Annals of Oncology 24 (Supplement 6): vi73–vi80, 2013
doi:10.1093/annonc/mdt209
Published online 27 June 2013

Familial risk-colorectal cancer: ESMO Clinical Practice Guidelines†

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These Clinical Practice Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO)

Lynch syndrome

prevalence and penetrance of mismatch repair gene mutations

Lynch syndrome is the most common hereditary colorectal cancer (CRC) syndrome and it accounts for ∼1%–3% of all CRC burden [1]. The syndrome is transmitted with an autosomal-dominant pattern, and it is associated with mutations in the mismatch repair (MMR) genes, *MLH1, MSH2, MSH6* and *PMS2.* These alterations lead to tumour DNA microsatellite instability (MSI) and foster inactivating mutations in tumour suppressors containing microsatellites in the coding regions (i.e. *TGFBR2* and *BAX*) [2]. Mutations in the MMR genes may lead to a loss of expression of the corresponding protein and be detected by immunohistochemistry techniques (IHCs) [3, 4].

Overall, mutation carriers mainly have an increased risk of CRC (lifetime risk 30%–70%) and endometrial cancer (lifetime risk 30%–60%) [1]. Individuals with Lynch syndrome also have an elevated risk of developing cancers of the urinary tract (8%), small intestine, ovary (4%–12%), gastric, pancreas (4%), biliary tract, brain and skin [5]. A genotype–phenotype correlation has been observed in which *MLH1* mutation carriers are at higher risk of young onset CRC cancer, *MSH2* at higher risk of extracolonic cancers, *MSH6* at increased risk of endometrial cancer, and *PMS2* carriers show a lower absolute lifetime risk of CRC and endometrial cancer (15%–20%) compared with other mutation carriers [6] (Figure 1).

The term Turcot syndrome refers to patients with MMR gene mutations and brain tumours, and the term Muir–Torre syndrome to patients with cutaneous gland tumours (keratoacanthomas, sebaceous adenomas or adenocarcinomas).

referral for molecular screening and mismatch repair gene testing

Several clinical criteria were developed for the clinical suspicion of Lynch syndrome, such as the Amsterdam criteria and the revised Bethesda guidelines (Table 1) [2–4, 7, 8]. Nevertheless, several studies report that the Amsterdam criteria lack sensitivity and specificity for identification of individuals with Lynch syndrome and some studies have shown that the Bethesda guidelines may miss between 6% and 25% of mutation carriers [3]. Since >90% of Lynch syndrome CRC cases show MSI and/or loss of the corresponding protein by IHC, upfront molecular screening might be a good strategy to identify candidates for germline testing. Recently, a pooled-data analysis of four large population-based cohorts of CRC probands has shown that universal screening of CRC with tumour MMR testing was more sensitive than the Bethesda guidelines (100% versus 87.8%) [9]. On the other hand, the strategy of selecting patients younger than 70 years, along with those older than 70 years fulfilling one of the Bethesda guidelines, missed only 4.9% of Lynch syndrome cases, resulted in 34.8% fewer cases of MMR tumour testing, and 28.6% fewer cases undergoing germline genetic testing than universal screening. This strategy should be considered for clinical purposes, as the diagnostic yield was similar to universal screening (2.1% versus 2.2%) [III, B].

Regarding MMR tumour testing, MSI analysis is equivalent to IHC for case finding. The advantage of IHC is that it may direct germline mutation analysis because loss of expression of a protein is suggestive of an underlying genetic defect. If a tumour with MMR deficiency is detected, germline genetic testing would be indicated. Nevertheless, in ∼10%–15% of sporadic CRC cases, MSI and loss of expression of MLH1 are due to hypermethylation of the *MLH1* gene promoter [10].

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†Approved by the ESMO Guidelines Working Group: August 2006, last update May 2013. This publication supersedes the previously published version—Ann Oncol 2010; 21 (Suppl. 5): v78–v81.

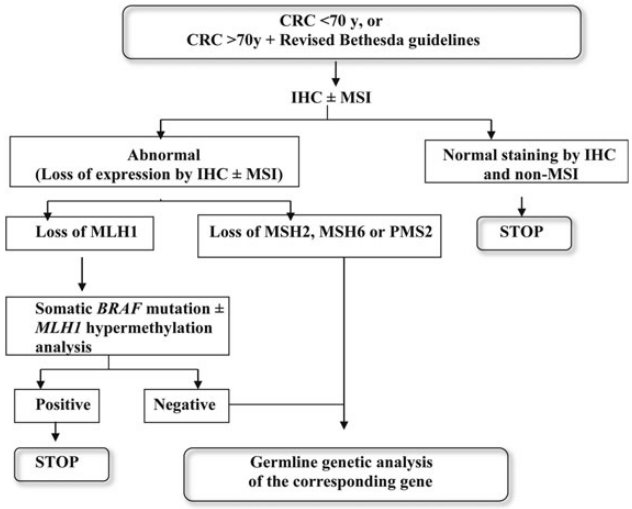

Figure 1. Algorithm for molecular diagnosis of Lynch syndrome.

Table 1. The Revised Bethesda Guidelines for testing colorectal tumours for microsatellite instability (MSI) [2]

Tumours from individuals should be tested for MSI in the following situations:

1) Colorectal cancer diagnosed in a patient who is <50 years of age.
2) Presence of synchronous, metachronous colorectal or other Lynch-associated tumours,[a] regardless of age.
3) Colorectal cancer with the MSI-H histology[b] diagnosed in a patient who is <60 years of age.[c]
4) Colorectal cancer diagnosed in one or more first-degree relatives with a Lynch-related tumour, with one of the cancers being diagnosed under age 50 years.
5) Colorectal cancer diagnosed in two or more first- or second-degree relatives with Lynch-related tumours, regardless of age.

[a]Lynch syndrome-related tumours include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract and brain (usually glioblastoma as seen in Turcot syndrome) tumours, sebaceous gland adenomas and keratoacanthomas in Muir–Torre syndrome, and carcinoma of the small bowel.
[b]Presence of tumour infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation or medullary growth pattern.
[c]There was no consensus among the workshop participants on whether to include the age criteria in guideline 3 above; participants voted to keep <60 years of age in the guidelines.
Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst. 2004 Feb 18; 96(4): 261–268.
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These sporadic cases are also frequently associated with the somatic *BRAF V600E* mutation. Therefore, if loss of MLH1/PMS2 expression is observed, analysis of the methylation of the *MLH1* promoter in the tumour or analysis for somatic *BRAF V600E* mutation should be performed first [III, B]. On the other hand, analysis of constitutional *MLH1* epimutations should be considered in a patient with suspected Lynch syndrome with loss of MLH1/PMS2 expression if no germline mutation is identified in the *MLH1*gene [III, B] [11].

Prediction models that estimate the likelihood of finding a MMR gene mutation constitute an effective clinical tool to identify individuals at risk of Lynch syndrome which may help in clinical decision-making for referral and germline genetic testing, especially in cases when no tissue is available from any CRC patient in the family [III, B] [7, 12].

mutation detection

Approximately 80% of mutations are located in the *MLH1* and *MSH2* genes, ∼10%–12% in the *MSH6* gene, and *PMS2* may account for 2%–3% [1]. Deletion of 3′*EPCAM* leading to subsequent somatic hypermethylation of *MSH2* may account for up to 20% of the tumours with loss of expression of MSH2 [13]. Pathogenic genetic alterations might be frameshift, nonsense or splice site mutations that lead to truncating or unstable proteins, but large deletions and rearrangements are also common. Therefore, full germline genetic testing should include both DNA sequencing and large rearrangement analysis [III, A].

risk reduction: non-surgical preventive options

surveillance

Studies have shown that the adenoma-carcinoma sequence is faster in patients with Lynch syndrome. Colonoscopy at 3-year intervals has demonstrated reduction in CRC incidence and CRC-related mortality [III] [14]. However, cancers occurring during this interval have been detected in observational studies. We recommend initiating colonoscopy at age 20–25 years and repeating every 1 to 2 years [III, C]. No specific upper limit is established, and it should be based on the individual's health status.

Endometrial and ovarian cancer screening may be carried out on an annual basis from age 30–35 years with gynaecological examination, pelvic ultrasound, Ca125 analysis and aspiration biopsy [III, C].

For gastric cancer, the search for the presence of *Helicobacter Pylori* and subsequent eradication is recommended in mutation carriers. In case of a high incidence of gastric cancer in some populations, some experts recommend upper gastrointestinal endoscopy every 1–3 years.

Surveillance for other Lynch-associated cancers is not recommended due to the low sensitivity and specificity of the surveillance techniques [IV, C].

chemoprevention

Recent data from the Colorectal Adenoma/Carcinoma Prevention Program (CAPP2) have shown in a randomised, placebo-controlled trial a significant 60% reduction in the incidence of CRC and other Lynch syndrome-associated cancers among those using 600 mg of aspirin per day for at least 2 years [15]. The rate of adverse events among patients taking

aspirin or placebo did not differ. This study, along with earlier data, supports the use of aspirin in the chemopreventive treatment of patients with Lynch syndrome, although the dose and timing of use have not been established [I, C].

risk reduction: prophylactic surgical options

prophylactic colectomy

There are no data to support carrying out a prophylactic colectomy in healthy mutation carriers and it is not recommended [IV, D].

prophylactic hysterectomy and bilateral salpingo-oophorectomy

A retrospective observational study showed an absence of gynaecological cancers in women with Lynch syndrome who underwent a prophylactic hysterectomy and/or bilateral salpingo-oophorectomy, compared with a 33% and a 5% incidence of endometrial and ovarian cancer, respectively, among women who did not have surgery [16]. Prophylactic gynaecological surgery might be an option in female carriers from age 35 and after childbearing is completed [IV, C].

cancer treatment

colorectal surgery

In Lynch syndrome there is an increased risk of synchronous and metachronous CRC. A 16% risk of developing a second CRC after 10 years of follow-up has been reported. Therefore, the need for intensive surveillance after surgery versus the option of an extended colectomy should be discussed at the time of diagnosis of a CRC, especially in young patients [IV, C].

chemotherapy

Although some preclinical and clinical data suggest that the MSI status may play a role as a predictive factor of chemosensitivity (i.e. resistance to 5-fluorouracil and sensitivity to irinotecan), current evidence does not allow definitive recommendations to be given regarding chemotherapy regimens based on the MSI status [II, C] [17, 18]. Studies that have assessed the impact of MSI status in the adjuvant setting were based on chemotherapy regimens which differ from current standard practice and, therefore, do not translate into clinical practice.

familial colorectal cancer X syndrome

This syndrome represents the 40% of families who fulfil the Amsterdam-I criteria and who do not exhibit tumour MMR deficiency or a germline MMR gene defect [19]. The cancer risk in these families seems to impact only the colorectum, and the genetic basis has not been identified. Surveillance would include colonoscopy at 3–5 year intervals, starting 5–10 years earlier than the age at diagnosis of the youngest case in the family [IV, C].

APC-associated familial adenomatous polyposis

Familial adenomatous polyposis (FAP) is an autosomal-dominant disorder characterised by the presence of multiple adenomas distributed in the colon and rectum [1]. It is responsible for ≤1% of all CRC cases.

In many patients, extracolonic manifestations are present, in particular gastric and duodenal polyps, desmoid tumours, thyroidal and brain tumours, osteomas, congenital hypertrophy of the retinal pigmented epithelium, supernumerary teeth and epidermoid cysts among others [20]. Combination of colorectal and extracolonic manifestations is known as Gardner's syndrome, whereas association between the colorectal polyposis and brain tumours corresponds to Turcot's syndrome.

diagnosis

Clinical diagnosis of classical FAP is based on the identification of more than 100 colorectal adenomas. Attenuated FAP (AFAP) is characterised by the presence of fewer adenomas and a later onset of the disease. Clinical definition of AFAP is controversial and should be considered in any patient with 10–99 adenomas, although a precise diagnosis is often difficult in a single patient [21]. *APC*-associated AFAP can mimic *MUTYH*-associated polyposis (MAP, see below) or even sporadic polyp development. Examination of multiple family members can often determine the phenotype.

genetics

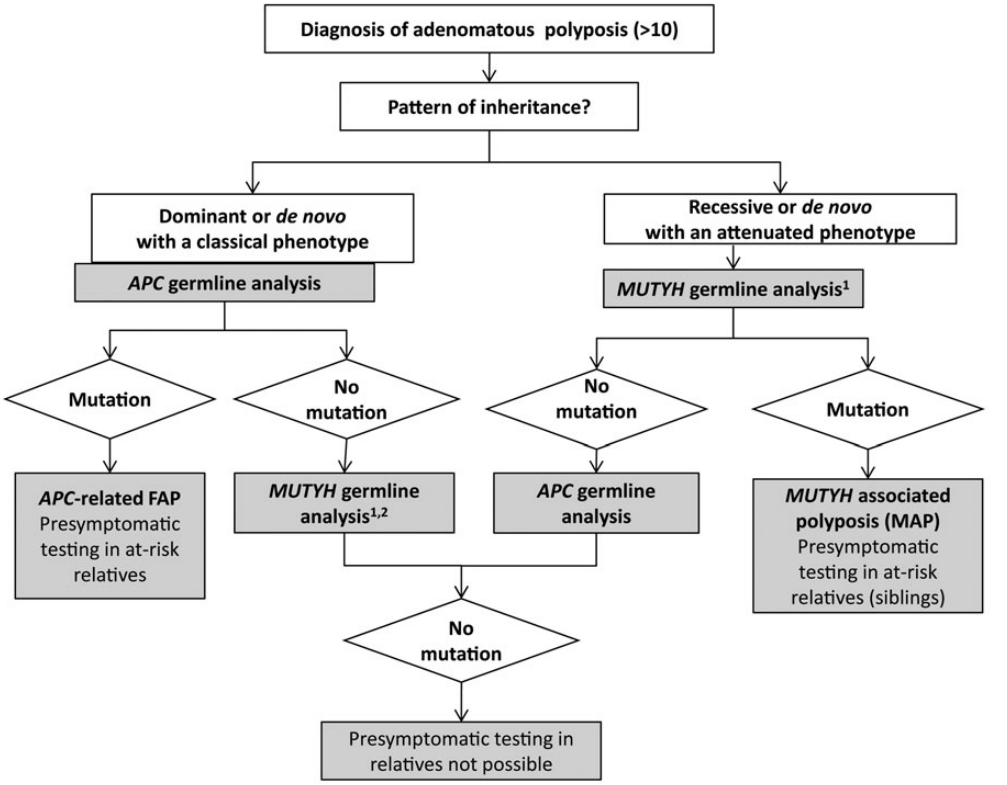
In a recent large cross-sectional study, APC mutations were found in 80% (95% CI, 71%–87%) of individuals with more than 1000 adenomas, 56% (95% CI, 54%–59%) in those with 100–999 adenomas, 10% (95% CI, 9%–11%) in those with 20–99 adenomas and 5% (95% CI, 4%–7%) in those with 10–19 adenomas [22]. There is a genotype–phenotype correlation with potential implications for clinical management (i.e. mutations between codons 1250 and 1464, especially those in codon 1309, are associated with a severe form). In 30%–40% of cases, no family history of FAP is present, thus suggesting a *de novo* origin.

Gene testing should commence by investigating an affected individual. If the causative mutation is detected, then presymptomatic diagnosis can be offered to at-risk family members (Figure 2).

screening

CRC screening is justified by the disease's high penetrance, since virtually all patients with classic FAP will develop a carcinoma at the age of 40–50 years if the colon is left in place [23]. CRC penetrance in AFAP is incomplete, and tumours usually appear at the age of 50–60 years if no intervention is done. Gene testing allows carrying out the most cost-effective screening by driving colorectal examinations to gene carriers. However, when the causative mutation is not identified, all at-risk family members should undergo colorectal screening.

In families with classic FAP, flexible sigmoidoscopy is an adequate technique because of the almost universal distribution of adenomas [23]. This examination should be carried out every



[1] Germline testing of *MUTYH* can be initiated by the screening for the most common mutations (G396D, Y179C) in Caucasian populations, followed by analysis of the entire gene in heterozygotes. If common mutations are not present consider sequencing the entire gene in cases with high suspicion.
[2] A dominant pattern may be seen between a biallelic mutation carrier and a heterozygous mutation carrier (1%-2% of the general population).

Figure 2. Algorithm for genetic diagnosis in Polyposis syndromes.

2 years, starting at the age of 12–14 years and be continued lifelong in mutation carriers. In at-risk individuals from families without an identified *APC* mutation, surveillance should be carried out every 2 years until age 40, every 3–5 years between 40–50 years, and may be discontinued at age 50 if no polyposis has developed. Once adenomas are detected, colonoscopy should be carried out annually until colectomy is planned (see Surveillance) [III, A].

In AFAP cases, since adenomas can be localised in the right colon, colonoscopy is recommended instead of sigmoidoscopy [23]. In this setting, examination should be carried out every 2 years until polyposis is diagnosed. Screening should start at the age of 18–20 years and continue lifelong because of the more heterogeneous penetrance of AFAP. Again, once adenomas are detected, colonoscopy should be carried out annually (see Surveillance) [III, B].

Screening for extracolonic manifestations should start when colorectal polyposis is diagnosed or at the age of 25–30 years, whichever comes first.

Gastroduodenal endoscopy using both front and side-view scopes, with special attention to the papillary area, should be carried out every 5 years until adenomas are detected [III, B] [24, 25]. Although high-resolution endoscopy, chromoendoscopy or narrow band imaging improve the quality of endoscopic imaging, the benefit of adding these techniques for the evaluation of duodenal adenomatosis is uncertain [IV, C] [26]. Since gastrointestinal adenomas may also develop in the jejunum and ileum, it has been suggested to carry out regular screening by barium contrast series or wireless capsule endoscopy [IV, C]. Screening for thyroid cancer should be carried out with annual cervical ultrasonography [IV, C]. Development of desmoid tumours is mainly related to a positive family history and abdominal surgery. In this setting, regular physical examination and abdominal computed tomography (CT) or magnetic resonance imaging (MRI) should be carried out [IV, B]. Screening for other extracolonic manifestations is not justified because of their low prevalence and/or limited clinical impact.

treatment

The goal of colorectal therapy is to prevent CRC and includes both endoscopic polypectomy and surgery. Whereas surgical resection is the standard of care in patients with classical FAP, the former can be considered in some patients with AFAP. Most patients with classical FAP undergo surgery between the age of 15 and 25 years.

Surgical resection includes both proctocolectomy with ileal pouch-anal anastomosis (IPAA) and total colectomy with ileorectal anastomosis (IRA). IRA is a relatively simple and straightforward operation, compared with IPAA. The complication rate is low, and the bowel function after surgery is usually good. For IPAA, more extensive surgery is needed (including pelvis dissection), causing reduction of fertility and worse bowel function. The decision on the type of surgery depends on many factors including age, severity of polyposis (i.e. involvement of the rectum), risk of developing desmoids,

the wish to have children and the site of the mutation (see above). When a diffuse distribution or severe phenotype is present, IPAA is recommended. On the contrary, when no or only scarce adenomas are detected in the rectum and a mild familial phenotype is observed, including AFAP, total colectomy with IRA can be carried out. Because of the need of endoscopic surveillance of the rectum in the latter context (see below), proctocolectomy should be considered in patients reluctant to undergo regular follow-up [III, B].

Duodenal adenomas are usually managed with endoscopic polypectomy based on the Spigelman stage (see Surveillance) [25]. In patients with advanced duodenal disease (Spigelman stage III/IV, see below), intensive surveillance and treatment may lead to reduction of duodenal cancer-related mortality [IV, B]. Surgical options include duodenotomy with polypectomy, pancreas-sparing duodenectomy and duodenal-pancreatectomy [23].

Because of the high recurrence rate of desmoid tumours, surgical resection should be delayed unless complications appear. The first line of treatment in patients with large or growing intra-abdominal or abdominal wall tumours is sulindac (300 mg), usually in combination with tamoxifen (40–120 mg), toremifene (180 mg) or raloxifene (120 mg) [III, C]. In patients with progressive intra-abdominal tumours that do not respond to this treatment, chemotherapy (e.g. doxorubicin and dacarbazine or methotrexate and vinblastine) or radiation therapy is indicated. [III, B] [23]. The role of surgery in intra-abdominal desmoids is controversial [III, B].

surveillance

The risk of rectal adenoma and cancer remains after colectomy with IRA and even in the pouch after IPAA. Accordingly, regular endoscopic surveillance every 12 months after surgery is needed to detect adenoma recurrence early. Some patients with AFAP can be conservatively managed with annual colonoscopy and polypectomy [III, B].

Surveillance of duodenal adenomatosis will depend on its extension based on the Spigelman classification, since the risk of cancer appears to be related to stage. When it corresponds to Spigelman stage I or II, upper endoscopy can be carried out every 5–3 years, respectively, whereas in more advanced forms, intervals between examinations should be shortened to every 1 to 2 years (Spigelman stage III) or to 6 months (Spigelman IV) [III, B] [23].

chemoprevention

Primary chemoprevention has never been demonstrated to delay the appearance of FAP.

Secondary chemoprevention with the use of non-steroidal anti-inflammatory drugs has been shown to reduce the number and extent of colorectal adenomas and, less reliably, duodenal adenomas. Accordingly, sulindac and celecoxib can be considered as adjuvant treatment when adenoma recurrence is detected after surgery. As cardiovascular side-effects have recently been reported in patients receiving selective COX-2 inhibitors, caution is warranted [II, B].

Table 2. Surveillance recommendations

Lynch syndrome	
Colon and rectum	Colonoscopy every 1 to 2 years, starting at age 20–25 or 5 years before the youngest case in the family. No upper limit is established.
Endometrium and ovary	Gynaecological examination, pelvic ultrasound, Ca125 analysis, and aspiration biopsy every year, from age 30–35 years. Consider prophylactic hysterectomy and salpingo-oophorectomy when childbearing is completed.
Gastric cancer	For gastric cancer, the search for the presence of Helicobacter Pylori and subsequent eradication is recommended in mutation carriers. In case of a high incidence of gastric cancer in some populations, some experts recommend upper gastrointestinal endoscopy every 1–3 years.
Other Lynch-associated cancers	Surveillance is not recommended due to the low sensitivity and specificity.
Classic Familial Adenomatous Polyposis	
Colon and rectum	Sigmoidoscopy every 2 years, starting at age 12–14 years and continued lifelong in mutation carriers. Once adenomas are detected, annual colonoscopy should be carried out until colectomy is planned.
Gastroduodenal adenomas	Gastroduodenal endoscopy using both front and side-view scopes starting when colorectal polyposis is diagnosed or at age 25–30 years, whichever comes first. Surveillance intervals are based on the Spigelman stage.
Thyroid cancer	Annual cervical ultrasonography, starting at age 25–30 years.
Desmoid tumours	Computed tomography (CT) scan or magnetic resonance imaging (MRI), if risk factors (positive family history for desmoids and site of the mutation in *APC*).
Attenuated Familial Adenomatous Polyposis	
Colon and rectum	Colonoscopy every 2 years, starting at age 18–20 years and continued lifelong in mutation carriers. Once adenomas are detected, colonoscopy should be carried out annually.
Gastroduodenal adenomas	Gastroduodenal endoscopy using both front and side-view scopes starting when colorectal polyposis is diagnosed or at age 25–30 years, whichever comes first. Surveillance intervals are based on the Spigelman stage.
Thyroid cancer	Annual cervical ultrasonography, starting at age 25–30 years.
Desmoid tumours	CT scan or MRI, if risk factors (positive family history for desmoids and site of the mutation in *APC*).

MUTYH-associated polyposis

MAP is inherited as an autosomal recessive trait with high penetrance [27]. Clinically, MAP resembles AFAP, with an average age of onset around the mid-50s with often fewer than

Table 3. Summary of recommendations

(i)	Tumour testing with immunohistochemistry for MMR proteins and/or MSI should be considered in all CRC patients. As an alternate strategy, tumour testing should be carried out in individuals with CRC younger than 70 years, or those older than 70 years who fulfil any of the Revised Bethesda guidelines.
(ii)	If loss of MLH1/PMS2 is observed in the tumour, analysis of *BRAF V600E* mutation or analysis of the methylation of the *MLH1* promoter should be carried out first to rule out a sporadic case.
(iii)	If loss of any of the other proteins (MSH2, MSH6, PMS2) is observed, germline genetic testing should be carried out.
(iv)	Full germline genetic testing should include DNA sequencing and large rearrangement analysis.
(v)	Follow-up recommendations in mutation carriers include colonoscopy every 1 to 2 years, and gynaecological examination (with transvaginal ultrasound, Ca125 and aspiration biopsy) on a yearly basis. Prophylactic gynaecological surgery might be an option in female carriers from age 35 and after childbearing is completed.
(vi)	Individuals with Familial CRC X syndrome are recommended colonoscopy at 3–5 year intervals, starting 5–10 years earlier than the youngest case in the family.
(vii)	Patients with multiple colorectal adenomas (>10) should be considered for germline genetic testing of *APC* and/or *MUTYH*.
(viii)	Full germline genetic testing of APC should include DNA sequencing and large rearrangement analysis.
(ix)	Germline testing of *MUTYH* can be initiated by screening for the most common mutations (G396D, Y179C) in the Caucasian population, followed by analysis of the entire gene in heterozygotes. Founder mutations among ethnic groups should be taken into account.
(x)	In families with classic-FAP, sigmoidoscopy should be carried out every 2 years starting at the age of 12–14 years and continued lifelong in mutation carriers. Surgery is indicated if there are large numbers of adenomas, including adenomas showing a high degree of dysplasia.
(xi)	In families with attenuated-FAP, colonoscopy should be carried out every 2 years starting at the age of 18–20 years and continued lifelong in mutation carriers. Surgery is indicated if there are large numbers of adenomas, including adenomas showing a high degree of dysplasia. Some patients with AFAP can be conservatively managed with annual colonoscopy and polypectomy.
(xii)	The decision on the type of colorectal surgery in FAP (total colectomy + IRA versus proctocolectomy + IPAA) depends on the age of the patient, the severity of rectal polyposis, the wish to have children, the risk of developing desmoids and possibly the site of the mutation in the *APC* gene.
(xiii)	After colorectal surgery, surveillance of the rectum or pouch should be carried out.
(xiv)	In both classic and attenuated FAP, screening for extracolonic manifestations (gastroduodenal polyposis, thyroid cancer, desmoid tumours) should start when colorectal polyposis is diagnosed or at the age of 25–30 years, whichever comes first.
(xv)	The suggested surveillance protocol for MAP patients is similar to that for patients with AFAP.

100 adenomas, and, accordingly, patient management is very similar. Of note, up to one-third of biallelic *MUTYH* mutation carriers identified in population-based CRC studies developed CRC without a colorectal polyposis [28].

genetics

Biallelic mutations in the *MUTYH* gene are responsible for this disorder. In the Caucasian population, >80% of mutations correspond to the G396D and Y179C missense variants (formerly annotated as G382D and Y165C, respectively) [29]. Initial studies showed that biallelic *MUTYH* mutations accounted for 10%–20% of classical FAP cases without an APC mutation, and for 30% of AFAP cases [27]. However, a recent study found biallelic *MUTYH* mutations in 2% (95% CI, 0.2%–6%) of patients with >1000 adenomas, 7% (95% CI, 6%–8%) of patients with 100–999 adenomas, 7% (95% CI, 6%–8%) of patients with 20–99 adenomas and 4% (95% CI, 3%–5%) of patients with 10–19 adenomas [12]. Due to the presence of founder mutations among ethnic groups, differences in the frequency of MAP are likely to exist. The frequency of *MUTYH* heterozygotes in the general European population is 1%–1.5%. Gene testing should commence with the investigation of an affected individual. If the causative mutation is detected, then presymptomatic diagnosis can be offered to at-risk family members (i.e. siblings, because of the recessive nature of the disease).

screening

Because of the similarity with AFAP, individuals should undergo total colonoscopy every 2 years, starting at the age of 18–20 years and continuing lifelong. Gene testing allows the most cost-effective screening to be carried out by driving colorectal examinations only to gene carriers. However, when the causative mutation is not identified, all at-risk family members should undergo colorectal screening [III, B].

Although less frequently than in FAP, patients with MAP may develop extracolonic manifestations, i.e. duodenal adenomas. Accordingly, upper endoscopy starting at the age of 25–30 years is recommended, following the same strategy described for *APC*-associated FAP [III, B].

CRC risk associated with monoallelic *MUTYH* carriers is still under debate. The magnitude of the association has been recently estimated, with a pooled odds ratio of 1.15 (95% CI = 0.98–1.36) [30, 31]. In such a context, it has been suggested that the Y179C mutation confers a much stronger pathogenicity compared with the G396D mutation. To date, CRC screening as recommended for first-degree relatives of a patient with sporadic CRC is advised [IV, C].

treatment

Colorectal management is similar to that proposed for patients with AFAP. Because of the small number of adenomas, in some patients endoscopic polypectomy can be considered. However, when polyp burden exceeds the number that could be safely

Table 4. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America US Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large, randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,…), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001;33:139–144. By permission of the Infectious Diseases Society of America.

managed by endoscopy, total colectomy with IRA should be offered. However, if rectal polyposis is severe, an IPAA is advised. Duodenal adenomas are usually managed as in AFAP [III, B].

surveillance

After total colectomy, regular endoscopic surveillance of the rectum every 12 months is recommended. In patients conservatively managed with endoscopic polypectomy, colonoscopy should be carried out annually [III, B].

The suggested protocol for surveillance of duodenal adenomatosis in MAP patients is similar to that for AFAP [III, B].

chemoprevention

So far, there is no evidence of the usefulness of any primary or secondary chemoprevention strategy in this setting.

note

Tables 2 and 3 provide summaries of recommendations. Levels of evidence and grades of recommendations have been applied using the system shown in Table 4.

Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

conflict of interest

The authors have declared no potential conflicts of interest.

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