SEOM clinical guideline on hereditary colorectal cancer (2019)

C. Guillén-Ponce[1] · E. Lastra[2] · I. Lorenzo-Lorenzo[3] · T. Martín Gómez[4] · R. Morales Chamorro[5] ·
A. B. Sánchez-Heras[6] · R. Serrano[7] · M. C. Soriano Rodríguez[8] · J. L. Soto[9] · L. Robles[10]

Abstract

In the last 2 decades, clinical genetics on hereditary colorectal syndromes has shifted from just a molecular characterization of the different syndromes to the estimation of the individual risk of cancer and appropriate risk reduction strategies. In the last years, new specific therapies for some subgroups of patients have emerged as very effective alternatives. At the same time, germline multigene panel testing by next-generation sequencing (NGS) technology has become the new gold standard for molecular genetics.

Keywords Lynch syndrome · Adenomatous polyposis · Hereditary colorectal cancer · Colon cancer

Introduction

Identification of individuals and families with clinical criteria for early referral to a specialized genetic counseling unit (GCU) has been the basis for preventive medicine in familial–hereditary susceptibility to colorectal cancer so far. Genetic counseling and risk reduction strategies have avoided many new cancer diagnoses and have helped these individuals understand and adapt to all the implications of genetic predisposition to colorectal cancer.

In the near future, somatic and germline multigene panel testing will be incorporated into the routine care of cancer, early from its diagnosis. Targeted therapies candidates will be identified through these predictive molecular profiles and

C. Guillén-Ponce, E. L. Aras, I. Lorenzo-Lorenzo, T. M. Gómez, R. M. Chamorro, A. B. S. Heras, R. S. Blanch, M. del Carmen Soriano Rodríguez, J. L. Soto, L. Robles contributed equally to the preparation of the manuscript.

✉ C. Guillén-Ponce
carmen.guillen@salud.madrid.org

✉ L. Robles
luis.robles@salud.madrid.org

E. Lastra
elastra@saludcastillayleon.es

I. Lorenzo-Lorenzo
isabel.lorenzo.lorenzo@sergas.es

T. Martín Gómez
teremg111@hotmail.com

R. Morales Chamorro
rmchamorro@sescam.jccm.es

A. B. Sánchez-Heras
sanchez_ana@gva.es

R. Serrano
rsblanch@hotmail.com

M. C. Soriano Rodríguez
mamsoro@hotmail.com

J. L. Soto
soto_jos@gva.es

1   Medical Oncology Department, Hospital Universitario Ramón y Cajal, IRYCIS, Carretera de Colmenar Viejo, Km 9,100, 28034 Madrid, Spain

2   Medical Oncology Department, Hospital Universitario de Burgos, Burgos, Spain

3   Medical Oncology Department, Complejo Hospitalario Universitario de Vigo (CHUVI), Pontevedra, Spain

4   Medical Oncology Department, Hospital Universitario de Salamanca, Salamanca, Spain

5   Medical Oncology Department, Hospital General La Mancha Centro, Alcázar de San Juan, Ciudad Real, Spain

6   Medical Oncology Department, Hospital General Universitario de Elche, Elche, Alicante, Spain

7   Medical Oncology Department, Hospital Universitario Reina Sofía, IMIBIC, CIBERONC, Córdoba, Spain

8   Medical Oncology Department, Hospital General Virgen de la Luz, Cuenca, Spain

9   Molecular Genetics Laboratory, Hospital General Universitario de Elche, Elche, Alicante, Spain

10 Medical Oncology Department, Hospital Universitario Doce de Octubre, Madrid, Spain

at the same time all known and actionable hereditary colorectal cancer syndromes will be screened as well.

The main hereditary colorectal cancer syndromes will be reviewed in this guideline with their main clinical, molecular features and their appropriate surveillance recommendations.

Materials and methods

A medical literature review was conducted in NCBI Pub-Med/EMBASE databases on the topics of the guideline. Evidence level and strength of the recommendations were based on GRADE http://www.gradeworkinggroup.org/ [1–3] (Table 1).

Lynch syndrome (OMIM 120435)

Lynch syndrome (LS) is an autosomal dominant inherited cancer predisposition disease. Its estimated general population prevalence is 1 in 279 [4]. LS accounts for about 3% of colorectal cancer (CRC) [5] and 2% of endometrial

Table 1 Evidence levels and strength of recommendation

Evidence levels

A: High. Randomized well-designed clinical trials/well-conducted meta-analysis. It is unlikely that future studies on the topic will modify confidence in the outcome

B: Moderate. Non-randomized prospective studies. It is likely that future studies on the topic will modify the confidence in the estimated outcome

C: Low or very low. Observational studies. Future studies on the topic will very likely change not only the confidence in the outcome but the outcome itself

Strength of recommendation

1. Strong recommendation on the measure/intervention we are considering: advantages of the intervention outweigh the risks and also are cost-efficient

2. Weak recommendation: advantages and disadvantages are not far from each other

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cancer (EC) cases [6]. CRC is the most common associated tumor, usually right-sided, poorly differentiated, with mucinous features or medullary growth pattern, abundant infiltrating lymphocytes, propensity for synchronous and/or metachronic tumors [7], and a better prognosis in the non-metastatic setting [8, 9]. LS also predisposes to EC, small intestinal, urinary tract, pancreaticobiliary, gastric and ovarian tumors, and slightly to breast and prostate cancers [7, 10–12]. Muir–Torre syndrome is characterized by skin tumors (sebaceous neoplasms, keratoacanthomas) and Turcot's syndrome includes glial brain tumors [7, 10]. The age of onset is younger compared with sporadic counterparts: 45–60 years old (years) for CRC and 50 years for EC [13].

Lynch syndrome is caused by pathogenic germline variants in the DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, or *PMS2* (and in the non-MMR gene *EpCAM*, in which deletions induce epigenetic silencing of *MSH2*) [10, 14]. When a second "hit" of somatic mutation occurs, the MMR function fails leading to cancers with microsatellite instability (MSI) and hypermutation phenotype. Deficient MMR (dMMR) and MSI are not exclusive to the LS and are also likely in sporadic cancers caused by *MLH1* promoter hypermethylation [15] or double somatic MMR mutations [16].

The age-specific cumulative risk could depend on genotype and sex [12, 13, 17–19] (Table 2). *MSH2* mutation carriers have a higher risk of extracolonic cancers [12]. *EpCAM* deletions close to the *MSH2* promoter are associated with increased risk of EC [20]. *MSH6* and *PMS2* mutations have a lower penetrance [4], except for EC in *MSH6* carriers, who also present with cancer at later ages [19, 21].

LS diagnosis

Universal strategy with molecular analyses in unselected CRC or EC adds diagnostic sensitivity for LS over clinical criteria, with a favorable cost-effectiveness profile [22–25]. This information has prognostic and therapeutic value for

Table 2 Lifetime cancer risks related to LS genotype and sex

Cancer site	MLH1 male	MLH1 female	MSH2 male	MSH2 female	MSH6 male	MSH6 female	PMS2 male	PMS2 female
Any LS cancer	59%	80%	71%	75%	31%	71%		
CRC	34–47%	36–45%	37–47%	33–37%	14–22%	10–26%	13–20%	11–15%
EC		42.7%		56.7%		46.2%		13–24%
Ovarian		10.1%		16.9%		13.1%		
Urinary tract	1.2%	3%	8%	10%	0.7%			
Gastric	20%	8%	2%	9%				
Small bowel	0.4%		1.1%					
Biliary/pancreatic	1.9%		0.02%					
CNS gliomas	1.0%		5.3%		1.4%			

CNS central nervous system, *CRC* colorectal cancer, *EC* endometrial cancer

common clinical practice. Multigene NGS in CRC, including MMR and *BRAF* genes, with computational tools for MSI testing, has a higher diagnostic sensitivity compared with a universal strategy based on immunohistochemistry (IHC) and *BRAF* analyses (100% sensitivity [95% CI 93.8–100] versus 89.7%, [95% CI 78.8–96.1], $p = 0.04$) [26]. In a prospective study of > 15.000 unselected cancer patients with 50 different histologies, a similar NGS device increased LS diagnostic sensitivity over revised Bethesda Criteria (rBC) plus universal strategy [27]. Somatic NGS panels are available in clinical practice for precision oncology due to their predictive value. Direct germline multigene NGS in unselected patients with CRC increases diagnostic sensitivity for less prevalent hereditary syndromes more than for LS [5, 28] (Fig. 1). When there are no tumor samples, fulfillment of rBC or a ≥ 2.5% likelihood of LS on the validated PREMM₅ prediction model [29] can be used for referral to a GCU. Although NGS is continuously less expensive,

cost-effectiveness studies for LS diagnostic strategies that incorporate these platforms are lacking.

Recommendation Different screening strategies for LS of all newly diagnosed CRC and EC can be considered including tumor tests for defective MMR function and/or high-level MSI and/or NGS tumor sequencing including *BRAF*.

In case of lack of expression of MLH1 and PMS2 by immunohistochemistry, *BRAF*V600E mutation and/or *MLH1* promoter hypermethylation should be carried out to rule out sporadic cases.

Patients with molecular profiles compatible with LS should be referred to GCU for appropriate counseling and NGS germline genetic testing.

In families with fulfillment of rBC or a ≥ 2.5% likelihood of LS on the PREMM₅ prediction model, prevalent and/or previous CRC and/or EC should follow the same screening procedure before considering referral to GCU (evidence level B, strength 1).
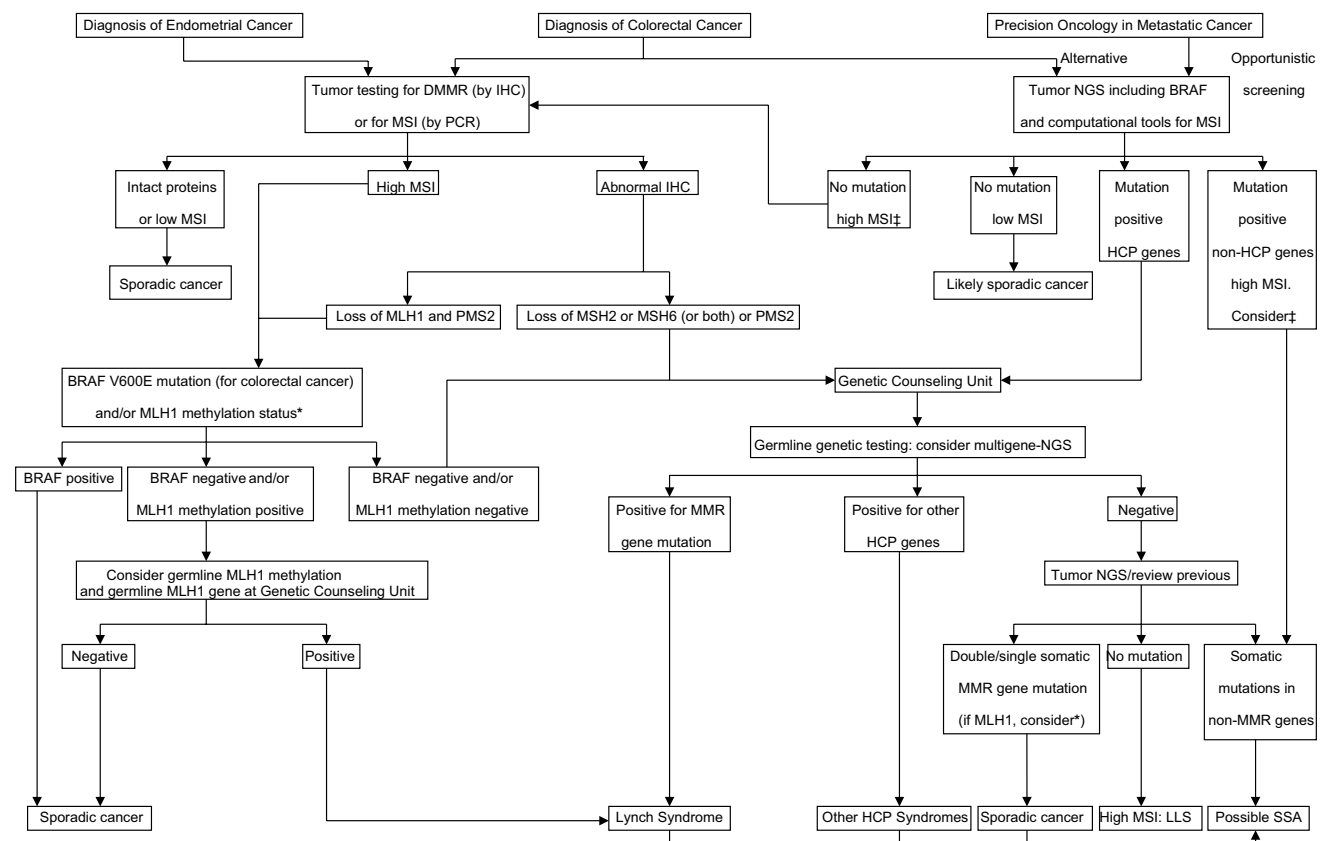

Fig. 1 Lynch Syndrome diagnostics. *HCP* hereditary cancer predisposition, *LLS* Lynch-like syndrome, *MMR* mismatch repair, *MSI* microsatellite instability, *NGS* next-generation sequencing, *SSA* secondary somatic alterations

Management of LS: cancer prevention

Screening and surgical management for CRC prevention

Prospective data with long-term follow-up demonstrate that early colonoscopy repeated frequently in LS carriers significantly reduces CRC incidence, CRC associated mortality, and overall mortality [30].

Recommendation Colonoscopies should be performed every 1–2 years for healthy individuals with LS, beginning at 20–25 years or 2–5 years before the youngest age at which CRC was diagnosed in the family if this occurred before 25 years (evidence level B, strength 1).

Risk of metachronous CRC is up to 62% at 30-year follow-up among patients with LS and segmental resection of the primary tumor [31]. In a meta-analysis of 6 studies (mean 9-year follow-up), rates of metachronous CRC were reduced by 3.4 times with subtotal colectomy, although a survival benefit was not found [32].

Recommendation Extended colonic resection may be an option for young patients with CRC, severe LS phenotype, good bowel function, no comorbidities, and compliance with endoscopic surveillance after surgery (evidence level A, strength 1).

Risk-reducing surgery for EC and ovarian cancer (OC)

Observational data have shown that hysterectomy and salpingo-oophorectomy have efficacy for prevention of EC and OC in women with LS, although it remains unclear whether surgery confers any survival benefit [33]. Psychological, cardiovascular, endocrinologic, skeletal, and sexual consequences of early onset menopause, and the risk burden associated with specific genes must be kept in mind to discuss the optimal timing of risk-reducing surgery.

Recommendation Risk-reducing hysterectomy and salpingo-oophorectomy at the completion of childbearing and/or since the early 40s (evidence level C, strength 1) should be considered.

Chemotherapeutic prevention

A long-term analysis in CAPP2 study demonstrated a marked reduction in CRC incidence (incidence rate ratio [IRR], 0.37 [95% CI 0.18–0.78], $p = 0.008$) and in any LS-associated cancer (IRR, 0.42 [95% CI 0.25–0.72], $p = 0.001$) among LS carriers who took aspirin at dose of 600 mg/day for 2 or more years compared with those randomly assigned to placebo [34].

Recommendation Daily aspirin can be considered for LS cancer prevention, although the ideal dose and duration of use are as yet undefined (evidence level A, strength 2).

Management of LS: specific issues on cancer treatment

Adjuvant chemotherapy with 5-fluorouracil did not result in a survival benefit in subgroup analyses of patients with stage II colon cancer with dMMR [35].

In patients with dMMR metastatic CRC and previous cytotoxic agents failure, anti-programmed death 1 (PD-1) antibody nivolumab resulted in objective response rate (ORR) of 31.1% (95% CI 20.8–42.9) (median follow-up time, 12.0 months) [36]. In the same setting, the combination of nivolumab plus ipilimumab (anti-cytotoxic T-lymphocyte antigen 4 antibody) reached an ORR of 55% (95% CI 45.2–63.8) (median follow-up time, 13.4 months), with progression-free survival and overall survival rates at 12 months of 71% and 85%, respectively, and a manageable treatment-related grade 3–4 toxicity in 32% of patients [37]. In dMMR cancers across 12 different histologies, ORR of 53% (95% CI 42–64) and complete responses in 21% of patients (median follow-up time, 12.5 months) were observed with anti-PD-1 antibody pembrolizumab [38].

Recommendation Adjuvant chemotherapy is not indicated in stage II LS-associated colon cancer (evidence level B, strength 1). Different immunotherapy options are valid for pretreated recurrent or metastatic LS-associated cancers (evidence level B, strength 1).

Familial adenomatous polyposis

Familial adenomatous polyposis (FAP) was first associated with mutations in the *APC*, and later in the *MUTYH*. Additional genes such as *POLE*, *POLD1*, *NTHL1*, *MSH3, GREM1* have been recently associated. Extracolonic manifestations may be present and help with the clinical diagnosis (Table 3).

APC-associated polyposis, FAP or AAP (OMIM 175100) [39, 40]

It is an autosomal dominant inherited disease caused by germline mutations (> 85% point mutations, 10–15% large rearrangements) in *APC* which encodes a protein with a significant role in the *Wnt*-β-catenin signaling. Up to 30% of carriers are due to de novo mutations or to somatic mosaicism. There are genotype–phenotype correlations. The clinical presentations are: (a) classic FAP, ≥ 100 polyps, appearing between 10 and 30 years, first located in rectum and sigma afterwards along the colon and development of CRC in almost 100% if untreated, at a mean age of 39 years. (b) Attenuated FAP (AFAP), < 100 polyps located in proximal colon and lesser risk of CRC, 70%, at a mean age of 50–55 years. (c) Gastric adenocarcinoma and proximal polyposis of the stomach (GAPP), none or few polyps in colon.

Table 3 Main characteristics of Adenomatous polyposis, Hamartomatous polyposis and Non-adenomatous PS

Syndrome and estimated prevalence	OMIM	Gene	Main distinctive features	Endoscopic management (2)	Evidence level grade recommendation
Adenomatous polyposis					
APC associated Familial Adenomatous Polyposis (1/11,300–37,600) (Jasperson KW et al., GeneReviews®, 2019)	#175100	APC	FAP ≥100 polyps AFAP <100 polyps (Adenomatous and hyperplastic polyps) Extracolonic expression: gastric fundic gland polyps, gastric and duodenal adenoma, osteoma, dental anomalies, CHRPE, thyroid, adrenal, sebaceous gland tumours, epidermoid cysts. Malignant tumors: gastric, duodenal (4–12%), pancreas (1%), small bowell, thyroid cribiform-morular variant of papillary type (1–12%), medulloblastoma (<1%), hepatoblastoma (1.6%)	FAP: flexible sigmoidoscopy or colonoscopy every 1–2 years (y), starting at age12–15 y. If adenomas are found at sigmoidoscopy, annual colonoscopy. AFAP: colonoscopy every 1–2 y starting at age 18–20 y	B.1
		Promoter 1B of APC	Non o fewer colonic adenoma >100 Gastric fundic gland polyps	Upper endoscopy (including complete visualization of the ampulla of Vater) starting at 25–30 y or at the time of diagnosis of colonic polyposis. Surveillance intervals based on Spigelman stage of duodenal polypos	B.1
MUTYH associated polyposis MAP (1:20,000–1:60,000) (Nielsen M et al., GeneReviews®, 2019)	#608456		FAP ≥100 polyps AFAP <100 polyps (Adenomatous, hyperplastic and serrated polyps)	Colonoscopy every 1–2 y, starting at 18–20 y	B.1 C.2
			Extracolonic expression: may be similar to APC associated polyposis Malignant tumors: Duodenal (4%), ovarian, bladder, breast, endometrial	Upper endoscopy starting at 30–35	C.2
Hamartomatous polyposis					
Peutz Jegher Syndrome (1 in 250,000) (MCGarrity et al., GeneReviews®, 2019)	#175200	STK11 (90%)	European consensus statement [Beggs et al 2010]: Two or more histologically confirmed PJS-type hamartomatous polyps. Any number of PJS-type polyps detected in one individual who has a family history of PJS in at least one close relative. Characteristic mucocutaneous pigmentation in an individual who has a family history of PJS in at least one close relative. Any number of PJS-type polyps in an individual who also has characteristic mucocutaneous pigmentation	Upper endoscopy plus small bowel examination (MR enterography or wireless capsule endoscopy) beginning at age 8 y or when symptoms occur every 1–3 y. Colonoscopy beginning at age 8 y every 1–3 y. Once the burden of gastrointestinal polyps has been established by endoscopy and imaging studies, prophylactic polypectomy of polyps >10 mm is recommended. Extragastrointestinal surveillance: breast, pancreatic, gynecologic, and testicular	C.1
Juvenile Polyposis S. (>1 in 100,000) (Larsen et al. GeneReviews®, 2019)	#174900	SMAD4 BMPR1A (50–60%)	Proband with any: > 5 JP of the colorectum; multiple JP throughout the GI tract; any number JP and a family history of JPS. Risk for GI cancers ranges from 9 to 50% (mainly CRC)	Colonoscopy Starting: 12–15 y Every 1–3 y Elective polypectomy for polyps > 10mm	C.1

Table 3 (continued)

Syndrome and estimated prevalence	OMIM	Gene	Main distinctive features	Endoscopic management (2)	Evidence level grade recommendation
PTEN Hamartoma Tumor S. (PHTS) Cowden & PTEN MATCHS S. (LLhermitte-Duclos, Proteus-like, Bannayan-Riley-Ruvalcaba S.) (3) (1 in 200,000)	#158350 #158350 #605309	PTEN	PTEN MATCHS S (DiLiberti, 1998): MATCHS: macrocephaly, autosomal dominant, thyroid disease, cancer, hamartomata, and skin abnormalities CRC risk (early-onset) in PTEN mutation-carrier cohorts: 9–16% PHTS Clinical Diagnostic Criteria (3) For referral to counselling units Cleveland Clinic Score ≥ 3% http://www.lerner.ccf.org/gmi/ccscore/	Colonoscopy starting 35 y, every 5 y Extragastrointestinal specific recommendations for thyroid, breast, endometrial, renal cancer and melanoma. No consensus for brain tumours	C.1
Gastrointestinal Ganglioneuromatosis (GN), Diffuse GN and Ganglioneuromatous polyposis (Matthews et al. 2013; OMIM UniSTS 2019)	NA	RET MEN 1 CDKN1B PTEN	Diffuse ganglioneuromatosis is commonly associated with Neurofibromatosis Type 1, Multiple Endocrine Neoplasia Type 2b, and Cowden Syndrome	Not established Based on individual risk and specific hereditary syndrome if identified Extragastrointestinal surveillance as appropriate for specific hereditary syndromes	C.1
Unexplained hamartomatous mixed polyposis (Sweet et al. 2005; Gilad et al. 2019)	NA	ENG BMPR1A SMAD4 STK11	Significant overlap and redundancy in the clinical, endoscopic, and histologic findings, which may lead to improper diagnosis and management if genetic diagnosis is withheld (Sweet et al. 2005; Gilad et al. 2019)	Not established It is suggested based on individual risk including genetic risk if known	C.1
Serrated polyposis					
Serrated Polyposis S. (SPS) (Snover et al. 2010; WHO 2019)	NA	No germline mutation identified	Defined by WHO 2019 Criterion 1: ≥ 5 serrated lesions/polyps proximal to the rectum, all being ≥ 5 mm in size, with ≥ 2 being ≥ 10mm in size Criterion 2: > 20 serrated lesions/polyps of any size distributed throughout the large bowel, with ≥ 5 being proximal to the rectum The number of polyps to fulfil the definition of SPS is cumulative over colonoscopy surveillance	Colonoscopy: yearly: after ≥ 1 advanced polyp or ≥ 5 non advanced clinically relevant polyps; 2 y: after no advanced polyps and < 5 nonadvanced Clearing/surveillance phase: remove all polyps ≥ 5mm and all polyps of any size with optical suspicion of dysplasia Colonoscopy screening program for FDR should be offered (Hazewinkel Y et al, 2015)	C.1
Sessile Serrated Polyposis Cancer S. (SSPCS) (OMIM, 2019)	#617108	RNF43	Defined by WHO based on the presence of multiple sessile serrated polyps (OMIM #617108) Lifetime risk CRC: 54% and may have a strong personal or family history of extracolonic cancers FDR: 32% risk of developing multiple serrated polyps and a 5-fold increased risk CRC. An increased risk of pancreatic cancer has also been observed (Gala et al. 2014)	Colonoscopy: 1 year: after ≥ 1 advanced serrated polyp or ≥ 5 non advanced clinically relevant polyps; 2 years: after no advanced polyps and < 5 non-advanced Clearing/surveillance phase: remove all polyps ≥ 5mm and all polyps of any size with optical suspicion of dysplasia	C.1
Mixed polyposis and Hereditary MPS (2, 4, MCGarrity et al., GeneReviews®, 2019)	#601228 #610069	GREM1 BMPR1A	Multiple types of colorectal polyps including juvenile and adenomatous polyps and increased risk for CCR some families with mixed hereditary polyposis syndrome have SMAD4 pathogenic variants	Not established It is suggested based on individual risk including genetic risk if know	C.1

MUTYH-associated polyposis, MAP (OMIM 608456) [39, 41]

It is an autosomal recessive disease caused by bi-allelic, homozygous or compound heterozygous, germline mutations (> 99% point mutations, < 1% large rearrangement) in *MUTYH* which encodes a glycosylase of DNA base excision repair system. Somatic G:C to T:A transversions result in genes implicated in CRC carcinogenesis, such as *APC* or *KRAS*. The most frequent phenotype is AFAP, at a mean age of 45 years, but maybe classic FAP, serrated polyposis and few individuals develop CRC without polyposis. Genotype–phenotype correlation has been described. The risk of CRC is 43–100% at the age of 50 years.

For the study of FAP, single gene testing has been the traditional approach, but the use of a multigene panel should be specially considered in attenuated FAP.

Recommendation Criteria for referral to a GCU and *APC/MUTYH* or multigene panel testing (evidence level B, strength 1):

1. Patients with > 10 synchronous adenomatous colonic polyps histologically confirmed.
2. Family history of adenomatous colonic polyps (> 10 in > 1 relative), at young age and extracolonic manifestations.
3. Gastric polyps (> 100), in body and fundus, preponderantly fundic glands polyps. Proton pump inhibitor use must be excluded.
4. Consider in: hepatoblastoma, desmoid tumor, cribriform-morular variant of papillary thyroid carcinoma, multifocal or bilateral congenital hypertrophy of retinal pigmented epithelium.
5. Known familial mutation in at-risk relatives.

Colorectal surveillance

In classical FAP, flexible sigmoidoscopy or colonoscopy should be carried out every 1–2 years, starting at age 12–15 years. If adenomas are found at sigmoidoscopy, then it should be annual colonoscopy [43]. In AFAP, colonoscopy should be performed every 1–2 years starting at age 18–20 years and surgery is indicated if there is a high number of adenomas. In MAP, colonoscopy should be performed every 1–2 years, starting at 18–20 years and if polyps cannot be controlled endoscopically, colectomy should be considered [43, 44]. For *MUTYH* heterozygote, colonoscopy should be performed every 5 years, beginning at age 40 years or 10 years prior to age of first-degree relative's age at CRC diagnosis [42, 44].

Recommendation Surgery is indicated if there is a high number of adenomas or a high degree of dysplasia (evidence level B, strength 1).

Surgical options of colon and rectum

Surgical options in FAP patients are total abdominal colectomy with ileorectal anastomosis (TAC/IRA) or total proctocolectomy with pouch anal anastomosis (TPC/IPAA) [42–44]. Surveillance of rectum depends on the type of surgery [42, 43].

Recommendation TPC/IPAA or TAC/IRA should be carried out depending on age, severity of rectal polyposis and risk of developing desmoids. In FAP, it is usually recommended in the 2nd decade of life (evidence level B, strength 1). IPAA is generally recommended for FAP, and IRA for AFAP and MAP. Afterwards, surveillance of the rectum should be carried out every 6–12 months if rectal tissue remains, and every 1–3 years if ileoanal pouch is present, depending on polyp burden (evidence level B, strength 1).

Extracolonic manifestations

For gastroduodenal adenomas, upper endoscopy (including complete visualization of the ampulla of Vater) should be performed starting at 25–30 years or at the time of diagnosis of colonic polyposis [43]. Surveillance intervals are based on the Spigelman's stage of duodenal polyposis: 0 (no polyposis): 4 years; I (1–4 tubular adenomas, 1–4 mm): 2–3 years; II (5–19 tubular adenomas, 5–9 mm): 1–3 years; III ($\geq 20, \geq 1$ cm): 6–12 months; and IV (dense polyposis or high grade): surgery [42, 44]. Duodenal adenomas are managed by endoscopic polypectomy, although duodenectomy or duodenal pancreatectomy may be necessary in advanced cases [43].

Patients with classical FAP have a lifetime thyroid cancer risk of 2–6% and annual surveillance is recommended [42, 44].

Treatments for desmoid tumors are surgery, non-steroid anti-inflammatory drugs (NSAIDs), anti-oestrogen agents, chemotherapy, imatinib, sorafenib, pazopanib and radiotherapy [44].

The absolute risk for hepatoblastoma in FAP is estimated at less than 2% and it occurs prior to the age of 3 years [42].

Recommendation Surveillance of duodenal adenomas is based on the Spigelman's stage (evidence level B, strength 1). In MAP, upper endoscopy is recommended at 30–35 years (evidence level C, grade 2). For thyroid cancer, annual thyroid examination and thyroid ultrasound should start at 25–30 years (evidence level C, strength 2). For desmoid tumors, annual abdominal palpation and magnetic resonancy (MRI) or computer tomography (CT) scan should be done within 1–3 years post-colectomy and then every 5–10 years (evidence level C, strength 2); also surgery should be reserved for small, well-defined tumors, and if a

Table 4 Refering to clinical genetics for CRC

Identifying individual with hereditary colorectal cancer syndromes	Colorectal cancer syndromes	Evidence levels	Strength of recommendation
Colorectal or endometrial cancer diagnosed < 50 years Colorectal or endometrial cancer and another synchronous or metachronous Lynch syndrome-related cancers[a] Colorectal or endometrial cancer and ≥ 1 first–second-degree relative (FSDR) with Lynch syndrome-related cancers[a] Family history of ≥ 1 first-degree relative (FDR) with colorectal or endometrial cancer diagnosed < 50 years Family history of ≥ 2 FDR or FSDR with Lynch syndrome-related cancer[a] regardless of age at diagnosis Colorectal or endometrial cancer at any age showing evidence of mismatch repair deficiency (MMR), either by microsatellite instability or loss of MMR protein expression	Lynch syndrome	C	1
> 10 adenomatous polyps	APC-associated polyposis conditions[b] MUTYH-associated polyposis	C	1
≥ 2 hamartomatous polyps	Peutz–Jeghers syndrome PTEN hamartoma tumor syndrome[c] Juvenile poliposis syndrome	C	1
≥ 5 serrated polyps proximal to the sigmoid colon	Serrated polyposis syndrome	C	1

[a]Lynch syndrome-related cancers: colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvis, brain, small intestinal cancer and sebaceous adenoma, sebaceous carcinoma, keratoacanthoma

[b]APC-associated polyposis conditions: familial adenomatous polyposis, attenuated familial adenomatous polyposis

[c]PTEN hamartoma tumor syndrome: Cowden syndrome, Bannayan–Riley–Ruvalcaba syndrome, PTEN-related proteus syndrome, proteus-like syndrome

clear margin can be obtained (evidence level B, strength 2). For hepatoblastoma, consider liver palpation, abdominal ultrasound and alpha-fetoprotein (AFP) measurement every 3–6 months before 5 years (evidence level C, strength 2).

Chemoprevention

The use of NSAIDs (sulindac or celecoxib) has been shown to reduce the number and extent of CRC and duodenal adenomas, but without the clinical benefit of decrease in cancer risk [42, 43]. Due to the cardiovascular risk of NSAIDs, no drug has been approved.

Recommendation The use of NSAIDs to prevent CRC and duodenal adenomas needs to be balanced with the side effects (evidence level A, strength 2).

Hamartomatous polyposis and other non-adenomatous polyposis

There are several classifications for hereditary syndromes with polyposis; one of the most accepted distributes them into four large groups: adenomatous, hamartomatous, serrated and mixed polyposis [45].

These PS are very rare with the exception of serrated polyposis syndrome (SPS); the estimated incidence for PTEN hamartoma tumor syndrome is 1 in 200,000–250,000; for

Peutz–Jeghers syndrome it is 1 in 250,000; for juvenile polyposis syndrome it is from 1 to 1.6 in 100,000. The SPS prevalence is higher than for other PS, including FAP; overall, its seems lower than 0.09–42 in 10,000 in colonoscopy-based CRC screening programs, but it is considerably higher in positive fecal occult blood test populations, with estimates of 0.34–0.66% or 31–80 in 10,000 [46–51]. Sessile serrated polyposis cancer syndrome (SSPCS) is a very rare disorder caused by heterozygous mutation in the *RNF43* gene [49]. While most SPS cases are sporadic, evidence suggests that this syndrome exhibits a genetic component at least occasionally. The higher prevalence of CRC and serrated polyps in first-degree relatives (FDRs) as compared to the general population supports this theory.

Table 3 summarizes the main characteristics and recommendations of surveillance of Adenomatous polyposis, Hamartomatous polyposis and Non-adenomatous PS according to recommendations of the European Society of Gastrointestinal Endoscopy (ESGE) Guideline [46] or, in the rest of the cases, suggested by other referenced authors.

Multigene panel testing in familial CRC

The introduction of NGS technologies for the genetic diagnosis of hereditary cancer predisposition syndromes represents a surpassing progress in the knowledge of this field. Multigene panel testing allows the simultaneous analysis

Table 5 List of genes associated to CRC and polyposis with their classification attending to their strength of evidence and the risk level

Gene	Disease entity (inheritance)	Strength of evidence/classification			Notes	Risk level [53]
		ClinGen [54]	NCCN [53]	Lorans et al. [55]		
APC	Familial adenomatous polyposis (AD)	Definitive	Well established	Established		High
AXIN2	AXIN2-related attenuated familial adenomatous polyposis (AD)	Moderate	Not well established	Strong		Uncertain—presumed high risk from limited case reports
BLM	CRC/polyposis susceptibility (AD)	Definitive	Not well established	Limited		Uncertain—none to low
BMPR1A	Juvenile polyposis syndrome (AD)	Definitive	Well established	Established		High
EPCAM	Lynch syndrome (AD)	Definitive	Well established	Established	Genetic evidence for 3'UTR deletions/exonic deletions at 3'end of *EPCAM* [53]	High
GREM1	Hereditary mixed polyposis syndrome (AD)	Strong	Not well established	Established	Genetic evidence for single tandem duplications upstream of *GREM1* [53]	Uncertain—presumed high risk from limited case reports
MLH1	Lynch syndrome (AD)	Definitive	Well established	Established		High
MSH2	Lynch syndrome (AD)	Definitive	Well established	Established		High
MSH6	Lynch syndrome (AD)	Definitive	Well established	Established		High
MUTYH	MUTYH-associated polyposis (AR)	Definitive	Well established	Established	Moderate genetic evidence for CRC risk in *MUTYH* monoallelic carriers (based on case–control studies) [53]	High
NTHL1	NTHL1-related attenuated familial adenomatous polyposis (AR)	Moderate	Not well established	Strong		Uncertain—presumed high risk from limited case reports
PMS2	Lynch syndrome (AD)	Definitive	Well established	Established		High
POLD1	CRC/polyposis susceptibility (AD)	Definitive	Not well established	Strong	Genetic evidence for missense substitutions in the exonuclease domain [53]	Uncertain—presumed high risk from limited case reports
POLE	CRC/polyposis susceptibility (AD)	Definitive	Not well established	Strong	Genetic evidence for missense substitutions in the exonuclease domain [53]	Uncertain—presumed high risk from limited case reports
PTEN	PTEN hamartoma tumor syndrome (AD)	Definitive	Well established	Established		Moderate–high
SMAD4	Juvenile polyposis syndrome (AD)	Definitive	Well established	Established		High
STK11	Peutz–Jeghers syndrome (AD)	Definitive	Well established	Established		High
TP53	Li–Fraumeni syndrome	Limited	Well established	Moderate	CRC and polyposis are possible rare manifestations of Li–Fraumeni syndrome [53, 55]	High

In bold letter, genes with concordant classification among the three sources of information (with strong higher-ranking evidences). Underlined letter, genes with discordant classification, with at least one of the sources considering not well established, moderate or limited

of multiple genes by NGS increasing the diagnostic yield, reducing the response times in a cost-effective manner, when compared to iterative single gene or phenotype-driven testing [52]. On the other hand, there is a higher chance of identifying variants of uncertain significance that are not actionable, or variants for which clinical management is uncertain such as finding a pathogenic variant in a moderate risk gene [53].

There is a high variability in the genes included across the multigene panels for CRC. Although a batch of genes considered clinically actionable with quantified magnitude of risk are present in virtually all panels, there is a significant amount of genes that lack comprehensive validation or have less evidence of association with CRC/polyposis and consequently minimal clinical utility, that are included in many multigene panels. In fact, recent data from the ClinGen Clinical Validity framework show that < 60% of the genes on clinically available panels have strong or definitive evidence of association with hereditary colorectal cancer or polyposis, and > 40% have only moderate, limited, disputed, or refuted evidence [54].

The current lack of consensus regarding inclusion of genes in CRC panels represents a challenge in patient counseling and management (Table 4). There is an urgent need to provide consensus on the genes included in multigene panels. This consensus should be based on structured assessment of the clinical relevance of the genes, with standardized reporting and clinical management guidelines [55].

For the current guidelines, we have reviewed the available information from reputable sources with expert panels to define strength of evidence and evaluate the clinical utility of genes associated with CRC and polyposis. Therefore, we considered the following sources: (i) the NCCN Guidelines for colorectal cancer v1.2019 [53], (ii) ClinGen Clinical Validity framework [54] and (iii) Lorans et al.'s review [55]. The applied criteria to evaluate the level of validation are slightly different among them with some discordant results. In Table 5, the list of genes considered to have strong higher-ranking evidences for their association to hereditary forms of CRC/polyposis in at least one of the considered sources is shown. The total number of included genes is 18. Eleven genes have fully concordant classification among the three sources: *APC*, *BMPR1A*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *PMS2*, *PTEN*, *SMAD4* and *STK11*, while seven genes show discordant classification: *AXIN2*, *BLM*, *GREM1*, *NTHL1*, *POLD1*, *POLE* and *TP53*. Multigene panel testing for hereditary CRC and polyposis is a rapidly evolving landscape. A periodical review and consequent actualization of panels, if necessary, is recommended.

Recommendation Multigene panel testing for hereditary CRC and polyposis should include the genes:

- *APC*, *BMPR1A*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *PMS2*, *PTEN*, *SMAD4* and *STK11* (evidence level A, strength 1).
- *AXIN2*, *BLM*, *GREM1*, *NTHL1*, *POLD1*, *POLE* and *TP53* (evidence level B, strength 2).

Compliance with ethical standards

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