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 (keratoacanthomas, sebaceous adenomas or adenoacarcinomas).

referral for molecular screening and MMR gene testing

Clinical suspicion is based on fulfilment of clinical criteria. Both the Amsterdam criteria and the revised Bethesda guidelines are used to clinically identify individuals with suspicion of Lynch syndrome or candidates for molecular screening (Tables 1 and 2). Since >90% of Lynch syndrome CRC cases show MSI and/or loss of the corresponding protein by IHC, upfront molecular screening is another strategy to identify candidates for germline testing. Some groups recommend initial selection by fulfilment of clinical criteria while others suggest universal IHC of all CRC cases. The advantage of IHC is that it may direct mutation analysis because loss of expression of a protein is suggestive of an underlying genetic defect. Neither MSI nor IHC are 100% sensitive and they complement each other. If a tumour with MMR deficiency is detected, germline genetic testing would be indicated. If loss of MLH1/PMS2 expression is observed, methylation of the MLH1 promoter or testing of the somatic BRAF V600E mutation should be performed first to rule out hypermethylation of the MLH1 promoter (10%–15% of sporadic cases are related to this somatic event) [C].

Prediction models that estimate the likelihood of finding a MMR gene mutation constitute another clinical tool to identify individuals at risk of Lynch syndrome and help in clinical decision making for referral [C].

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%. Pathogenic genetic alterations might be frameshift, nonsense and splice site mutations that lead to truncating or unstable proteins, but also large deletions and rearrangements are common. Therefore, full germline genetic testing should include both DNA sequencing and large rearrangement analysis [C].

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
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**Table 1. Amsterdam II criteria**

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<th>Criteria</th>
<th>Description</th>
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<td>At least one should be diagnosed before age 50.</td>
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<td>At least two successive generations should be affected.</td>
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<td>One should be a first-degree relative of the other two.</td>
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<tr>
<td>There should be at least three relatives with an HNPCC-associated cancer</td>
<td>(CRC, cancer of the endometrium, small bowel, ureter or renal pelvis).</td>
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<td>FAP should be excluded in the CRC case(s) if any.</td>
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<td>Tumors should be verified by pathological examination.</td>
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**Table 2. Revised Bethesda guidelines**

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<th>Criteria</th>
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<td>Tumors should be tested for MSI when one or more of the following exist:</td>
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1. Colorectal cancer diagnosed in a patient who is <50 years old.        |                                                                            |
2. Presence of colorectal cancers that are synchronous or metachronous or other tumours associated with Lynch syndrome, regardless of age. |
3. Colorectal cancer with the MSI-H histology diagnosed in a patient who is <60 years of age. |
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. |

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.

Presence of tumour infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

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.

**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].

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].

**chemotherapy**

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

**familial CRC X syndrome**

This syndrome represents those individuals who fulfil the Amsterdam I criteria and do not exhibit MMR deficiency or a MMR gene defect. An increased risk of CRC but not of extracolonic cancers has been described. Surveillance would include colonoscopy at 3–5 year intervals, starting 5–10 years earlier than the youngest case in the family [C].

**familial adenomatous polyposis**

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder characterized by the presence of hundreds to thousands of adenomas distributed in the colon and rectum. 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. 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.
diagnosis

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.

Gastrointestinal endoscopy using both front and side-view scopes, with special attention to the papillary area, should be performed every 3 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. doxorubicin 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].
**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.

**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 may develop extracolonic manifestations, i.e. duodenal adenomas. Accordingly, sulindac and celecoxib 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 polyp 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].

**Note**

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

**Literature**