Familial colorectal cancer risk: ESMO Clinical Practice Guidelines

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On behalf of the ESMO Guidelines Working Group*

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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. 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 instability at microsatellites (MSI) and foster inactivating mutations in tumour suppressors containing microsatellites (i.e. TGF–βRII and BAX). Mutations in the MMR genes may lead to loss of expression of the corresponding protein and be detected by immunohistochemistry (IHC) techniques.

Overall, mutation carriers mainly have an increased risk of CRC (lifetime 30%–70%) and endometrial cancer (lifetime 30%–60%). Other extracolonic tumours observed at increased risk (lifetime 5%–15%) are urinary tract, small intestine, ovary, gastric, pancreas, biliary tract, brain and sebaceous gland tumours. 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 lifetime absolute risk of CRC and endometrial cancer (15%–20%) compared with other mutation carriers.

The name Turcot syndrome refers to patients with MMR gene mutations and brain tumours, and the name Muir–Torre syndrome to patients with cutaneous gland tumours, brain tumours, and the name Muir–Torre syndrome to patients with cutaneous gland tumours, gene mutations and brain tumours, and the name Muir–Torre syndrome to patients with cutaneous gland tumours, gene mutations and brain tumours. 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 lifetime absolute risk of CRC and endometrial cancer (15%–20%) compared with other mutation carriers.

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 been shown to reduce CRC incidence and CRC-related mortality [IIb]. However, interval cancers during this interval have been detected in observational studies. We recommend initiating colonoscopy at age 20–25 years and repeat...
Tumors should be verified by pathological examination. FAP should be excluded in the CRC case(s) if any. At least one should be diagnosed before age 50. At least two successive generations should be affected. One should be a first-degree relative of the other two. There should be at least three relatives with an HNPCC-associated cancer (CRC, cancer of the endometrium, small bowel, ureter or renal pelvis). The time of diagnosis of a CRC, especially in young patients [C], may be an option of an extended colectomy should be discussed at the time of diagnosis of a CRC, especially in young patients [C].

The use of aspirin or resistant starch may reduce the risk of adenoma or CRC among individuals with Lynch syndrome [Ib]. No specific chemoprevention is being recommended at the current time [Ib, A] nor specific dietary interventions [C].

**Table 1. Amsterdam II criteria**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Required Conditions</th>
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<tbody>
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<td>at age 50 or younger</td>
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<tr>
<td>One or more first-degree relatives with CRC</td>
<td></td>
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<tr>
<td>One or more first-degree relatives with endometrial cancer</td>
<td></td>
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<tr>
<td>One or more first-degree relatives with colorectal polyposis</td>
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</tr>
<tr>
<td>One or more first-degree relatives with extracolonic manifestations</td>
<td></td>
</tr>
<tr>
<td>One or more first-degree relatives with synchronous or metachronous colorectal cancers</td>
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<tr>
<td>At least one relative with Lynch-related tumour</td>
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<tr>
<td>Family history of Lynch syndrome</td>
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**Table 2. Revised Bethesda guidelines**

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Every 1–2 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 performed on a yearly basis from age 30–35 years with gynaecological examination, pelvic ultrasound, Ca125 analysis and aspiration biopsy [III, C], Surveillance for other Lynch-associated cancers is recommended based on the family history and may include upper endoscopy, and abdominal ultrasound with urine cytology from age 30–35 at 1–2 year intervals [III, C].

**Chemoprevention**

A recent randomized, placebo-controlled trial has shown no benefit for the use of aspirin or resistant starch on the incidence of adenoma or CRC among individuals with Lynch syndrome [Ib]. No specific chemoprevention is being recommended at the current time [Ib, A] nor specific dietary interventions [C].

**Risk reduction: prophylactic surgical options**

**Prophylactic colectomy**

There is no data to support the performance of a prophylactic colectomy in healthy mutation carriers and it is not recommended [C].

**Prophylactic hysterectomy and bilateral salpingo-oophorectomy**

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

In many patients, extracolonic manifestations are present, in particular gastric and duodenal polyps, desmoid tumours, thyroidal and brain tumours, oesteomas, congenital hypertrophy of the retinal pigmented epithelium, supernumerary teeth and epidermoid cysts, among others. Combination of colorectal and extracolonic manifestations is known as Gardner’s syndrome, whereas association between colorectal polyposis and brain tumours corresponds to Turcot’s syndrome.
Clinical diagnosis of classical FAP is based on the identification of >100 colorectal adenomas. Attenuated FAP is characterized by the presence of fewer adenomas and a later onset of the disease; suggested criteria are: (i) at least two patients with 10–99 adenomas at age >30 years; or (ii) one patient with 10–99 adenomas at age >30 years, a first-degree relative with CRC and few adenomas, and no family members with >100 adenomas before the age of 30 years.

**genetics**

FAP is due to germline mutations in the APC gene. Germline APC mutations are found in >70% of patients with classical FAP and ~25% of those with an attenuated form. There is a genotype–phenotype correlation with potential implications in clinical management. In 30%–40% of cases, no family history of FAP is present, thus suggesting a de novo origin.

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

**screening**

CRC screening is justified by the disease’s high penetrance, since virtually all patients will develop a carcinoma at the age of 40–50 years if the colon is left in place. Gene testing allows the most cost-effective screening to be performed by focusing colorectal examinations on 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. This examination should be performed every 2 years, starting at age 12–14 years and be continued lifelong in mutation carriers. In at-risk individuals from families without an identified APC mutation, surveillance should be performed 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 performed annually (see Surveillance) [III, B].

When an attenuated form is suspected, total colonoscopy is needed. In this setting, examination should be performed every 2 years until polyposis is diagnosed. Screening should start at age 18–20 years and continue lifelong because of the more heterogeneous penetrance of the attenuated form. Again, once adenomas are detected, colonoscopy should be performed annually (see Surveillance) [III, B].

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

Gastroduodenal endoscopy using both front and side-view scopes, with special attention to the papillary area, should be performed every 5 years until adenomas are detected. The benefit of adding narrow band imaging capability for such a purpose is uncertain [V, D]. Since gastrointestinal adenomas may also develop in the jejunum and ileum, it has been suggested that regular screening by barium contrast series or wireless capsule endoscopy should be performed [V, D].

Screening for thyroid cancer should be performed by annual cervical ultrasonography [V, D]. Development of desmoid tumours is mainly related to a positive family history and abdominal surgery. In this setting, regular physical examination and abdominal CT should be performed. 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 surgery and endoscopic polypectomy. Whereas surgical resection is the standard of care in patients with classical FAP, the latter can be considered in some patients with an attenuated form.

Surgical resection includes both proctocolectomy with ileal pouch–anal anastomosis and total colectomy with ileorectal anastomosis. 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 and site of the mutation (see above). When a diffuse distribution or severe phenotype is present, the former is recommended. In contrast, when no or scarce adenomas are detected in the rectum and a mild familial phenotype is observed, including the attenuated forms, total colectomy with rectal preservation can be performed. Because of the need of endoscopic surveillance of the rectum in this latter context (see below), proctocolectomy should be considered in patients reluctant to undergo regular follow-up [V, D].

Duodenal adenomas are usually managed with endoscopic polypectomy. When the disease corresponds to Spigelman stage IV (see below) duodenal–pancreatectomy may be considered [V, D].

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) or toremifene (180 mg). In patients with progressive intra-abdominal tumours that do not respond to this treatment, chemotherapy (e.g. doxorubicine and dacarbazine or methotrexate and vinblastine) or radiation therapy is indicated [III, C].

**surveillance**

The risk of rectal adenoma and cancer remains after colectomy and even in the pouch after proctectomy. Accordingly, regular endoscopic surveillance after surgery is needed to detect adenoma recurrence early. When proctocolectomy is performed, surveillance of the pouch can be repeated every 1–2 years, but if the rectum is in place the interval between examinations should be reduced to 6–12 months [V, D].

In patients with attenuated FAP conservatively managed with endoscopic polypectomy, examination of the entire colon and rectum should be performed annually [V, D].

Surveillance of duodenal manifestation will depend on its extension. When it corresponds to Spigelman stage I or II, upper endoscopy can be performed every 5 to 3 years, respectively, whereas in more advanced forms intervals between examinations should be shortened to 1–2 years (Spigelman stage III) or 6 months (Spigelman IV) [V, D].
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 extension of colorectal adenomas and, less reliably, duodenal adenomas. Accordingly, sulindac and celecoxib can be considered when adenoma recurrence is detected after surgery, as adjuvant treatment. As cardiovascular side-effects have recently been reported in patients receiving selective COX-2 inhibitors caution is warranted [II, B].

MUTYH-associated polyposis
MUTYH-associated polyposis (MAP) is inherited as an autosomal recessive trait with high penetrance. Clinically, MAP resembles the attenuated form of FAP syndrome, with an average age of onset around the mid-50s with often <100 adenomas and, accordingly, patient management is very similar.

genetics
Biallelic mutations in the MUTYH gene (formerly known as MYH) are responsible for this disorder. Mutations are found in 25%–30% of patients with 10–100 adenomas and in 5%–30% of patients with >100 adenomas.
In Caucasian populations, >80% of mutations correspond to the G382D and Y165C missense variants. Gene testing should start by investigating 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 to attenuated FAP, individuals should undergo total colonoscopy every 2 years, starting at age 18–20 years and continuing lifelong. Gene testing allows the most cost-effective screening to be performed by focusing colorectal examinations only on 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 every 5 years is recommended [V, D].
CRC risk associated with monoallelic MUTYH carriers is still under debate. Whereas a recent meta-analysis suggests a lack of significant risk (OR, 1.11; 95% CI 0.9–1.37), others did not exclude this possibility. In such a context, it has been suggested that the Y165C mutation confers a much stronger pathogenicity compared with the G382D mutation. To date, early-onset colonoscopy screening is not advised in this scenario [V, D].

treatment
Colorectal management is similar to that proposed for patients with attenuated FAP. Endoscopic polypectomy can be considered in some patients. However, when polypl burden exceeds the number that could be safely managed by endoscopy, total colectomy should be offered [V, D]. Duodenal adenomas are usually managed with endoscopic polypectomy. However, when the disease corresponds to Spigelman stage IV (see below) duodenal–pancreatectomy may be considered [V, D].

surveillance
After total colectomy, regular endoscopic surveillance of the rectum every 6–12 months is recommended. In patients conservatively managed with endoscopic polypectomy, examination of the entire colon and rectum should be performed annually [V, D].
Surveillance of duodenal manifestation will depend on its extension. When disease corresponds to Spigelman stage I or II, upper endoscopy can be performed every 5 or 3 years, respectively, whereas in more advanced forms intervals between examinations should be shortened to 1–2 years (Spigelman stage III) or 6 months (Spigelman IV) [V, D].

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

note
Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

literature