be economically viable and to which the patient can adhere best to over time. The latest guidelines suggest colonoscopy every 10 years or annual fecal immuno-chemical test (FIT) for people with normal risk, while for individuals with high risk or hereditary syndromes specific recommendations are provided.

Keywords: Colorectal cancer, Screening, Surveillance, Colonscopy, gFOBT, FIT.

1. Introduction

Colorectal cancer (CRC) is a major healthcare problem all over the world. Globally, it is the third most common cancer in males and second in females, and the fourth cause for cancer death worldwide [1,2]. The probability of developing CRC is higher for men than for women and increases with age, especially after 50 years old.

Incidence and mortality rates significantly varies around the world: in developed countries CRC ranks second for incidence and mortality, while in developing countries it is fourth for both incidence and mortality [3]. In 2013, incidence of CRC was the highest in Australasia, North America and Western Europe, and the lowest in south Asia and sub-Saharan Africa. Interestingly, recent data indicate that, if the incidence was calculated by country rather than by area/continent, then Korea should be the country with the highest CRC incidence. Indeed, the Asia-Pacific area is the region with the most rapid increase in CRC case numbers, and many countries in this area (Korea, Japan, Taiwan, Hong Kong, and Singapore) show a CRC incidence approaching or exceeding that in North America or Western Europe [3]. Such geographic differences can be explained, at least in part, by different dietary and environmental exposures across the world as well as to different genetic backgrounds.

The epidemiological trend of CRC has profoundly changed over the past 20 years. Between 1990 and 2013 the global incidence increased significantly (818 000 diagnoses in 1990, 1.6 million in 2013), with age-standardized incidence rates (ASIRs) remaining stable for women but increasing for men [1]. Besides this, mortality rates have decreased significantly since 1990 in western countries. This trend may be due to the introduction of screening protocols combined with the development of more effective therapies [1]. Several randomized controlled trials have shown that the mortality rate

has reduced up to 60% and the 5-year survival increased up to 73% in patients undergoing surveillance for CRC.

On this premise, the aim of this review is to review the current evidence from literature which supports performance and effectiveness of screening strategies for the early detection of CRC.

2. Rationale for screening of CRC

Screening is defined as the application of a test for preclinical detection of early-cancer or precancerous lesions, in an apparently healthy population, at risk of developing that specific condition. Surveillance is rather the repeated application of that test over time in subjects with previous detection of cancer or precancerous lesions.

Most CRCs arise from adenomas through the so-called “adenoma-carcinoma sequence” and the majority of adenomas present range from from small to large with advancing dysplasia and finally invasive cancer (Figure 1). The adenoma-carcinoma sequence takes more than 10 years to progress in sporadic cancer cases and, on this basis, screening is applied with the goal of interrupting the sequence [4].

However, in addition to this, there are two other pathways of colorectal carcinogenesis: “de novo pathway” and “serrated pathway”. According to the de novo pathway, a CRC can emerge directly from normal epithelium without going through a stage of adenoma [5]. Approximately 30% of CRCs can also develop via a serrated pathway, so called for the pattern of crypts in the precursor polyps [6]. Natural history of such CRCs seems different from those arising from the classic adenoma-carcinoma sequence: the rate of progression of non-polypoid or depressed lesion is faster (about 3 times) than that in

polypoid ones, while the natural course of sessile serrated adenomas/polyps remains unclear. Such heterogeneity of CRC may affect the effectiveness of screening programs by influencing the correct temporal intervals for the application of screening and surveillance.

Neoplastic transformation is the result of interplay between both inherited and acquired genetic defects [7]. Although the majority of CRCs arise from adenomas, less than 5% of adenomas progress to cancer [8]. Notably, large flat adenomas have a higher probability to harbour dysplastic changes or cancer than polypoid ones of similar size [9]. The removal of adenomas prevents cancer: in patients undergone endoscopic removal of one or more polyps, the incidence of colon cancer was 90% lower than in patients who had polyps that were not removed [10]. Another relevant issue to underline is the increased rate of detection of right-sided/proximal colon cancers [11]. Even if this increase may be partly due to increased screening by sigmoidoscopy with removal of adenomatous polyps in the left colon, a truely raised incidence of right-sided CRCs has been demonstrated [12].

For these reasons, screening for CRC also differs from others, such as prostate and breast cancers, since it allows not only detection of malignant lesions at an early stage, but also of precancerous lesions, such as adenomas [13].

3. Available screening tools and evidences for effectiveness

Currently, about 60-70% of CRC cases in non-screened populations are diagnosed at an advanced stage. In contrast, screening for CRC, for example with annual fecal occult-blood test, allows diagnosis at earlier stages reducing mortality and increasing

the 5-year survival [14]. Latest international guidelines recommend screening for medium-risk individuals after the age of 50 [15-18].

Guidelines on colorectal screening have been issued by several organizations, such as American Cancer Society (ACS), US Multi-Society Task Force on Colorectal Cancer (MSTF), and American College of Radiology, U.S. Preventive Services Task Force (USPSTF), American College of Physicians (ACP), American College of Gastroenterology (ACG), American Society of Gastrointestinal Endoscopy (ASGE), European Society of Gastrointestinal Endoscopy (ESGE), EU Health Program and National Comprehensive Cancer Network (NCCN).

There are two main approaches to screening worldwide: 1) *individual* or *opportunistic*, if proposed by the physician to the patient based on a direct evaluation, and 2) *population-based* or *organized*, if systematically offered to the entire at-risk population, from the National Health Service.

The main advantages of population-based over individual screening, are that everybody has equal access to the service, allowing systematic monitoring of coverage, outcomes and quality of service. Consequently, as denoted by the EU commission in 2010, a population-based screening needs a publicly funded organization with systematic invitational procedures involving the entire eligible population [18]. Despite this, evidence that organized screening is superior to opportunistic one is lacking.

In the last decades several test have been proposed for screening of CRC with different degrees of performance. Among these, fecal (guaiaic fecal occult blood test - gFOBT, fecal immuno-chemical test - FIT, fecal DNA test), endoscopic (colonoscopy, flexible

sigmoidoscopy, capsule endoscopy), radiologic (computed tomographic colonography) and blood (Septin9 gene test) tests can be identified.

3.1 Fecal tests

Guaiac FOBT (gFOBT) was among the first tests to be used for CRC screening and identifies the presence of haemoglobin in feces by the action of peroxidase between heme group and guaiac. The use of the FOBT started in the 1960`s during the pre-colonoscopic era. Furthermore, large proportions of the screening arm cohort underwent subsequently colonoscopy during the long surveillance period, and the first screening results based on FOBT were very promising, showing a reduction in CRC incidence and mortality [14, 19-22].

Three systematic reviews have evaluated the efficacy of gFOBT as a screening test and all of them found a significant reduction in CRC mortality ranging from 14 to 16% [23-25]. In particular, the meta-analysis by Cochrane collaboration showed a 16% reduction in the relative risk of CRC mortality, and a 15% relative risk reduction in CRC mortality for studies that used biennial screening. In addition, when adjusted for screening attendance, in the individual studies, there was a 25% relative risk reduction for those attending at least one round of screening using the FOBT. On the contrary, no impact on overall mortality was found [23]. Of interest, the meta-analysis by Heresbach et al found that CRC mortality was not decreased during the 5-7 years after the 10-year screening period, nor in the last phase (8-16 years after the onset of screening) of a long-term (16 years) biennial screening [24]. More recently, the Finnish nation-wide FOBT screening program performed between 2004-2012 showed no benefit on CRC mortality [26].

Nevertheless, gFOBT has the disadvantage that it needs to be repeated on three samples on three different days and that it is not able to distinguish the source of bleeding (upper or lower gastrointestinal tract); for the same reason, dietary constraints are needed in the days preceding the test. Furthermore, the overall diagnostic performance of the test is inferior to FIT (see further), so many experts currently suggest to replace the older guaiac-based faecal occult blood test with faecal immunochemical test [14-18].

The FIT can pinpoint whether bleeding is from the lower gastrointestinal tract, without needing dietary limitation in the days preceding the test. FIT also requires fewer stool samples than FOBT [27]. The FIT shows a sensitivity and specificity greater than that of gFOBT, respectively 79% (95% CI - 0.69 to 0.86) and 94% (95% CI - 0.92-0.95) [27-44], as showed by a recent meta-analysis including a total of 113 360 subjects, 437 of these had a diagnosis of neoplasia at follow-up colonoscopy at 2 years. These studies also showed that repeating the test twice did not improve the detection capacity [27]. The annual repetition of faecal tests is able to a reduce CRC mortality by about 32%, as shown in several randomized and controlled studies with a follow-up period of approximately 30 years. Compared to gFOBT, FIT has greater sensitivity to detect precancerous lesions (20-50% vs. 11-20%, respectively) and CRC (79% vs. 20-50%, respectively) and shows even greater compliance by patients [27, 45]. Furthermore, it can be both qualitative and quantitative. In fact, FIT may offer quantitative findings (ng Hemoglobin (Hb) per mL buffer or μg Hb per gram feces) with an automated reading of the results. However, an optimal cut-off value has yet to be defined; the desirable cut-off values should be established on the availability of several factors, such as the endoscopic capacity, the incidence and prevalence of CRC in the population studied,

and the expected adherence to the program [46,47]. Recently, Katsoula et al. performed a meta-analysis of twelve studies aiming to evaluate the diagnostic accuracy of FIT for CRC or advanced neoplasia in asymptomatic patients at average risk. The meta-analysis showed that the average sensitivity of FIT for CRC was 93% (95% CI, 53%-99%), and the average specificity was 91% (95% CI, 89%-92%), while the average sensitivity and specificity of FIT for advanced neoplasia (defined as CRC, or adenomas ≥10 mm or with ≥25% villous component and/or high-grade dysplasia) were 48% (95% CI, 39%-57%), and 93% (95% CI, 91%-94%), respectively. In this setting, subgroup analyses indicated that FIT cutoff values between 15- and 25-μg/g feces provided the best combination of sensitivity and specificity for the diagnosis of CRC (93% and 94%, respectively), even if the heterogeneity and the wide confidence intervals limited the validity of such results [48]. Studies worldwide using different Hb cut-off values demonstrated that a FIT cut-off value of 100 ng/mL Hb (20 μg/g) provided high sensitivity, specificity, and positive predictive value for detecting neoplasia [49-51], while other studies reported a decline in specificity with cut-off values below 100 ng/mL Hb. [50, 52-55]. Based on this information, a cutoff value between 75 and 100 ng/mL Hb might represent an optimum in most European populations, depending on the resources and availability of colonoscopy, and furthermore considering the best sensitivity/specificity balance of the examined test, as recommended by several European guidelines [46].

According to this evidence, FIT has been recommended as the preferred option for detecting fecal occult blood in CRC screening [56], and several European, Western Pacific, Eastern Asia and American countries, with organized screening programs, are currently using the quantitative FIT [46].

Faecal DNA detection test has been recently developed, and it is aimed to obtain qualitative detection of colorectal neoplasia associated DNA markers. Cologuard (Exact Science, Boston), a fecal test detects multiple DNA markers, in combination with occult hemoglobin biomarkers associated with CRC, in human stool, has been assessed in a large study by Imperiale et al in 2014, and subsequently approved by the FDA in the same year [57]. This test is able to detect genetic alterations such as DNA mutations, microsatellite instability, altered DNA mismatch repair and abnormal methylations [58]. These features make DNA testing superior to the FIT in terms of sensitivity for the detection of CRC (92.3% vs 73.8%), even at the expense of a lower specificity (86.6% and 94.9%, respectively) and consequently a greater probability of false positive results [59]. Moreover, according to a recent simulation study, the effectiveness of FIT-DNA every 3 years (as approved by FDA) was inferior to the annual FIT in term of life years gained [60]. Furthermore, DNA test has never been validated in a non-US population, and there are still several barriers for its application in population screening programs, especially in countries other than the US. Among these, the high price (10 times higher than that of the FIT alone and even higher than that of colonoscopy in many countries), the unknown public acceptance, and the unknown optimal inter-screening interval should be mentioned.

3.2 Endoscopic tests

Flexible sigmoidoscopy (FS) is one of the most widely used and investigated screening tests for CRC. It allows inspection of the distal colon, allowing at the same time the possibility of obtaining tissue biopsies and also polyp removal. Compared to colonoscopy, it has the advantage of a limited bowel preparation, a quicker examination with a minimal discomfort for the patient in absence of sedation, lower complication rates, and inferior costs. Nevertheless, it presents the disadvantage of not exploring the proximal colon, and therefore having a low impact on prevention of proximal CRC [15].

Sensitivity and specificity of sigmoidoscopy, limited to the first 60 cm of colon, are similar to those of colonoscopy with lower risks of perforations [61]. The validity of sigmoidoscopy as a screening test for CRC has been supported by numerous randomized controlled [62-67], case-control and cohort studies [68-72]. A meta-analysis of 5 RCTs with a total sample of 416,159 subjects, performed with the aim to assess the benefit of FS for screening of CRC, showed that screening by FS was associated with a relative risk reduction in the CRC incidence of 18% (0.82, 95% CI 0.73-0.91, p<0.001) and a 28% reduction in the mortality due to CRC (RR 0.72, 95% CI 0.65-0.80, p<0.001). The same rates were even higher in the subgroup of patients who actually adhered to the recommended treatment, reaching up to 32% and 50% respectively. The evidence support how FS significantly reduces the incidence and mortality of CRC. Unfortunately, this analysis is limited by the absence of data from some continents (Africa, Asia and South America) and the lack of comparative studies between FS and colonoscopy or FIT [73].

A recent meta-analysis of 4 RCTs and 10 observational studies assessing the effect of screening sigmoidoscopy and colonoscopy on CRC incidence and mortality, confirmed a major reduction in distal but not proximal CRC incidence and mortality. In particular, reduction in distal CRC incidence in RCTs and observational studies was 31% (95%CI - 26% to 37%) and 64% (95%CI - 50% to 74%), respectively, while reduction in mortality was 46% (95%CI - 33% to 57%) and 66% (95%CI - 38% to 81%), respectively [74].

Finally, since at-risk distal lesions (eg. multiple adenomas; at least one adenoma with high-grade dysplasia or villous component >20%; at least one polyp ≥10 mm in diameter) increase with age and reach a plateau at around 60 years, it is considered appropriate that screening with a single sigmoidoscopy in life at the age of 55-60 years

can prevent 70% of distal tumors in individuals of 58-74 years, and 50% in persons aged 75-79 [75].

Colonoscopy is the only tool able to evaluate the entire colon and to detect and remove precancerous lesions. It can be performed as a primary screening test or as a diagnostic test after a positive result of another primary screening modality. No RCTs assessing colonoscopy in the setting CRC screening have been performed so far. Nevertheless, several prospective cohort and case-control studies support the role of colonoscopy showing a reduction in incidence and mortality from CRC up to 80% for distal colon and up to 60% for proximal colon [76-81]. These data were also confirmed by the aforementioned meta-analysis by Brenner et al [74], which highlighted how mortality reduction was mainly due to the ability of colonoscopy to detect polyps and neoplasia of the proximal colon. In a recent microsimulation modeling study performed on a population undergoing CRC screening, assuming a 100% adherence, the strategies of colonoscopy every 10 years, annual FIT, flexible sigmoidoscopy every 10 years with annual FIT, and computed tomographic colonography every 5 years performed from ages 50 through 75 years provided similar life years gained and a comparable balance of benefit and screening burden [60]. Moreover, a randomized controlled trial comparing one-time colonoscopy vs biannual FIT on large sample of 53,302 asymptomatic adults 50 to 69 years of age, showed similar rates of CRC detection (0,1% in both groups), while detection rates of advanced and non-advanced adenomas were higher with colonoscopy compared to FIT (1.9 vs 0.9% and 4.2 vs 0.4%, $p<0.001$) [82].

Nevertheless, the effectiveness of colonoscopy as a screening tool strictly depends on the adequate detection and removal of colonic polyps, therefore consistent quality

measures that could help to quantify health-care processes and could aid in providing high-quality health care, are essential [83]. The primary, operator-dependent, quality indicator for colonoscopy is the adenoma detection rate (ADR), defined as the proportion of screening colonoscopies detecting at least one adenoma, which should be ideally ≥25% overall (≥30 for male patients and ≥20% for female patients) [84]. Furthermore, ADR is dependent on other quality measures, including cecal intubation rates (ideally ≥95% for screening colonoscopies), withdrawal times (recommended >6 minutes), and quality of bowel preparation (optimal if split-dosing) [83], which could preserve the overall effectiveness of CRC prevention and improve patient outcomes. Anyway, despite quality measures, the definition of colonoscopy accuracy, being defined as the detection of adenomas, is still suboptimal [85]. Therefore, in the future, new technological developments are expected to improve the diagnostic sensitivity of colonoscopy in detecting adenomas, reducing miss rate of advanced lesions.

Regardless of its performance, the invasiveness of the procedure, the need for bowel preparation, and the costs associated with the procedure, partially restricts the compliance and the use of colonoscopy as a screening test. In line with this, the study by Quintero and colleagues, cited above, showed adherence to colonoscopy screening was lower compared to the FIT group (24.6% vs. 34.2, $p<0.001$) [82].

Moreover, it must be pointed out that colonoscopy is burdened by numerous potential adverse events related to the examination itself and to the conscious sedation or anaesthesia performed for the procedure. Invasiveness of colonoscopy represents a major limitation for its application in screening, and a careful evaluation of the patient's comorbidities and the risk-benefit ratio is always needed [81].

Capsule endoscopy has been proposed as a promising alternative to colonoscopy, since it allows a non-invasive examination of colon without the associated discomfort of the procedure. Capsule endoscopy avoids the complications associated with the procedure and the risks of sedation, and increases adherence to screening. Unfortunately, studies evaluating this tool have shown lower performance compared to colonscopy with a sensitivity ranging from 56 to 76%, and specificity from 64 to 69% [86, 87]. Consequently, capsule endoscopy still plays a marginal role in CRC screening. The U.S. Multi-Society Task Force on Colorectal Cancer guidelines suggest its use only as last option for patients who decline endoscopic or fecal tests, while European guidelines recommend against its use for screening of CRC [15, 18].

3.3 Radiologic tests

Computed tomographic colonography (CTC) is becoming one of the emerging techniques for the study of the colon, especially in Western countries. It exposes patients to low rates of radiation, avoids the risks associated with intubation and sedation, and is a useful alternative for patients who cannot undergo or can not tolerate colonoscopy or sedation. Computed tomographic colonography allows the colon to be evaluated through a series of 3D images and can identify polyps > 10 mm in 90% of cases and 6-9 mm polyps in 70-80% of cases [88]. Between 2003 and 2008, a total of seven systematic reviews were performed with the aim to compare the performance of computed tomographic colonography with that of colonoscopy. All reported a sensitivity that was low for small polyps and increased with polyp size, they also reported a good tolerability of procedure, and a low incidence of adverse events [89-95].

Three, more recent, RCTs were subsequently published on the use of computed tomographic colonography as a primary screening test. The first one showed that

participation in CRC screening with CTC was significantly better than with colonoscopy, even if colonoscopy identified significantly more advanced neoplasia per 100 participants compared to CTC. The diagnostic yield for advanced neoplasia per 100 invitees was similar for both strategies, suggesting that both techniques can be used for population-based CRC screening [96]. A second Italian trial was performed with the aim to assess the participation rate and detection rate for cancer or advanced adenoma comparing reduced and full cathartic preparation CTC, FIT, and optical colonoscopy [97]. Reduced preparation increased participation in CTC, and detection rates for advanced neoplasia were 1.7% for first-round FIT, 5.5% for reduced cathartic preparation CTC, 4.9% for full cathartic preparation CTC, and 7.2% for colonoscopy, with all differences being statistically significant between CTC groups and FIT, but not between reduced cathartic preparation and full cathartic preparation CTC. The last Italian trial showed that participation and detection rates for advanced neoplasia between flexible sigmoidoscopy and CTC, in a screening setting, were comparable, even if detection rate was twice as high in the proximal colon and lower in the distal colon with CTC than with flexible sigmoidoscopy [98].

Despite the advantages over other more invasive techniques, computed tomographic colonography still presents some drawbacks, among these the necessity of bowel preparation, the inability to recognize small sized polyps, flat adenomas and serrated lesions (harboring a greater malignant potential), the need to perform colonoscopy if lesions are found, and finally higher costs compared to other techniques [99, 100]. Furthermore, the technique is affected by radiation exposure and, even with the low dose exposure to radiation, the cumulative risk of exposure to radiations over time, with testing every 5 years, remains undesirable.

Finally, it should be noted that the detection of extracolonic findings could lead to possible over-diagnosis and over-treatment of associate, and not always pathologic, conditions that may trigger panic within patients, unnecessary investigations, and a waste of resources [101-103]. Therefore, the application of computed tomographic colonography in screening is still limited and reserved to a minority of patients.

3.4 Blood tests

The plasma Septin9 methylation assay was developed in 2008 by Lofton-Day [104]. Following this first test, marketed by Epigenomics as the Epi proColon 1.0, many companies have developed similar tests [105, 106]. More recently, the Epi proColon 2.0 has been made available, with better sensitivity and specificity results in several case-control and cohort studies, as well as being used in the PRESEPT study [107]. Nevertheless, the Septin9 assay may not be currently applicable in adenoma detection, due to the low sensitivity showed in several studies and the U.S. Multi-Society Task Force on Colorectal Cancer guidelines recommend against its use for screening of CRC [15]. Although unsuitable for primary screening, this test could retain however a limited application, used with caution, in patients who reject all other screening tests.

4.0 Target population for screening

As discussed above, the decision to enter a patient into a screening program is triggered by the risk level of developing a cancer. Proper selection of the target population requires thorough knowledge of congenital and acquired risk factors for that cancer. Herein we aimed to summarize the different sets of recommendations existing among the principal guidelines published on the topic of CRC screening (Table 1 and 2) [15 - 18].

Although genetics plays an important role in risk stratification, the risk of developing CRC is mainly influenced by acquired factors. Many of them have been identified, including age, race, male gender, dietary habits, and smoking. Age and family history are the only risk factors that have been taken into account in most screening recommendations, as the role of other factors – considered singularly - is not sufficiently high to influence screening schedules [15]. On this basis, the role of clinicians in determining who and when to screen for CRC lies in the assessment of the individual patient's level of risk. This evaluation can be performed by questioning the patient about a personal history of CRC or adenomatous polyps, the presence of one or more first-degree relatives, or two or more second-degree relatives with CRC, or a genetic syndrome at high-risk of CRC (i.e. hereditary nonpolyposis colorectal cancer and familial adenomatous polyposis), a previous diagnosis of inflammatory bowel disease causing extensive colitis, and a personal history of childhood cancer requiring abdominal radiation therapy. In the absence of any of the aforementioned points, the patient is considered at normal risk, whereas the presence of any of these points determines an increased risk for CRC and different screening/surveillance strategies should be employed.

4.1 Screening in individuals with baseline normal risk

The U.S. Multi-Society Task Force on Colorectal Cancer guidelines [15] recommend 10-year colonoscopy or annual FIT as the preferred screening strategy. Patients with baseline normal risk aged 50 and older should be screened for CRC. Indeed, even if CRC may develop in normal-risk people under the age of 50, this event is infrequent and screening is not cost-effective in patients younger than 50. Additionally, screening should begin at age 45 - rather than 50 - for African Americans, who have a slightly higher risk. Surveillance intervals for colonoscopy are suggested to be set every 10

years; however, for persons who are up to date with screening and have negative prior screening tests, stopping screening/surveillance at age 75 years or when life expectancy is less than 10 years should be considered; conversely, persons without prior screening may be considered for screening up to age 85, depending on consideration of their age and comorbidities. Similar, although not identical, European guidelines have been proposed [18]: as the prevalence of neoplastic lesions in the population below 50 years of age is too low to justify endoscopic screening, while in the elderly population (75 years and above) lack of benefit could be a major issue, the optimal age for a screening colonoscopy is around 55 years, and it should not be performed (or surveillance discontinued) after age 74. Regarding surveillance, the optimal interval for colonoscopy screening is suggested to be not less than 10 years, it may also be extended up to 20 years [18].

4.2 Screening in individuals with baseline high risk

Several conditions increase the risk of CRC. Herein we discuss those sufficiently important as to influence recommendations for screening and surveillance.

4.2.1. Family history

One out of four patients with CRC has a positive family history [7]. Furthermore, 3-4% of patients with CRC harbour a susceptibility syndrome caused by two autosomal dominant genetic mutations: familial adenomatous polyposis (FAP) and hereditary nonpolyposis colon cancer (HNPCC) (see further). Consequently, clinicians must investigate family history of CRC, focusing on the presence of a previous diagnosis of CRC or adenomatous polyps among relatives and, if so, at what age and how many cancers/polyps were diagnosed, and the degree of kinship (first-degree versus second-degree relatives). This information is essential. On one hand, these findings should be

analysed in order to decide whether the suspicion of FAP or HNPCC exists; on the other hand, the magnitude of CRC risk depends upon the number of family members affected, age at onset (e.g. younger than 50 years) in the relatives, and whether they are first-degree [108]. In addition, CRC may occur earlier in life, even in the third or fourth decade, in case of family history of CRC [109]. Interestingly, patients with a family member with a history of adenomatous polyp ≥ 1 cm, or with high-grade dysplasia, or with villous elements may also be at increased risk for adenoma or CRC [110]. As a result, several guidelines formulated similar recommendations for CRC screening in patients with family history. The recent U.S. Multi-Society Task Force on Colorectal Cancer guidelines [15] recommended that, if a single first-degree relative was diagnosed at age 60 years or older with CRC or an advanced adenoma (≥1 cm, or with high-grade dysplasia and/or villous elements), screening with colonoscopy should be performed every 10 years – the same recommendation was made for patients with normal risk at baseline – but should begin earlier, at age 40. If a single first-degree relative was diagnosed before 60 years with CRC or an advanced adenoma, or two or more first-degree relatives had CRC or advanced adenomas at any age, screening with colonoscopy is recommended at age 40 or 10 years before the youngest relative's diagnosis, to be repeated every 5 years. Finally, in case of one or more first-degree relatives with a documented advanced serrated lesion (SSP or traditional serrated adenoma ≥ 10 mm in size or an SSP with cytological dysplasia), screening and surveillance should be performed according to above recommendations for persons with a family history of a documented advanced adenoma.

4.2.2. Familial adenomatous polyposis (FAP)

FAP is an autosomal dominant disease caused by mutations in the adenomatous polyposis coli gene [111]. Beginning in adolescence, hundreds to thousands of polyps

develop throughout the colon, whereas tumors may occur also in the 20s, and nearly all patients ultimately develop CRC. Of note, patients with FAP are also at risk of several extracolonic malignancies. Consequently, genetic testing is recommended in at-risk family members of known FAP carriers, or in individuals with more than 100 adenomas [112]. If subjects are identified as having an increased genetic risk profile, annual colonoscopy starting around age 10 years is recommended. In patients with numerous polyps, multiple large (>1 cm) adenomas, or advanced adenomas, colectomy should be performed. Patients who have undergone proctocolectomy will require pouchoscopy for cancer surveillance [113]. An attenuated form of FAP is also caused by APC mutations, but is characterized by fewer polyps, later age of onset and lower risk of CRC [114]. In this setting, genetic testing of at-risk family members of known attenuated FAP families or in individuals with more than 10-20 adenomas is recommended. Annual colonoscopy in gene carriers should be performed starting at the age of 20-25 years. Even if patients with attenuated FAP are managed with polypectomy plus surveillance, prophylactic colectomy is recommended when adenomas are too numerous or difficult to be managed with endoscopic polypectomy [115].

4.2.3. Lynch Syndrome and Hereditary nonpolyposis colorectal cancer

Lynch syndrome (LS) is an autosomal dominant disease with genetic mutations in one of the four mismatch repair genes (MLH1, MSH2, MSH6, PMS2). Hereditary nonpolyposis colorectal cancer (HNPCC) is a characterization for families fulfilling the clinical criterion of LS, but no identified pathogenic gene variant (not found or not studied). These conditions account for approximately 3% of all CRC. The colon cancers in LS/HNPCC differ from sporadic CRC in two characteristics: they develop at an earlier age, and are mainly right-sided cancers. In addition, approximately 10% of patients have synchronous or metachronous cancers, and the mean age at diagnosis is 48

years, with some patients also presenting in their 20s [116]. Similarly to FAP, LS/HNPCC is also associated with a higher risk of several extracolonic tumors [117]. Given these data, caution is warranted with these patients: annual colonoscopy may be recommended starting at the age of 20-25 years, or 10 years prior to the earliest age of colon cancer diagnosis in the family [118]. Recently, an observational, international, multicentre study based on the prospective LS database aimed to determine the observed incidences of cancers and survival in path-MMR carriers up to 75 years of age; interestingly, the cumulative risk of each cancer for each MMR gene could be estimated for LS patients in colonoscopic surveillance using a risk calculation tool on the webpage www.lscarisk.org [119].

4.2.4. Peutz-Jeghers syndrome and juvenile polyposis syndrome

Both these syndromes are associated with an increased risk of CRC. Detailed reviews have been published about these rare conditions [120,121].

4.2.5. Colonic inflammatory bowel disease

Patients with longstanding colonic inflammatory bowel disease (IBD) have an increased risk of CRC compared to the general population [122]. Of note, most of the evidence on this topic is derived from patients with ulcerative colitis (UC), while less is known about colonic Crohn's disease, even if most of the recommendations may apply also fto this latter category. The risk of CRC in UC is associated with disease duration and extent: cumulative CRC risks of 2% at 10 years, 8% at 20 years and 18% at 30 years of disease duration are reported, and patients with extensive disease carry the highest risk, while the risk is not increased in patients with disease limited to the rectum [123]. These estimates are mainly derived from studies performed before the introduction of biological drugs, while the cumulative risk of CRC in UC has recently decreased with

the use of effective anti-inflammatory drugs. In this regard, one recent nation-wide analysis covering all patients with UC in Finland between 1987-93 and 2000-2007 and followed up to 2010 showed that the risk of CRC was lower than the risk of biliary tract cancer or others, such as thyroid cancer or lymphoma [124]. However, an initial screening colonoscopy is highly recommended in all patients with UC – independently of known colitis extent - in order to re-evaluate disease extent and to rule out the presence of dysplastic lesions. The suggested timing for this endoscopic examination is 6–8 years after the beginning of symptoms. Subsequently, surveillance colonoscopies should be carried out at defined intervals according to the risk profile of the individual patient. In patients with concurrent primary sclerosing cholangitis, surveillance colonoscopies should be performed yearly, as the risk of developing CRC in these patients is very high [123], and may occur early in the course of the disease [125], with tumours developing most frequently in the right-hand side of the colon [126]. Conversely, the risk of CRC is only minimally increased in patients with proctitis with no other risk factors, and no regular monitoring is required [127]. In both extensive and left-sided colitis, risk stratification depends on four factors: presence of pancolitis, history of pseudopolyps, persistent endoscopic and/or histological inflammation, and family history of CRC. According to the presence of these factors, patients can be stratified as low-risk (colonoscopy every 3-4 years) or high-risk (colonoscopy every 1-2 years) [128].

In this setting, advanced endoscopic imaging (chromoendoscopy, electronic chromoendoscopy, image-enhanced endoscopy, confocal laser endomicroscopy, endocitoscopy, fluorescence endoscopy, etc) and techniques involving the detection of alterations in mucosal antigens and genetic abnormalities (sialosyl-Tn) are being investigated. There are promising results that may lead to more efficient surveillance in IBD patients and more general acceptance of its use [129].

4.2.6. Abdominal radiation

Patients who received abdominal radiation due to malignancy in childhood have an incidence of CRC 11 times higher compared with individuals not exposed to radiation in childhood [130,131]. The Children's Oncology Group recommends colonoscopy every five years for survivors of childhood cancer who received abdominal radiation, with screening beginning 10 years after radiation or at age 35 years [132].

5.0 Recall policies and surveillance strategies

After first screening examination, all positive tests need further evaluation by diagnostic algorithms, defined recall policies, with the aim to confirm or exclude the diagnosis. Negative results should be followed-up over time by surveillance strategies. In the latter case, timing of surveillance generally differs depending on type of primary test used and test results.

5.1 Recall policies and surveillance after gFOBT and FIT

Fecal occult blood tests (gFOBT and FIT) are economic, non-invasive, well tolerated, and have a broad application worldwide. Once the test is performed with a negative result, high-quality evidence supports new testing every 1 or 2 years, while, for positive tests, colonoscopy should be used as a recall strategy with the aim of confirming or excluding whether the positive test is due to a tumor. The best time-to-colonscopy after a positive fecal test remains to be properly defined. A recent retrospective cohort study performed on 70124 participants eligible for CRC screening, with a positive FIT, undergoing a follow-up colonoscopy, showed no difference in CRC or advanced-stage disease between colonoscopy performed within 8 to 30 days and 10 month intervals. In contrast, colonscopy performed after 10 months was associated with a higher risk of CRC and advanced-stage disease [133].

5.2 Recall policies and surveillance after endoscopy

Flexible sigmoidoscopy is commonly used as screening test however, no studies directly assessing the ideal surveillance intervals have been performed to date. Based on indirect evidence, international guidelines recommend to repeat sigmoidoscopy 5 to 10 years after the first examination and not later than 10 years [15,18]. Colonoscopy can be performed as the primary screening test or as the recall policy after a positive result of another primary screening test. If no adenoma is detected at primary colonoscopy, all guidelines recommend exiting national screening programs or to repeat the colonoscopy 10 years after the index colonoscopy.

Though a 10-year surveillance interval is recommended for patients with negative primary screening colonoscopy, it is unclear whether such an interval is also justified in patients with a negative colonoscopy performed after positive fecal-based screening tests. In particular, subjects with positive FIT usually represent an extremely high-risk group with a higher proportion of advanced adenoma and cancers and a higher probability of an interval CRC being found after a negative colonscopy. In view of this, further studies are needed to assess the optimal surveillance intervals after a negative colonoscopy performed as recall policy following a positive FIT.

In contrast, if during primary colonoscopy one or more polyps are detected then management should be tailored to the endoscopic findings. Since colonic polyps are variably classified, for the purposes of this review we will take into account only adenomatous polyps and serrated polyps (which can be neoplastic or non-neoplastic).

5.2.1. Adenomatous polyps

Approximately two-thirds of all colonic polyps are adenomas, which are by definition dysplastic and thus have malignant potential. Low and high grades of dysplasia should be used to classify the polyps, as the terms "carcinoma in situ" or "intramucosal adenocarcinoma" should be included in the condition of high-grade dysplasia [134]. Due to the absence of lymphatic vessels in the lamina propria, these polyps cannot be associated with metastasis [135]. However, adenomas with high-grade dysplasia may also coexist with areas of invasive cancer in the polyp. Within an individual adenoma, three factors are associated with an increased risk of focal cancer: polyp size, villous histology, and high-grade dysplasia [134]. Adenomatous polyps >1 cm in diameter are at risk of containing CRC or for metachronous cancer development [135]. Of note, the proportion of adenomas with high-grade dysplasia or >25 percent villous histology increases from 1- 2% in small adenomas (<5 mm) to 7-12% for medium-sized adenomas (5 to 10 mm) and 20-30% for adenomas >1 cm [136]. Consequently, villous histology (and dysplasia) are closely linked with size of the polyp.

According to US Multi-society Task Force guidelines, adenomatous polyps are commonly divided into two main categories: low-risk vs. advanced adenomas [15] (Table 3). The low-risk group includes patients with 1-2 small tubular adenomas ≤ 10 mm at baseline colonoscopy, for which first surveillance colonoscopy is recommended after 5 to 10 years. If no adenoma is found on the first surveillance colonoscopy, a second surveillance colonoscopy should be performed in 10 years. Conversely, if a low-risk adenoma is detected, the second surveillance colonoscopy should be performed at 5 years. Of note, if 3 to 10 tubular adenomas are found, a repeated colonoscopy is recommended at three years, and a shorter timeframe is advisable if more than 10 adenomas (regardless of histological subtype) are detected. The advanced group

includes patients with adenomas ≥10 mm, and/or villous histology and/or high-grade dysplasia, for which the first surveillance colonoscopy should be performed in 3 years.

Similarly, ESGE guidelines classify lesions in 1) low-risk and high-risk group [137] (Table 3). For the low risk group (patients with 1-2 tubular adenomas < 10 mm with low grade dysplasia), participation in existing national screening programs or, in absence of these, repetition of colonoscopy after 10 years is recommended. For the high-risk group (patients with adenomas with villous histology or high grade dysplasia or ≥ 10 mm in size, or ≥ 3 adenomas), the ESGE recommend surveillance colonoscopy 3 years after the index colonoscopy. If at subsequent surveillance examinations high-risk adenomas are detected, it is recommended to continue surveillance with a 3-year interval. If no high-risk adenomas are detected, a 5-year interval is suggested.

Finally, European Guidelines divide patients into low, intermediate and high risk groups, according to findings at baseline colonoscopy (Table 3) [18]. Patients with only one or two small (<10 mm) adenomas are at low-risk. For these, the benefit of surveillance with colonoscopy seems to be low, therefore patients should be returned to national screening programs. Patients with three or four small adenomas or at least one adenoma of size 10 mm and <20 mm are classified as intermediate-risk and should undergo surveillance at 3-yearly intervals. After one negative exam, the interval can be extended to 5 years. After two consecutive normal exams, the patient can return to routine screening program. Patients with 5 or more adenomas, or one or more adenomas >20 mm, are classified as high-risk and a first colonoscopy should be undertaken within 12 months, in order to check for missed lesions, before initiating 3-yearly surveillance [18].

Different recommendations are given for surveillance after piecemeal resection of polyps, for which both US, ESGE and European Guidelines recommend an early surveillance colonoscopy, within 1 year, 6 months and 2-3 months respectively [15, 18, 137].

5.2.2. Serrated polyps

Serrated polyps are a heterogeneous group of lesions with variable malignant potential. They include hyperplastic polyps, traditional serrated adenomas, and sessile serrated adenomas (SSA) [138]. Hyperplastic polyps are the most common non-neoplastic polyps in the colon. Even if they are generally located in the sigmoid and rectum and are less than 5 mm in size, they may be indistinguishable from adenomatous polyps [139]. Their neoplastic transformation potential is rare. Indeed, patients with isolated hyperplastic polyps, ≤10 mm, should undergo their next surveillance examination after 10 years [15]. However, it should be noted that the presence of large (≥10 mm) serrated polyps is associated with an increased risk of synchronous advanced adenoma and CRC [140]. Serrated polyposis syndrome is a rare condition characterized by multiple, large and/or proximal hyperplastic polyps and, occasionally, serrated adenomas or typical adenomas, which has been associated to an increased risk of CRC [141].

Annual colonoscopy is appropriate in patients with serrated polyposis syndrome, and endoscopic screening is advisable at age 40 (or 10 years earlier than the earliest cancer in the family) for first-degree relatives of individuals with serrated polyposis [79]. Traditional serrated adenomas are rare, they are more prevalent in the distal colon and are generally sessile and dysplastic. Several studies showed significant malignant potential and the association with subsequent development of metachronous polyps [142].

Sessile serrated adenomas are more prevalent in the proximal colon, and compared to traditional adenomas, they are generally flat or sessile with few or even no surface blood vessels. For this reason, colonoscopy has a great benefit over other tests in the detection of sessile SSA, since flexible sigmoidoscopy is not restricted to the exploration of the proximal colon, CTC has a low sensitivity for flat lesions and FIT has a lower sensitivity for SSA since they do not always bleed due to the absence of superficial vessels. According to US guidelines, patients with serrated adenomas <10 mm and no dysplasia should repeat a colonoscopy in 5 years, while individuals with serrated adenomas ≥10 mm and/or with dysplasia should undergo a new colonoscopy after 3 years [15]. Similarly, ESGE guidelines consider serrated adenomas <10 mm and no dysplasia as low-risk and suggest returning patients to the CRC screening program. For serrated polyps ≥ 10 mm or with evidence of dysplasia, the recommendation is repeat colonoscopy after 3 year [137].

In contrast, European guidelines state that for surveillance purposes serrated adenomas should be dealt with like any other adenoma since there are no data to suggest surveillance intervals differ from those of other polyps [18]. Therefore, strictly following the guidelines, the endoscopist has the main responsibility to establish the surveillance interval and provide a written recommendation considering, together with the histological findings, the following four issues: a) the completeness of the colonoscopy; b) the withdrawal time; c) the characterization of each lesion detected, according the current classifications; d) the endoscopic techniques used (i.e., “en bloc” polypectomy is more radical than “piecemeal” polypectomy), according to the size and the morphologic features of the lesions [143].

5.3 Recall policies and surveillance after other tests

FIT-DNA, CTC and capsule endoscopy are not considered as appropriate screening tool for CRC screening by European Guidelines [18]. On the other hand, the more recent US Multi-Society Task Force on Colorectal Cancer guidelines recommended FIT-DNA and CTC as a second option in patients who decline colonoscopy or FIT, and recommend capsule endoscopy as a third option for patients who refuse all other tests. In the case of negative findings, FIT-DNA test should be repeated after 3 years, while CTC and capsule endoscopy should be repeated after 5 years. In the case of positive results, patients should undergo colonoscopy as a recall strategy after screening [15]. Septin9 assay has been proposed at 3-year intervals. All current guidelines recommend against its use as screening for CRC [15,18].

6.0 Expert commentary

Colorectal cancer represents a significant public health issue with high rates of morbidity and mortality.

Due to the slow rate of transformation from premalignant lesions to carcinoma, the detection of early-stage disease, through adequate screening tests, can reduce the incidence and mortality due to CRC, since the removal of colonic polyps can absolutely prevent progression to cancer.

Current evidence supports the overall effectiveness of screening for CRC on the basis of several high quality studies performed on large populations.

While screening effectiveness is clearly demonstrated, a greater uncertainty concerns the best strategy to be applied. To date, there are still insufficient evidence to define

which approach is definitively superior, and no screening strategy for CRC can be defined as universally ideal. The best approach is the one that can be economically viable and to which the patient can best adhere to over time.

According to latest guidelines, we suggest performing colonoscopy every 10 years or annual FIT for people with normal baseline risk as the best option for individual-based CRC screening. In this regard, colonoscopy limits and risks should always be taken into account and communicated to patients at the same time as discussing alternative options.

In people who decline or are unfit for colonoscopy and FIT, flexible sigmoidoscopy every 5 to 10 years and CTC every 5 years are recommended as second line strategies. FIT-DNA is also recommended as a second line option, but the absence of validation in non-US countries and high costs still limit its application in non-US populations, and therefore it should be used with caution. For individuals with elevated baseline risk or hereditary syndromes, colonoscopy with shortened surveillance intervals according to international guidelines is recommended.

Regardless of the screening test used, any positive result requires a colonoscopy examination as recall strategy, for diagnostic confirmation of tumors and removal of precancerous lesions. For this reason, endoscopy still plays a pivotal role in CRC screening. In this regard, both in the screening and during the surveillance after polypectomy, consistent quality measures, that could help to quantify health-care processes and can aid in providing high-quality health care, are needed to preserve the effectiveness of CRC prevention and to improve patient outcomes.

Considerable steps forward have been made in the field of CRC screening in recent years, which has helped improve the overall survival associated with this disease. However, in the future, further efforts must be made to optimize prevention strategies. Firstly reasonable attempts to strengthen health policy interventions aimed to modifying behavioral risk factors in asymptomatic people already at increased risk (primary prophylaxis) are required. Second, a risk-stratification of the population to be screened is necessary, in order to refine screening on a tailored approach and reduce costs. Thirdly, it is mandatory to improve rates of early detection of tumors (secondary prophylaxis). This can be achieved by both refining the knowledge of risk factors and improving performance of screening tests.

With regard to the first point, in addition to known risk factors, several others (e.g. comorbidities like diabetes, thyroid disease, metabolic syndrome, etc) should be better studied to identify target populations that could enter into CRC screening programs [144-147]. This could be helpful in order to better educate the population and reduce CRC incidence. In addition to this, primary cancer prophylaxis with pharmaceuticals and/or dietary agents has become a relevant topic, particularly in certain high-risk populations, and should be further explored in the future [148]. For example, although controversial, treatment with 5-ASA or thiopurines as CRC chemopreventive drugs may be advisable in patients with long-standing ulcerative colitis and Crohn's colitis [149, 150]. In FAP, celecoxib reduces polyp formation and subsequent CRC development [151], while in LS 600 mg aspirin may have a preventive effect on CRC development [152].

Concerning the second point, several non-invasive scores for risk assessment of the population to be screened, have been developed in the last decade, but none have

been widely introduced in clinical practice so far. Indeed some of them have limited accuracy in discriminating high- and low-prevalence subgroups, others are too complex to be considered in clinical practice, or have been developed with the aim of predicting the future risk for developing CRC rather than to stratify people into different class of risk [153-159]. Nevertheless, recent validated models appear to be simple to apply and have substantial accuracy in defining high- and low-risk groups for advanced adenomas. For example, the Asia-Pacific Colorectal Screening (APCS), a simple scoring system including 4 variables (age, sex, family history, and smoking) has been recently assessed on a large sample of Asiatic patients. The score was shown to have good discrimination power and to be effective in risk stratifying for advanced colorectal neoplasm [160]. Though simple and accurate, the score has been assessed only in the Asia Pacific area and an external validation in different ethnic groups, especially in Western countries, is necessary.

Similarly, another risk index based including 5 variables (age, sex, waist circumference, cigarette smoking, and family history of CRC), has been recently assessed by Imperiale et al [161]. The score was shown to accurately stratify lower-risk groups, for which non-colonoscopy strategies may be effective, from higher-risk group for which colonoscopy may be preferred as primary screening test. Currently, few data on risk-stratified approaches in clinical practice are available, as well as a lack of RCTs comparing compliance and effectiveness of a risk-stratified approach versus the opportunistic approaches. In the future, further efforts to develop effective risk-stratified approaches are needed in order to achieve tailored screening strategies.

Regarding the last point, screening techniques, especially colonoscopy, need to be technologically improved in order to maximize their diagnostic sensitivity. In this regard,

during the last few years, several technologies have been used, including chromoendoscopy, digital chromoendoscopy, magnification endoscopy, high-definition and full-spectrum endoscopy with the aim of enhancing the sensitivity of the colonoscopy in detecting adenomas. However, further efforts are needed to improve imaging techniques.

Finally, one more debated topic concerns when to stop surveillance. International guidelines recommend beginning screening at 50 years of age in an 'at risk' population, to tailor screening for patients between 76 and 85 years of age on the basis of comorbidity and to stop screening for patients aged more than 85 years [18, 162,163]. In contrast to this, U.S. Multi-Society Task Force on Colorectal Cancer guidelines suggest consideration for screening persons without prior screening up to age 85, depending on consideration of their age and comorbidities [15].

As discussed above, we believe that CRC screening should be stopped as soon as it becomes reasonably futile, for instance when age or general status of the patient exclude "a priori" any treatment options for the tumor.

7.0 Five-year view

A better knowledge of the pathogenesis of CRC and its risk factors will help physicians to apply a tailored approach to the patient, with the aim of increasing accuracy of screening and improving outcomes. In the coming years, further technological progress is needed to increase the diagnostic sensitivity of screening tests and to minimize the number of false negatives. At the same time, additional non-invasive tests should be implemented to reduce the need for invasive screening and to help increase adherence to surveillance programs.

In conclusion, in the future it will be necessary for regulatory authorities to increase economic resources for oncological prevention, ensuring a widespread diffusion of screening programs beyond the borders of developed countries, and by standardizing screening procedures.

8.0 Key issues

- Colorectal cancer (CRC) is a major healthcare problem all over the world. Globally, it is the third most common cancer in males and second in females, and the fourth cause for cancer death worldwide.
- Currently, about 60-70% of CRC cases in non-screened populations are diagnosed in an advanced stage. Screening strategies for CRC have been shown to be effective in reducing incidence and mortality from CRC.
- International guidelines on CRC screening recommend beginning screening at 50 years of age in at risk population, to tailor screening for patients between 76 and 85 years of age on the basis of comorbidity and to stop screening for patients aged more than 85 years, or when age or general status of the patient exclude "a priori" any treatment option.
- In the last 10 to 15 years, several approaches to CRC screening have been proposed. Among these fecal tests (guaiaic fecal occult blood test, gFOBT; fecal immuno-chemical test, FIT; fecal DNA test), endoscopic tests (colonoscopy, flexible sigmoidoscopy, capsule endoscopy), radiologic tests (computed tomographic colonography) and blood tests (Septin9 gene test).
- Fecal occult blood tests (FOBT and FIT) are economic, non-invasive and well tolerated. High-quality evidence supports testing every year or every 2 years.

Positive tests require subjects have to colonoscopy as a recall strategy with the aim of confirming or excluding the presence of a tumor.

- The recently developed FIT-DNA test allows the qualitative detection of colorectal neoplasia associated DNA markers and the presence of occult hemoglobin in feces. Nevertheless it showed inferior performance compared to FIT, especially in terms of specificity and risks of false positive results. When used for screening, 3-years intervals are recommended.
- Among endoscopic techniques, flexible sigmoidoscopy (FS) is one of the most widely used and investigated. International guidelines recommend to repeat sigmoidoscopy 5 to 10 years after the first examination and no later than 10 years.
- Colonoscopy is the only tool able to evaluate the entire colon and to be able to detect and remove precancerous lesions. If no adenoma is detected, all guidelines recommend returning to national screening programs or to repeat colonoscopy 10 years after the index colonoscopy. If colonic polyps are detected and removed, timing of surveillance intervals needs to be shortened.
- Septin9 assay is the only available plasmatic test proposed for CRC screening and is recommended at 3-year intervals. It cannot be utilized for adenoma detection, due to the low sensitivity showed in several studies and current guidelines recommend against its use for CRC screening.
- To date, there are still insufficient evidence to identify which approach is definitively superior, and no screening strategy for CRC can be therefore defined as universally ideal. The best option is the one that is economically viable and to which patients can adhere best over time.
- According to the latest guidelines, we suggest performing colonoscopy every 10 years or annual FIT in subjects with normal baseline risk as best option for

individual-based CRC screening. In people who decline colonoscopy and FIT, CT colonography every 5 years or flexible sigmoidoscopy every 5 to 10 years are recommended as second-line strategies. FIT-DNA is also recommended as a second line option, but the absence of validation in non-US countries and high costs still limit its application in population based screening programs.

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Reference annotations

* Of interest

** Of considerable interest

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164)

POPULATION	US MULTI-SOCIETY TASK FORCE ON COLORECTAL CANCER [15]	EUROPEAN GUIDELINES FOR QUALITY ASSURANCE OF CRC SCREENING [18]
INDIVIDUALS WITH BASELINE NORMAL RISK	Screening: Age 50 and older (age 45 for African Americans) Surveillance: every 10 years[1]	Screening: Around age 55 Surveillance: not less than 10 years and may even extended up to 20 years[2]
INDIVIDUALS WITH BASELINE HIGH RISK -First-degree relative diagnosed before 60 years with CRC or advanced adenoma, or two or more first-degree relatives with CRC or advanced adenomas at any age	Age 40, or 10 years before the youngest relative's diagnosis Surveillance: Every 5 years	
-Single first-degree relative diagnosed at age 60 years or older with CRC or advanced adenoma	Screening: Age 40 Surveillance: every 10 years[1]	
-One or more first-degree relatives with a documented advanced serrated lesion	Same recommendations of patients with history of a documented advanced adenoma	

165)

166)

167) Table 1. Overview on timing of endoscopic screening and surveillance according to baseline risk of colorectal cancer

168)

169) Abbreviations: CRC: Colorectal cancer;

[1] Persons who are up to date with screening and have negative prior screening tests, consider stopping screening/surveillance at age 75 years or when life expectancy is less than 10 years; persons without prior screening should be considered for screening up to age 85, depending on consideration of their age and comorbidities.

[2] Should be discontinued after age 74.

POPULATION	FIRST SCREENING EXAMINATION	SURVEILLANCE INTERVALS
FAP	Around age 10 years	Every year (consider colectomy)
Attenuated FAP	Around age 20-25 years	Every year (consider colectomy)
HNPCC	Around age 20-25 years (or 10 years prior to the earliest age of colon cancer in the family)	Every year
Colonic IBD	6–8 years after the beginning of symptoms	Proctitis: no surveillance. Extensive and left-sided colitis: every 3-4 years if low-risk, every 1-2 years if high-risk[1] Every year in patients with PSC
Abdominal radiation in childhood	10 years after radiation	Every 5 years

Table 2. Overview on timing of endoscopic screening and surveillance: special situations

Abbreviations: FAP: Familial adenomatous polyposis; HNPCC: Hereditary nonpolyposis colorectal cancer; IBD: inflammatory bowel disease; PSC: Primary sclerosing cholangitis.

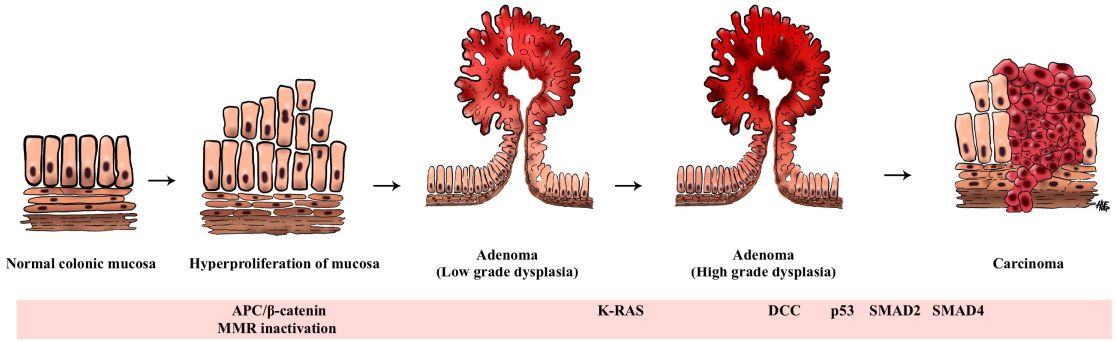
179) [1] Risk stratification depending on four factors: presence of pancolitis, history of pseudopolyps, persistent endoscopic and/or histological inflammation, and family history of CRC.

180) POLYPS REMOVED BY 'EN BLOC' RESECTION			
US MULTI-SOCIETY TASK FORCE ON COLORECTAL CANCER [15]	**EUROPEAN SOCIETY OF GASTROINTESTINAL ENDOSCOPY [137]**	**EUROPEAN GUIDELINES FOR QUALITY ASSURANCE OF CRC SCREENING [18]**	**First surveillance interval**
	No adenomas; 1 – 2 tubular adenomas <10 mm with low grade dysplasia; serrated polyps <10 mm and no dysplasia	No adenomas; one or two small (<10 mm) adenomas	**Return to national screening programs**
No adenomas; distal small (<10 mm) hyperplastic polyps			**10 years**
1–2 tubular adenomas <10 mm			**5 to 10 years**
sessile serrated polyp(s) 10 mm with no dysplasia	<3 adenomas, < 10 mm in size, without villous histology and without high grade dysplasia		**5 years**
- 3–10 adenomas - one or more tubular adenomas >10 mm, - one or more tubular adenomas with villous features of any size - one or more tubular adenomas with high grade dysplasia - sessile serrated polyp(s) 10 mm or with dysplasia	≥ 3 adenomas, and/or ≥ 10 mm in size, and/or with villous histology or high grade dysplasia; serrated polyps ≥ 10 mm or with dysplasia	3-4 small adenomas or at least one adenoma >10 mm and <20 mm	**3 years**
Serrated polyposis syndrome		5 or more adenomas, or an adenoma >20 mm	**1 year**
POLYPS REMOVED BY 'PIECEMEAL' RESECTION			
US MULTI-SOCIETY TASK FORCE ON COLORECTAL CANCER [15]	**EUROPEAN SOCIETY OF GASTROINTESTINAL ENDOSCOPY [137]**	**EUROPEAN GUIDELINES FOR QUALITY ASSURANCE OF CRC SCREENING [18]**	**Surveillance interval**
Flat and sessile adenomatous and serrated polyps >15 mm removed by piecemeal resection technique			**Within 1 year**

	Piecemeal resection of adenomas larger than 10 mm		**Within 6 months**
		Large sessile lesions removed piecemeal	**Within 2-3 months**

Table 3. Colonoscopy surveillance after screening or polypectomy according to current practice guidelines.

181)



182)

Figure 1: Adenoma-carcinoma sequence and common genetic aberrations in sporadic colorectal cancer.