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CLINICAL PRACTICE GUIDELINES

Clinical practice guideline. Diagnosis and prevention of colorectal cancer. 2018 Update☆

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KEYWORDS
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Abstract This document updates the recommendations made by the Spanish Society of Family and Community Medicine and the Spanish Association of Gastroenterology for the diagnosis and prevention of colorectal cancer (CRC). In order to evaluate the quality of the evidence and determine the recommendation levels of the interventions, we used the Grading of

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Clinical practice guideline;
Population screening;
Faecal occult blood test;
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Lynch syndrome;
Polyposis;
Inflammatory bowel disease

Recommendations, Assessment, Development and Evaluation (GRADE) methodology. This document establishes optimal delay intervals based on symptoms and the faecal immunochemical test (FIT) and recommends reducing the barriers for diagnostic confirmation in symptomatic subjects. With regard to CRC screening in the average-risk population, we propose strategies to achieve the universal implementation of organised CRC screening programmes based on biennial FIT and to increase the participation of the target population, including the involvement of Primary Healthcare. This clinical practice guideline recommends universal screening for Lynch syndrome with mismatch repair proteins immunohistochemistry or microsatellite instability in incident CRCs and the use of gene panels in patients with adenomatous polyposis. It also updates the strategies to reduce the incidence and mortality of both CRC and other tumours associated with hereditary syndromes. Regarding non-hereditary familial CRC and surveillance after resection of adenomas, serrated lesions or CRC, we established the recommendations based on the attributable risk and the risk reduction of the proposed intervention. Finally, the document includes recommendations regarding surveillance intervals in inflammatory bowel disease and the attitude towards dysplasia.

PALABRAS CLAVE
Cáncer colorrectal;
Prevención;
Diagnóstico;
Guía de práctica clínica;
Cribado poblacional;
Test de sangre oculta en heces;
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Síndrome de Lynch;
Poliposis;
Enfermedad inflamatoria intestinal

Guía de práctica clínica. Diagnóstico y prevención del cáncer colorrectal. Actualización 2018

Resumen Este documento actualiza las recomendaciones realizadas por la Sociedad Española de Medicina Familiar y Comunitaria y la Asociación Española de Gastroenterología para el diagnóstico y la prevención del cáncer colorrectal (CCR). Para establecer la calidad de la evidencia y los niveles de recomendación de las intervenciones se ha utilizado la metodología basada en el sistema GRADE (*Grading of Recommendations Assessment, Development and Evaluation*). Este documento establece intervalos de demora óptimos en función de los síntomas y el test de SOH inmunológico (SOHi) y recomienda reducir las barreras para la confirmación diagnóstica en los pacientes con síntomas. En cuanto al cribado en población de riesgo medio, se proponen estrategias para conseguir la implantación universal del cribado poblacional basado en SOHi bienal e incrementar la participación de la población diana, incluyendo la implicación de atención primaria. Esta guía de práctica clínica recomienda el cribado universal del síndrome de Lynch mediante la inmunohistoquímica de las proteínas reparadoras o la inestabilidad de microsatélites en los CCR incidentes y el uso de paneles de genes en los pacientes con poliposis adenomatosas. También actualiza las estrategias para reducir la incidencia y la mortalidad tanto de CCR como de otros tumores asociados a los síndromes hereditarios. En cuanto al CCR familiar no hereditario y la vigilancia tras resección de CCR, adenomas y lesiones serradas, se establecen recomendaciones en función del riesgo atribuible y la reducción del riesgo de la intervención propuesta. Finalmente, en el documento se incluyen recomendaciones respecto a los intervalos de vigilancia en la enfermedad inflamatoria intestinal y la actitud ante la displasia.

Introduction

Colorectal carcinoma (CRC) is one of the most common malignancies in western countries.. In Spain, it is the second most common cancer after prostate cancer in men, and after breast cancer in women. An estimated 40,000 new cases of CRC are diagnosed every year in Spain and 39% of those affected die from this disease.[1–3]

The clinical practice guidelines (CPG) of the *Asociación Española de Gastroenterología* (AEG) [Spanish Association of Gastroenterology] and the *Sociedad Española de Medicina Familiar y Comunitaria* (semFyC) [Spanish Society of Family and Community Medicine] were first published in 2004[4] and their first update was in 2009.[5] The guidelines were put together and subsequently updated essentially in response to the high incidence and morbidity and mortality rates of CRC in our setting, with the consequent significant impact on the different levels of care of the Spanish health service. Moreover, CRC was known to be a disease that is eminently preventable, whether through primary, secondary or tertiary prevention, both in the medium-risk and increased-risk populations.

In this update of the CPG, the clinical questions formulated explicitly following the PICO (patient, intervention, comparison and outcome) model have been expanded on.[6] We have also reviewed the scientific literature available

from 2008 to January 2017. Unlike the previous version, in order to establish the quality of the evidence and the levels of recommendation of the different interventions evaluated in these CPG, we have used the methodology based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system[7] which, in addition to the quality of the evidence, considers the balance between benefits and risks, costs and values and the people's preferences. No recommendations have been made in the sections where it was not necessary (e.g., in aetiology); in these cases, only the quality of the evidence is described.

Although the original structure of the guide has been maintained, a number of subjects not dealt with previously have now been included. For example, new sections referring to serrated lesions (serrated polyposis syndrome, serrated lesions) have been incorporated and strategies for identifying Lynch syndrome and monitoring hereditary syndromes are updated. In the chapter on follow-up after adenoma resection, we have included strategies aimed at reducing the risk of developing metachronous CRC after CRC resection with curative intent. In the section referring to screening in the medium-risk population, we have included strategies to increase participation in population programmes. The chapter on assessing the signs and symptoms that should warn of the possibility of CRC has been extended to include prioritisation criteria, predictive models and the use of biomarkers in the diagnosis of CRC. However, these CPG do not address the treatment and follow-up of patients with CRC. This article only includes the recommendations proposed by the authors based on review of the evidence. The full text is accessible online at https://www.aegastro.es/publicaciones/publicaciones-aeg/guias-de-practica-clinica/actualizacion-2018-guia-practica-clinica-sobre-el-diagnostico-y-prevencion-del-cancer-colorrectal. The CPG will be reviewed in the 2024, or earlier if necessary should important information emerge. Any significant changes in the meantime will be reflected in the electronic format.

Summary of the evidence and recommendations

Epidemiology of colorectal cancer

- In Spain, CRC is the most common cancer overall, with an estimated total of 39,553 new cases in 2014. Rates increase markedly over the age of 50 and the incidence is on an upward trend.
- In 2014, in Spain there were 9244 deaths due to CRC in men and 6205 in women. CRC-related mortality rates are on a downward trend.
- The EUROCARE-5 study places five-year relative survival at 57.1% (Europe 57.0%) for colon cancer and 56.4% (Europe 55.8%) for rectal cancer.

Risk factors and prevention of colorectal cancer

Consumption of fats, meat, fibre, fruit, vegetables, fish and milk for the prevention of colorectal cancer

- We suggest moderating the consumption of red meat, processed meat and cooked meat which is very well done or in direct contact with flames for the prevention of CRC (*quality of evidence moderate, strength of recommendation weakly in favour*).
- We suggest promoting a high-fibre (whole grain, wholemeal products) diet rich in fruit and vegetables to reduce the risk of CRC (*quality of evidence moderate, strength of recommendation weakly in favour*).
- We suggest promoting a diet rich in fish and poultry to reduce the risk of CRC (*quality of evidence low, strength of recommendation weakly in favour*).
- We suggest consuming a diet rich in milk and other dairy products to reduce the risk of CRC (*quality of evidence moderate, strength of recommendation weakly in favour*).
- We suggest consuming a low-fat diet to prevent obesity and reduce the risk of CRC (*quality of evidence low, strength of recommendation weakly in favour*).

Micronutrients for the prevention of colorectal cancer

- It is necessary to ensure an adequate intake of folate, vitamin B, calcium and vitamin D in the diet, but these micronutrients should not be administered in the form of supplements for the prevention of CRC (*quality of evidence moderate, strength of recommendation strongly against*).
- In people with a history of polyps, administering calcium supplements is suggested for the prevention of recurrence of adenomas (*quality of evidence low, strength of recommendation weakly in favour*).
- It is necessary to ensure an adequate intake of foods high in beta-carotene, vitamins and minerals, but these antioxidants should not be administered in the form of supplements for the prevention of CRC (*quality of evidence high, strength of recommendation strongly against*).

Lifestyles for the prevention of colorectal cancer

- Maintain a healthy body mass index and control the risk factors related to metabolic syndrome (abdominal obesity, hyperinsulinaemia) for the prevention of the development of CRC and other diseases (*quality of evidence moderate, strength of recommendation strongly in favour*).
- Physical exercise should be taken on a regular basis to prevent the development of CRC and other diseases (*quality of evidence moderate, strength of recommendation strongly in favour*).
- Smoking should be avoided and given up to prevent CRC (*quality of evidence moderate, strength of recommendation strongly in favour*).
- Alcohol intake should be reduced to prevent CRC (*quality of evidence moderate, strength of recommendation strongly in favour*).

Chemoprevention of colorectal cancer

- We suggest that non-steroidal anti-inflammatory drugs (NSAIDs) (including acetylsalicylic acid [ASA]) should not

be administered systematically for the primary prevention of CRC (*quality of evidence moderate, strength of recommendation weakly against*).

- In the general population, primary prevention of risk factors associated with CRC is an alternative with a better risk–benefit ratio than the administration of NSAIDs (including ASA).
- In the medium-risk population, primary prevention of the risk factors associated with CRC and screening are alternatives with a better risk–benefit ratio than the administration of NSAIDs (including ASA).
- In people with cardiovascular disease aged 50–59, the benefits of low-dose ASA for the primary prevention of CRC and cardiovascular disease may outweigh the risks.

Diagnosis of colorectal cancer in symptomatic patients

Symptoms for the diagnosis of colorectal cancer

- The diagnostic assessment of patients with lower gastrointestinal symptoms requires a thorough medical history and a detailed physical examination, including anorectal examination.

- Patients with a rectal or abdominal mass suspected to be CRC, palpable and/or visible by radiological imaging, should be referred without delay to the specialist service to confirm the diagnosis (*quality of evidence high, strength of recommendation strongly in favour*).
- Patients with rectal bleeding suspected of being CRC (dark blood and/or mixed with faeces and/or weight loss and/or change in bowel habit and/or absence of perianal symptoms) should be called for an urgent colonoscopy and/or referred without delay to the specialist service for a colonoscopy and definitive diagnosis (*quality of evidence moderate, strength of recommendation strongly in favour*).
- Patients with unexplained iron-deficiency anaemia (haemoglobin $\leq$10 g/dl in women and <11 g/dl in men) should be called for an urgent colonoscopy and/or referred without delay to the specialist service to rule out a possible gastrointestinal origin (*quality of evidence moderate, strength of recommendation strongly in favour*).

Faecal immunochemical test in patients with lower gastrointestinal symptoms

- Patients with lower gastrointestinal symptoms of recent onset who do not meet criteria for referral without delay to a specialist service due to high suspicion of CRC (rectal or abdominal mass, rectal bleeding or iron-deficiency anaemia) should have a faecal immunochemical test (FIT) (*quality of evidence low, strength of recommendation strongly in favour*).
- Patients with a positive FIT ($\geq$10 μg/g of faeces) should be called for a priority colonoscopy and/or referred without delay to the specialist service for a colonoscopy and definitive diagnosis (*quality of evidence moderate, strength of recommendation strongly in favour*).
- Setting the positive cut-off point at 10 μg of Hb/g of faeces ensures an optimal balance between sensitivity and specificity in the FIT. A lower cut-off point would increase the number of colonoscopies. A higher cut-off point could delay the diagnosis of some patients with CRC.
- Patients with a negative FIT (<10 μg/g of faeces) and persistence of the recent-onset (2–4 weeks) symptoms should be called for a colonoscopy and/or referred to the specialist service for a colonoscopy and definitive diagnosis (*quality of evidence moderate, strength of recommendation strongly in favour*).

Predictive models and diagnostic tests in symptomatic patients

- The construction and validation of predictive models from the demographic and clinical variables of patients with symptoms of CRC can make it easier to identify the individual risk of CRC.
- Optical colonoscopy is the test of choice in the diagnosis of CRC.
- In patients in whom the optical colonoscopy would be difficult to perform (advanced age, poor preparation, technical difficulties, comorbidities) a computed tomography (CT) colonography is suggested (*quality of evidence moderate, strength of recommendation weakly in favour*).

Delayed diagnosis in colorectal cancer

- The stage at the time of diagnosis is an important prognostic factor in CRC.
- The delay that can affect the diagnostic and therapeutic processes in CRC can be attributed to the patient (time from developing symptoms until first visit to the doctor for this reason), the general practitioner (time from first contact with the patient until referral to specialist care) and the system (time from referral to specialist care to the definitive diagnosis).
- Campaigns are needed to raise awareness among the general population so that if they develop gastrointestinal symptoms potentially suggestive of CRC, they consult their general practitioner without delay.
- Having criteria and referral networks for confirming diagnosis of CRC improves coordination between levels of care and helps reduce the delays attributed to the health system as a whole (primary and specialist care).

Prioritisation systems and fast-track diagnosis to facilitate diagnosis of colorectal cancer in symptomatic patients

- The rapid diagnosis of CRC in symptomatic individuals should be guaranteed through healthcare resources that facilitate the reduction of waiting times: fast-track diagnosis networks, healthcare routes, high resolution consultations and/or endoscopy units with open access from primary care to specialist care (*quality of evidence low, strength of recommendation strongly in favour*).
- In patients in whom CRC is highly suspected (rectal or abdominal mass, rectal bleeding or significant iron

deficiency anaemia and suspicion of chronic intestinal bleeding, and/or lower gastrointestinal symptoms with a positive FIT) the time interval between referral from primary care and having the colonoscopy and/or confirmation of diagnosis in specialist care should be less than two weeks (*quality of evidence low, strength of recommendation strongly in favour*).
- In patients with recent-onset and persistent lower gastrointestinal symptoms and negative FIT, the time interval between the referral from primary care and having the colonoscopy and/or confirmation of diagnosis in specialist care is recommended to be as short as possible.

Colorectal cancer screening in the medium-risk population

Screening tests in the medium-risk population

- In the medium-risk population, screening with a single FIT determination every two years from age 50 to 75 is recommended (*quality of evidence moderate, strength of recommendation strongly in favour*).

- Strategies should be introduced to minimise false negatives in the FIT associated with temperatures over 30 °C.

- In the medium-risk population, screening with the stool DNA test is not recommended (*quality of evidence low, strength of recommendation strongly against*).
- In the medium-risk population, population screening with colonoscopy is not recommended (*quality of evidence low, strength of recommendation weakly against*).

- Screening colonoscopy (direct or for investigation of a positive test) should be performed under sedation, in conditions of adequate cleanliness, with caecal intubation and a withdrawal time of not less than 6–8 min.
- In the case of a previous full, good quality colonoscopy without significant findings, we suggest returning to the screening programme at 10 years.

- In the medium-risk population, flexible sigmoidoscopy is recommended as a screening test for CRC, if available (*quality of evidence moderate, strength of recommendation strongly in favour*).

- The interval between sigmoidoscopy screenings should be 10 years.
- After the detection by sigmoidoscopy of an adenomatous polyp or a distal serrated polyp larger than 10 mm or with high-grade dysplasia, a complete colonoscopy is required.
- Complete colonoscopy after detection by sigmoidoscopy of distal hyperplastic polyps is not recommended.

- In the medium-risk population, offering CT colonography as a CRC screening strategy is not recommended (*quality of evidence low, strength of recommendation strongly against*).

- CT colonography is recommended for investigation of a positive faecal occult blood test (FOBT) in individuals in whom colonoscopy is contraindicated or with an incomplete colonoscopy for a cause other than inadequate bowel cleansing.

- In the medium-risk population, offering colon capsule endoscopy as a CRC screening strategy is not recommended (*quality of evidence low, strength of recommendation strongly against*).

- We suggest offering colon capsule endoscopy for the investigation of a positive FIT in individuals in whom colonoscopy is contraindicated or with incomplete colonoscopy for a cause other than inadequate bowel cleansing.

- The use of peripheral blood biomarkers as a CRC screening strategy is not recommended (*quality of evidence very low, strength of recommendation strongly against*).

Population screening programmes in colorectal cancer

- CRC screening should be organised from a population perspective while fulfilling quality standards (*quality of evidence low, strength of recommendation strongly in favour*).
- In the CRC population screening programmes, getting primary care professionals involved to promote population participation and adherence is recommended (*quality of evidence moderate, strength of recommendation strongly in favour*).

- In our setting, and in accordance with the established guidelines, performing population-based CRC screening with the biennial quantitative FIT on the population aged 50–75 without risk factors is recommended.
- Universal coverage of the population at medium risk should be obtained with the population-based programmes in the shortest possible time.
- Standardised methods of modelling for the CRC population screening programmes should be used to speed up implementation and monitor follow-up.
- We suggest raising the cut-off point for faecal Hb, extending the intervals between rounds (3 years) or increasing the starting age for screening in women, based on the results of the modelling.
- Awareness should be raised among the population, healthcare professionals and health authorities of the importance of CRC prevention.
- In the context of population screening programmes, implementing strategies that increase the participation and adherence of the population is recommended (for example, sending the FOBT to the home and/or handing the test in at the health centre or at the chemist's).
- Higher-risk groups should be identified in order to offer them screening strategies adapted to their risk of developing CRC.
- Screening of people at higher risk should meet similar quality standards to those established in the CRC population screening programmes.

Screening in colorectal polyposis

Genetic analysis in adenomatous polyposis

- We recommend referring individuals with more than ten adenomas to high-risk clinics for investigation of hereditary risk and monitoring.
- The criteria for performing genetic analysis in patients with adenomatous polyposis are as follows:

1. The finding of >20 colorectal adenomas in an individual, regardless of age.
2. The finding of >10 colorectal adenomas under the age of 40.
3. The finding of >10 adenomas when there is a personal or family history of CRC under the age of 60, and/or
4. The finding of >10 adenomas when there is a family history of attenuated adenomatous polyposis.

- We recommend the simultaneous analysis of various genes using multi-gene panels in individuals with more than 20 adenomas or more than 10 adenomas if detected under the age of 40, if there is a personal or family history of CRC under the age of 60 and/or a family history of attenuated adenomatous polyposis (*quality of evidence low, strength of recommendation strongly in favour*).
- We recommend offering mutational analysis to first-degree relatives (parents, siblings and children) of individuals with a pathogenic germline mutation (*quality of evidence moderate, strength of recommendation strongly in favour*).

Familial adenomatous polyposis (FAP)

- In individuals with a classic FAP pathogenic mutation or direct relatives of patients with FAP without a known pathogenic mutation, commencing CRC screening at 10–12 years of age with annual sigmoidoscopy is recommended and, after detection of the phenotype, annual colonoscopy (*quality of evidence low, strength of recommendation strongly in favour*).
- In individuals with a mutation in *APC* associated with attenuated FAP (aFAP), commencing surveillance with yearly or two-yearly colonoscopies at 18–20 years of age is recommended (*quality of evidence low, strength of recommendation strongly in favour*).
- In individuals with aFAP associated with *APC*, we suggest performing endoscopic resection of colorectal polyps as a strategy to reduce the risk of developing CRC and/or the need for colectomy (*quality of evidence very low, strength of recommendation weakly in favour*).
- In classic FAP, the finding or suspicion of CRC is an absolute indication for colectomy. Relative indications are: a significant increase in the number of adenomas or inability to guarantee an adequate follow-up due to the presence of multiple minute polyps (*quality of evidence low, strength of recommendation strongly in favour*).
- We recommend discussing the surgical technique with the patient (total proctocolectomy or total colectomy with ileorectal anastomosis, depending on the age at diagnosis, the phenotype and family history of FAP and the patient's preferences) (*quality of evidence very low, strength of recommendation strongly in favour*).
- After surgery, we recommend endoscopic surveillance at intervals of 6–12 months for patients with rectum intact and 2 years for those with ileal pouch (*quality of evidence moderate, strength of recommendation strongly in favour*).
- The administration of NSAIDs is suggested in FAP as adjuvant to surgery in patients with residual polyps (*quality of evidence moderate, strength of recommendation weakly in favour*).
- We suggest surveillance of gastric lesions and duodenal adenomas by upper gastrointestinal endoscopy, including duodenoscopy, from the age of 25–30 at intervals according to the Spigelman classification. Endoscopic resection of stage I–III duodenal adenomas is suggested. In patients with stage IV duodenal adenomas, prophylactic cephalic pancreaticoduodenectomy is suggested (*quality of evidence very low, strength of recommendation strongly in favour*).
- Surveillance of papillary thyroid tumour by yearly ultrasound scan is suggested in women aged 15–35 and of hepatoblastoma by alpha-foetoprotein and abdominal ultrasonography up to 7 years of age (*quality of evidence very low, strength of recommendation weakly in favour*).

MUTYH-associated polyposis

- Analysis of mutations in the *MUTYH* gene is suggested in couples who are both carriers of biallelic mutations to establish the recommendations for offspring (*quality of evidence very low, strength of recommendation weakly in favour*).
- It is suggested in monoallelic *MUTYH* mutation carriers that the recommendation of CRC screening be carried out according to familial clustering (*quality of evidence very low, strength of recommendation weakly in favour*).
- In individuals with a biallelic mutation in *MUTYH*, we recommend that surveillance with colonoscopy be commenced at the age of 18–20 at yearly or two-yearly intervals (*quality of evidence low, strength of recommendation strongly in favour*).
- In individuals with a biallelic mutation in the *MUTYH* gene, we suggest endoscopic resection of colorectal polyps as a strategy to reduce the risk of developing CRC and/or the need for colectomy (*quality of evidence very low, strength of recommendation weakly in favour*).
- The finding or suspicion of CRC is an absolute indication for colectomy. Relative indications are: a significant increase in the number of adenomas or inability to guarantee an adequate follow-up due to the presence of multiple minute polyps (*quality of evidence low, strength of recommendation strongly in favour*).
- We recommend discussing the surgical technique with the patient, according to their age at diagnosis, the phenotype and family history and the patient's preferences (*quality of evidence very low, strength of recommendation strongly in favour*).
- After surgery, we recommend endoscopic surveillance at intervals of 6–12 months for patients with rectum intact and 2 years for those with ileal pouch (*quality of*

evidence moderate, strength of recommendation strongly in favour).

- We suggest surveillance of gastric lesions and duodenal adenomas by upper gastrointestinal endoscopy, including duodenoscopy, from the age of 25–30 at intervals according to the Spigelman classification. Endoscopic resection of stage I–III duodenal adenomas is suggested. In patients with stage IV duodenal adenomas, prophylactic cephalic pancreaticoduodenectomy is suggested (*quality of evidence very low, strength of recommendation strongly in favour*).

Síndrome asociado a la actividad reparadora de la polimerasa *(SAARP) [Syndrome associated with the repairing activity of polymerase] and* NTHL-1-*associated polyposis*

- In individuals with monoallelic mutation in the *POLE* and *POLD1* genes or biallelic mutation in the *NTHL-1* gene the same preventive strategy is suggested for CRC as for aFAP associated with *APC* (*quality of evidence very low, strength of recommendation weakly in favour*).

Attenuated adenomatous polyposis without identified genetic mutation and individuals with multiple polyps

- In individuals with attenuated adenomatous polyposis without genetic cause or with oligopolyposis, it is suggested that endoscopic surveillance be carried out according to the quality of the colonoscopy and the number and histological characteristics of the polyps resected in the last colonoscopy (*quality of evidence very low, strength of recommendation weakly in favour*).
- In individuals with attenuated adenomatous polyposis without genetic cause, we suggest surveillance of gastric lesions and duodenal adenomas by upper gastrointestinal endoscopy, including duodenoscopy, at the time of diagnosis and then at intervals according to the Spigelman classification (*quality of evidence very low, strength of recommendation weakly in favour*).
- In individuals with attenuated adenomatous polyposis without genetic cause or with oligopolyposis, no screening for extraintestinal manifestations is recommended (*quality of evidence very low, strength of recommendation strongly against*).
- In first-degree relatives (parents, siblings and offspring) of individuals with attenuated adenomatous polyposis without genetic cause commencing screening with complete colonoscopy is suggested at the age of 40 or 10 years prior to the age of the youngest affected family member. In families with more aggressive phenotype (e.g. >40 polyps or history of CRC, and/or extensive family history, and/or extracolonic manifestations), commencing surveillance at 20–25 years of age is suggested (*quality of evidence very low, strength of recommendation weakly in favour*).

Hamartomatous polyposis

- In individuals with mucocutaneous pigmentation, >2 Peutz-Jeghers-type hamartomatous polyps and/or family history, we recommend analysis for mutations in the *STK11* gene (*quality of evidence low, strength of recommendation strongly in favour*).
- Screening measures in Peutz-Jeghers syndrome should include examination of the testicles, gastrointestinal tract (via gastroduodenal endoscopy, colonoscopy, intestinal transit and/or capsule endoscopy), mammography and pancreatic endoscopic ultrasonography (or magnetic resonance imaging) (*quality of evidence low, strength of recommendation weakly in favour*).
- In patients with a clinical diagnosis of juvenile polyposis (5 or more juvenile polyps in the colon, multiple juvenile polyps in the gastrointestinal tract and/or any number of juvenile polyps and a family history of juvenile polyposis syndrome) we recommend analysing for mutations in the genes involved, mainly *SMAD4* and *BMPR1A* (*quality of evidence low, strength of recommendation strongly in favour*).
- The screening measures in juvenile polyposis syndrome should include colonoscopy and gastroscopy commencing at the age of 15, every 2–3 years if no polyps are detected, otherwise yearly. Surveillance of vascular lesions in individuals with mutation in *SMAD4* is suggested due to the risk of hereditary haemorrhagic telangiectasia (*quality of evidence low, strength of recommendation weakly in favour*).
- Individuals with multiple gastrointestinal hamartomas or ganglioneuromas should be investigated to rule out Cowden syndrome, including analysis of mutations in the *hj* gene (*quality of evidence low, strength of recommendation strongly in favour*).
- Screening of colon, stomach, small intestine, thyroid, breasts, endometrium, kidney and melanoma in individuals with Cowden syndrome is suggested (*quality of evidence low, strength of recommendation weakly in favour*).

Serrated polyposis syndrome

- In individuals diagnosed with serrated polyposis syndrome (SPS) (5 or more serrated polyps [SP] proximal to the sigma, at least 2 of them >1 cm in size, any number of SP in a first-degree relative of a patient diagnosed with SPS, or presence of more than 20 SP distributed throughout the entire colon), we recommend colonoscopy (contrast techniques to be assessed) every 1–3 years and endoscopic resection of any visualised lesions (*quality of evidence low, strength of recommendation weakly in favour*).
- Colectomy (total or segmental) is recommended before the detection of CRC or before it becomes impossible to control the serrated lesions endoscopically (*quality of evidence low, strength of recommendation strongly in favour*).
- After surgery, post-operative endoscopic surveillance is recommended on a yearly basis (*quality of evidence low, strength of recommendation weakly in favour*).
- In first-degree relatives of individuals with SPS, commencing screening with complete colonoscopy is suggested at the age of 40 or 10 years prior to the age of the youngest affected family member (*quality of evidence very low, strength of recommendation weakly in favour*).

Hereditary non-polyposis colorectal cancer

Genetic analysis in Lynch syndrome

- We recommend referring individuals with suspicion or diagnosis of Lynch syndrome to genetic counselling units or high-risk clinics (*quality of evidence very low, strength of recommendation strongly in favour*).
- We recommend immunohistochemistry testing of the tumours of all patients with CRC for repair proteins or microsatellite instability (MSI) to identify candidates for analysis of germline mutations for Lynch syndrome (*quality of evidence moderate, strength of recommendation strongly in favour*).
- We recommend determining the presence of mutations in BRAF or *MLH1* promoter hypermethylation in tumours with no *MLH1* expression (*quality of evidence low, strength of recommendation strongly in favour*).
- We recommend analysis of germline mutations in DNA repair genes when MSI or loss of protein expression is demonstrated (in absence of *MLH1* hypermethylation) (*quality of evidence moderate, strength of recommendation strongly in favour*).
- We suggest analysis of germline mutations in DNA repair genes in individuals with a family history suggestive of Lynch syndrome without access to molecular study if the likelihood of detecting a mutation in repair genes in predictive models is greater than 5% (*quality of evidence very low, strength of recommendation weakly in favour*).
- We recommend offering analysis of germline mutations in DNA repair genes to first-degree relatives (parents, siblings and children) of individuals who are carriers of a germline mutation in any of these genes (*quality of evidence moderate, strength of recommendation strongly in favour*).

Screening in Lynch syndrome

- We recommend periodic screening with colonoscopy in individuals with Lynch syndrome (*quality of evidence moderate, strength of recommendation strongly in favour*).
- It is suggested that yearly or two-yearly endoscopic screening commence at the age of 20–25 (*quality of evidence low, strength of recommendation weakly in favour*).
- It is suggested that women with Lynch syndrome be screened for gynaecological cancers by transvaginal ultrasound and/or endometrial aspirate/biopsy yearly from the age of 30–35 (*quality of evidence very low, strength of recommendation weakly in favour*).
- We suggest testing for and eradication of *Helicobacter pylori* if positive in individuals with Lynch syndrome. We suggest endoscopic surveillance for gastric cancer every 1–3 years from the age of 30–35 in families with a high degree of familial clustering of gastric cancer (*quality of evidence very low, strength of recommendation weakly in favour*).
- We suggest more intensive surveillance strategies than those recommended for the general population for other cancers (breast, prostate, urological, pancreas) only if there is familial clustering (*quality of evidence very low, strength of recommendation weakly in favour*).

Surgical treatment in Lynch syndrome

- In patients belonging to families with Lynch syndrome who develop CRC, we recommend extensive resection (preferably colectomy with ileorectal anastomosis) as a strategy for preventing the development of metachronous tumours (*quality of evidence low, strength of recommendation strongly in favour*).
- In women carrying mutations in the genes responsible for Lynch syndrome, hysterectomy and bilateral oophorectomy should be offered at the age of 40–45 once they have completed their families to reduce the risk of gynaecological cancer (*quality of evidence low, strength of recommendation weakly in favour*).

Chemoprevention in Lynch syndrome

- Chemoprevention with ASA can be considered individually after discussion of the risks, benefits and uncertainties with the patient (*quality of evidence low, strength of recommendation weakly in favour*).

Lynch-like syndrome

- We suggested analysis of somatic mutations in repair genes and multigene panels to exclude germline mutations in other genes in patients with Lynch-like syndrome (*quality of evidence very low, strength of recommendation weakly in favour*).
- We recommend individualising surveillance strategies in families with Lynch-like syndrome based on personal history and familial clustering (*quality of evidence very low, strength of recommendation strongly in favour*).

Familial colorectal cancer type X

- In individuals belonging to families with familial CRC type X, we suggest offering endoscopic screening every 3–5 years from the age of 35, or 10 years prior to the age of diagnosis of the youngest affected family member (*quality of evidence low, strength of recommendation weakly in favour*).
- We do not recommend screening for extracolonic malignancies in individuals belonging to families with familial CRC type X (*quality of evidence low, strength of recommendation strongly against*).

Familial colorectal cancer

Risk of colorectal cancer and advanced malignancy in non-syndromic familial colorectal cancer

- Before establishing a preventive strategy, we recommend determining whether or not the familial clustering corresponds to any of the known hereditary syndromes

associated with CRC (*quality of evidence low, strength of recommendation strongly in favour*).
- Once a hereditary syndrome has been ruled out, individuals with only one first-degree relative (FDR) with CRC should be put into the population-based screening programmes (*quality of evidence moderate, strength of recommendation strongly in favour*).
- We recommend that for individuals with two FDR with CRC, the current recommendation based on colonoscopy every 5 years should be maintained (*quality of evidence moderate, strength of recommendation strongly in favour*).

Screening strategies in a population with non-syndromic familial colorectal cancer

- Screening with FIT is recommended as an alternative to colonoscopy in individuals with FDR with CRC (*quality of evidence moderate, strength of recommendation strongly in favour*).
- After a first colonoscopy, endoscopic surveillance intervals should be adapted to the endoscopic findings (*quality of evidence moderate, strength of recommendation weakly in favour*).

Surveillance after resection of colon polyps or colorectal cancer

Surveillance according to risk groups

- Before carrying out surveillance recommendations, it should be verified that the baseline colonoscopy was performed under high-quality conditions: complete examination, adequate bowel cleansing and complete removal of the polyps.

- Patients with 1–2 tubular adenomatous lesions with low-grade dysplasia and <10 mm do not require endoscopic surveillance. They should be reincorporated into the population screening programme, preferably at 10 years, or indicate a colonoscopy at 10 years if there is no population screening programme for CRC (*quality of evidence moderate, strength of recommendation strongly in favour*).
- Patients with serrated lesions without dysplasia <10 mm do not require endoscopic surveillance, regardless of the number of lesions. They should be reincorporated into the population screening programme, preferably at 10 years, or indicate a colonoscopy at 10 years if there is no population screening programme for CRC (*quality of evidence low, strength of recommendation strongly in favour*).
- Patients with hyperplastic polyps in rectum/sigmoid colon <10 mm do not require endoscopic surveillance. They should be reincorporated into the population screening programme, preferably at 10 years, or indicate a colonoscopy at 10 years if there is no population screening programme for CRC (*quality of evidence low, strength of recommendation strongly in favour*).
- Patients with 3 or more tubular adenomatous lesions with low-grade dysplasia <10 mm or at least one villous adenomatous lesion with high-grade dysplasia (HGD) or ≥10 mm should have their first endoscopic surveillance at 3 years (*quality of evidence moderate, strength of recommendation weakly in favour*).
- Patients with at least one serrated neoplastic lesion with dysplasia or ≥10 mm should have their first endoscopic surveillance at 3 years (*quality of evidence low, strength of recommendation strongly in favour*).
- For patients with 5 or more adenomas or any adenoma ≥20 mm who constitute the high-risk group in the European guidelines,[3] at present there is no evidence either for or against shortening the follow-up interval to one year (*quality of evidence low, strength of recommendation weakly in favour*).

Surveillance in special situations

- Surveillance recommendations should always be established after complete resection of lesions found in baseline colonoscopy.

- When resection is incomplete, colonoscopy should be repeated until the goal of leaving the colon completely explored and free of neoplastic lesions is achieved (*quality of evidence low, strength of recommendation strongly in favour*).
- In large sessile or flat lesions (≥20 mm) which are resected in a fragmented manner, an endoscopic review should be performed within 6 months after the baseline colonoscopy (*quality of evidence high, strength of recommendation strongly in favour*).
- In large sessile or flat lesions (≥20 mm) which are resected in a fragmented manner, a first endoscopic surveillance should be carried out at one year after confirmation of complete resection (*quality of evidence high, strength of recommendation strongly in favour*).

- Complete evacuation of all resected lesions is recommended.
- Lesions ≥10 mm which are resected and not evacuated will be considered as advanced and lesions <10 mm as not advanced. Lesions <10 mm in the rectum/sigmoid colon which are resected and not evacuated will not be taken into account.
- To establish the surveillance recommendation, advanced and non-advanced lesions not evacuated will be added to those evacuated.

- After the resection of lesions suspected of being invasive cancer or with difficulty for later localisation, the lesion should be tattooed (*quality of evidence low, strength of recommendation strongly in favour*).

- Individuals at high risk of CRC (≥10 adenomas; ≥5 proximal serrated polyps; ≥2 serrated polyps ≥10 mm; >10 polyps with >50% serrated polyps or with criteria for serrated polyposis syndrome) require personalised investigation and should be referred to a specific high-risk clinic or for a specialist gastroenterology consultation.

Surveillance following a first surveillance colonoscopy

- The endoscopic surveillance intervals should be established on the basis of the findings in the last colonoscopy.

- In patients with advanced lesions in surveillance colonoscopy, the next endoscopic follow-up should be at 3 years (*quality of evidence moderate, strength of recommendation weakly in favour*).
- In patients without advanced lesions in surveillance colonoscopy, the next endoscopic follow-up should be at 5 years (*quality of evidence low, strength of recommendation weakly in favour*).
- After two surveillance colonoscopies with no advanced colorectal lesions, patients should be reincorporated into the CRC population screening programme or a colonoscopy at 10 years should be indicated if there is no population screening programme for CRC (*quality of evidence low, strength of recommendation weakly in favour*).

- It is advisable to integrate the surveillance strategies within the CRC population screening programmes.
- Patients who have had colon polyps removed and who consult with symptoms require careful assessment in the clinical setting.

- Endoscopic surveillance for CRC should be discontinued in adults over the age of 75 or, exceptionally, at 80 in selected patients without comorbidities (*quality of evidence low, strength of recommendation weakly in favour*).

Surveillance in patients with resected colorectal cancer with curative intent

- Individuals with pT1 CRC resected endoscopically should be referred to a specific high-risk clinic or specialist gastroenterology consultation.

- Patients with adenomatous polyp with invasion of the submucosa (pT1) do not require surgical resection if all criteria for good prognosis are met (*quality of evidence low, strength of recommendation strongly in favour*).
- If the baseline colonoscopy was incomplete, we recommend performing a complete preoperative colonoscopy or complete postoperative colonoscopy within the 3–6 months after surgery. If CT colonography is available, we recommend that it be performed before the intervention (*quality of evidence low, strength of recommendation strongly in favour*).
- We recommend performing the first surveillance colonoscopy at one year after the intervention, 3 years after the first follow-up and then every 5 years if the colonoscopies are normal or show only non-advanced lesions (*quality of evidence low, strength of recommendation strongly in favour*).
- If metachronous colorectal lesions are detected, the same recommendations as for post-polypectomy surveillance described above should be followed (*quality of evidence low, strength of recommendation strongly in favour*).
- In patients with rectal cancer without total excision of the mesorectum, surveillance is suggested for the first two years after resection, with no evidence in favour of any specific strategy (*quality of evidence low, strength of recommendation weakly in favour*).

Surveillance in inflammatory bowel disease (IBD)

Primary prevention of colorectal cancer in inflammatory bowel disease

- Primary prevention of CRC in IBD should focus on adequate long-term control of the inflammatory activity (*quality of evidence low, strength of recommendation strongly in favour*).
- Chemoprevention with oral mesalazine at doses above 1.2 g/day is recommended in all patients with ulcerative colitis (UC), except in proctitis, from diagnosis onwards (*quality of evidence moderate, strength of recommendation strongly in favour*).
- The exclusive use of thiopurines as CRC prophylaxis in IBD is not recommended (*quality of evidence moderate, strength of recommendation strongly against*).
- We recommend avoiding the use of ursodeoxycholic acid (UDCA) at doses >28–30 mg/kg/day in patients with primary sclerosing cholangitis (PSC) (*quality of evidence low, strength of recommendation strongly in favour*).
- In IBD associated with PSC, we suggest limiting the use of UDCA as chemoprophylaxis for CRC to high-risk patients only (widespread colitis), at doses no higher than 8–15 mg/kg/day (*quality of evidence low, strength of recommendation weakly in favour*).
- The generalised use of folic acid for CRC prophylaxis in patients with IBD is not recommended (*quality of evidence low, strength of recommendation strongly against*).
- The use of statins for CRC prophylaxis in patients with IBD is not recommended (*quality of evidence low, strength of recommendation strongly against*).
- We do not recommend the use of either ASA or NSAIDs for CRC prophylaxis in patients with IBD (*quality of evidence moderate, strength of recommendation strongly against*).

Endoscopic surveillance in inflammatory bowel disease

- We recommend that all patients with UC, Crohn's disease (CD) of the colon or indeterminate colitis should have a screening colonoscopy at 8 years from symptom onset or when they reach the age of 50 or over, regardless of the duration of their IBD (*quality of evidence low/moderate, strength of recommendation strongly in favour*).
- In patients with IBD and primary sclerosing cholangitis (PSC), we recommend commencing endoscopic surveillance at the time of diagnosis of PSC regardless of the activity and extent of IBD (*quality of evidence moderate, strength of recommendation strongly in favour*).
- We suggest performing an ileocolonoscopy every 5 years on patients with PSC with no evidence of IBD, in order to diagnose a subclinical IBD (*quality of evidence low, strength of recommendation weakly in favour*).

Endoscopic surveillance intervals in inflammatory bowel disease

- Endoscopic surveillance should be performed on all patients with IBD, except those with proctitis or CD with involvement of a single segment of the colon, with no evidence of macroscopic or microscopic, current or previous inflammation proximal to the rectum (*quality of evidence moderate, strength of recommendation strongly in favour*).
- Patients are considered to be high risk if they have widespread colitis with severe activity, or strictures or dysplasia in the previous 5 years, or family history of CRC <50 years of age, or concurrent PSC (including after a liver transplant). Patients are considered to be intermediate risk if they have widespread colitis with moderate or mild activity, or pseudopolyps, or family history of CRC aged 50 or over. Patients with no high or intermediate risk factors are considered to be low risk (*quality of evidence low, strength of recommendation strongly in favour*).
- We recommend that the interval for the next surveillance colonoscopy should be 1–2 years in high-risk cases, 2–3 years if the risk is intermediate and 5 years if the risk is low (*quality of evidence low, strength of recommendation weakly in favour*).
- The decision to perform endoscopic surveillance in older patients should be assessed taking into account their life expectancy, the potential complications related to colonoscopy or surgery, the expectations of managing IBD and the wishes of the patient (*quality of evidence low, strength of recommendation weakly in favour*).
- Endoscopic surveillance of strictures in IBD is recommended, including thorough and careful inspection with multiple biopsies (*quality of evidence moderate, strength of recommendation strongly in favour*).
- In patients with ileal pouch-anal anastomosis with a history of dysplasia or CRC, we recommend endoscopic surveillance with multiple biopsies that include the transitional zone and the pouch with a frequency of 1–2 years (*quality of evidence moderate, strength of recommendation strongly in favour*).
- We suggest not performing endoscopic surveillance without these risk factors (*quality of evidence low, strength of recommendation weakly against*).
- In patients with colectomy with intact rectum (ileorectal anastomosis or rectum excluded) we recommend endoscopic screening and surveillance with the same criteria as in patients without colectomy (*quality of evidence moderate, strength of recommendation strongly in favour*).
- Regular follow-up is recommended in patients with CD and chronic persistent perianal fistulas and/or anal strictures, especially when they have symptoms (*quality of evidence moderate, strength of recommendation strongly in favour*).
- We recommend performing the investigation under anaesthesia with curettage of the fistulas and biopsy of any suspicious area or lesion if an optimal examination cannot be performed (*quality of evidence low, strength of recommendation strongly in favour*).

Approach for dysplasia

- The diagnosis of dysplasia in IBD should be made following the Riddell classification into low-grade dysplasia, high-grade dysplasia, and undefined dysplasia. The definitive diagnosis of dysplasia requires confirmation by two pathologists, at least one habitually dedicated to gastrointestinal pathology.

- Chromoendoscopy (ChrE) is recommended – preferably with high-definition endoscopes – with resection of visible lesions suspected of being dysplasia and/or directed biopsy taking as a screening and surveillance technique for patients with IBD (*quality of evidence moderate, strength of recommendation strongly in favour*).
- Routinely taking random biopsies is not recommended when screening with ChrE (*quality of evidence moderate, strength of recommendation strongly against*).
- We suggest taking random biopsies when it is not possible to make a detailed inspection of the mucosa (important destructuring in the context of chronic quiescent inflammation, mucosal bridges, pseudopolyps) (*quality of evidence low, strength of recommendation weakly in favour*).
- Although endoscopic surveillance with IBD in remission is recommended, the colonoscopy should not be postponed if it is not expected that early remission will be achieved (*quality of evidence low, strength of recommendation strongly in favour*).
- We recommend repeating the colonoscopy in the case of inadequate bowel preparation (*quality of evidence moderate, strength of recommendation strongly in favour*).

- These CPG have followed the recommendations of the SCENIC consensus in terms of the definitions, terminology and characteristics of the endoscopy report in the screening and surveillance of patients with IBD.

- We recommend endoscopic treatment of resectable dysplastic lesions (*quality of evidence moderate, strength of recommendation strongly in favour*).
- With dysplastic lesions, after ensuring that they have been completely resected, we recommend endoscopic surveillance at 3–6 months and then at one year (*quality of evidence moderate, strength of recommendation strongly in favour*).
- In the case of small discrete lesions, performing the next colonoscopy at one year may be considered (*quality of evidence low, strength of recommendation weakly in favour*).
- The same guidelines should be followed if new visible lesions are found in the monitoring with ChrE (*quality of evidence low, strength of recommendation strongly in favour*).
- In the case of large lesions or after a fragmented resection, the interval between the subsequent surveillance colonoscopies should be decided on an individual basis. The whole set of variables that affect prognosis should be taken into account: concurrent risk factors and tumour progression; the difficulties of endoscopic follow-

up; and the opinion of the patient (*quality of evidence low, strength of recommendation strongly in favour*).

- We recommend colectomy for visible dysplastic lesions which are not resectable or where complete resection may not be assured by checking for the absence of dysplasia in and/or around the resection base (*quality of evidence moderate, strength of recommendation strongly in favour*).
- In the case of confirmed diagnosis of invisible dysplasia of any degree from a scan without ChrE, we recommend repeating the colonoscopy with ChrE and high definition, also taking multiple biopsies, within an interval no longer than 3 months (*quality of evidence low, strength of recommendation strongly in favour*).
- In the case of active disease, we would first advise intensifying the medical treatment, especially with the diagnosis of ''undefined for dysplasia'' (*quality of evidence low, strength of recommendation weakly in favour*).
- Colectomy is recommended in high-grade invisible dysplasia diagnosed from a quality examination with ChrE (*quality of evidence moderate, strength of recommendation strongly in favour*).
- Once a diagnosis of unifocal or multifocal low-grade invisible dysplasia or ''undefined for dysplasia'' is confirmed by ChrE, we suggest that the intervention should be individualised. Individualised intervention means including the set of updated data regarding risk factors and concurrent tumour progression, factors associated with an adequate quality and possibility of endoscopic follow-up, age, comorbidity and the patient's opinion (*quality of evidence low, strength of recommendation weakly in favour*).

- In the screening and endoscopic surveillance of patients with IBD, we recommend performing colonoscopies of the highest quality with adequate examination times and monitoring of outcomes to check interval cancer rates (from missed lesions).

Colectomy for dysplasia/colorectal cancer

- In patients with UC requiring colectomy due to dysplasia/CRC, proctocolectomy with ileoanal anastomosis is recommended. Total colectomy with ileorectal anastomosis may be considered in selected cases (*quality of evidence low, strength of recommendation strongly in favour*).

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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