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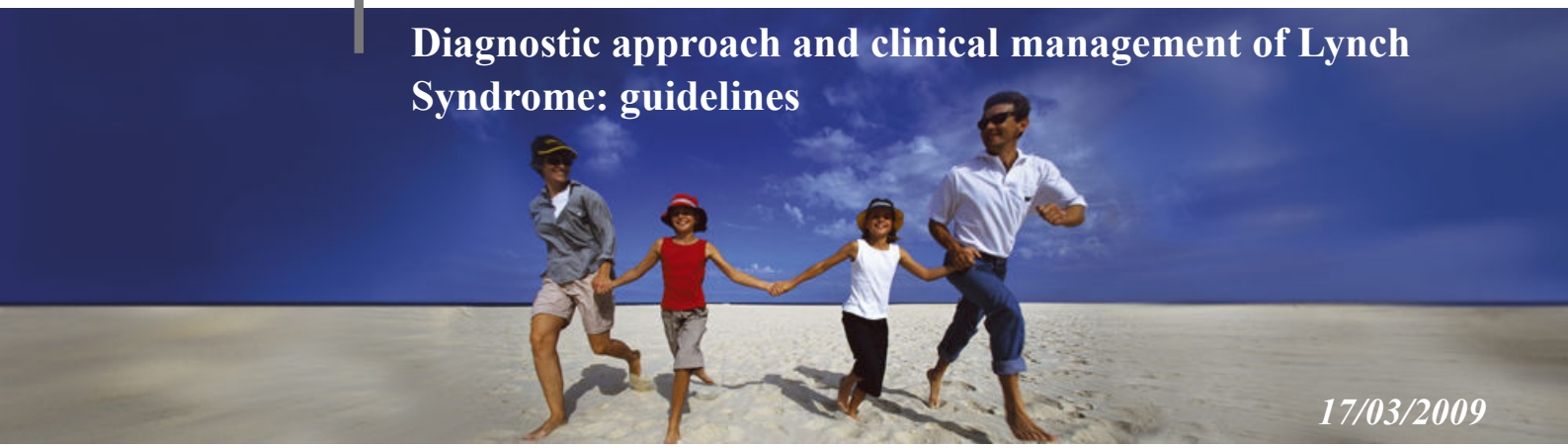
Belgian Polyposis Project
Hereditary Colorectal Cancer Project

Diagnostic approach and clinical management of Lynch Syndrome: guidelines



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Content

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Terminology

Currently, **Lynch syndrome (LS)** (also known as HNPCC) is defined as a hereditary predisposition to malignancy that is explained by a germline mutation in a DNA MMR gene.

Presumed Lynch syndrome families are 1) families that meet the clinical Amsterdam II criteria (even in the absence of mismatch repair deficiency) or 2) families that meet the revised Bethesda criteria and demonstrate MSI but with no pathologic germline mutation found (yet).

Familial colorectal cancer (CRC) refers to 1) families that meet the revised Bethesda criteria without evidence of mismatch repair deficiency (by MSI/IHC) or 2) other families with familial clustering of colorectal cancer without evidence of mismatch repair deficiency (by MSI/IHC). Families in this category are also APC negative.

Identification of LS

Since genetic testing for germline MMR mutations is complicated, time-consuming, and expensive, it is currently recommended to use a step-wise approach to detect cases of LS in a cost-effective manner.

The clinical diagnosis of LS can be made by applying the Amsterdam Criteria II. However, since these criteria are too stringent to identify all LS families, the revised Bethesda Criteria have been formulated to identify families who should be tested for MSI/IHC. Patients at increased risk for Lynch syndrome based on these criteria are recommended to undergo pre-screening with microsatellite instability (MSI) analysis and immunohistochemistry (IHC). Individuals with tumors that display high levels of microsatellite instability or loss of expression of MMR proteins by immunohistochemistry are then referred for germline mutation testing.

Amsterdam II criteria

There should be at least three relatives with colorectal cancer (CRC) or with a Lynch-Syndrome associated cancer: cancer of the endometrium, small bowel, ureter or renal pelvis.

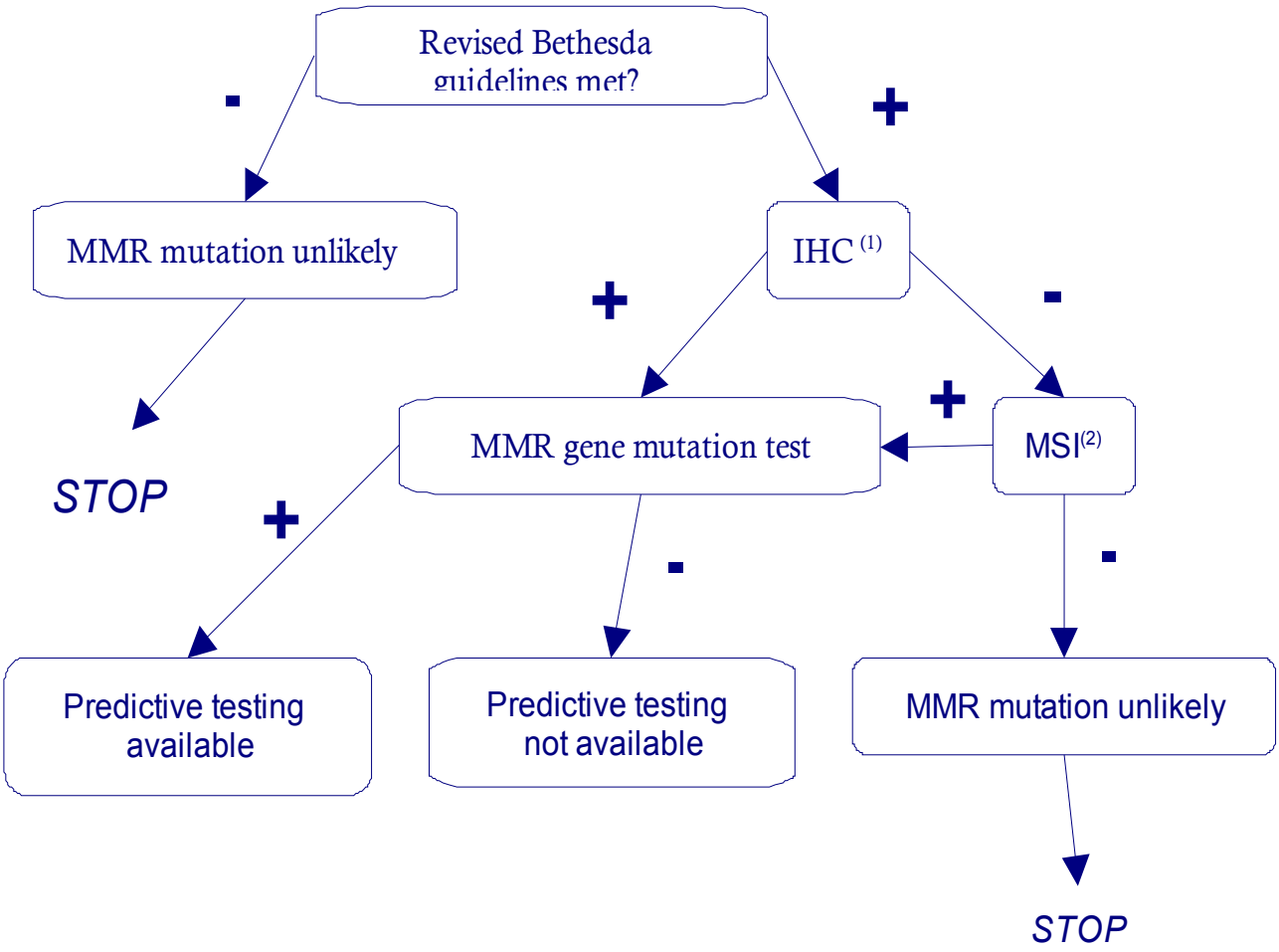
- one relative should be a first-degree relative of the other two,
- at least two successive generations should be affected,
- at least one tumour should be diagnosed before the age of 50 years,
- FAP should be excluded in the CRC case if any,
- tumours should be verified by histopathological examination

Revised Bethesda guidelines

- CRC diagnosed in a patient aged < 50 years
- presence of synchronous, metachronous colorectal or other Lynch Syndrome-related* tumours, regardless of age,
- CRC with MSH-phenotype diagnosed in a patient aged < 60 years
- patient with CRC and a first-degree relative with a Lynch Syndrome-related tumour, with one of the cancers diagnosed at the age < 50 years
- patients with CRC with two or more first-degree or second-degree relatives with a Lynch Syndrome-related tumour, regardless of age.

*Lynch Syndrome-related tumours include colorectal, endometrial, stomach, ovarian, pancreas, ureter, renal pelvis, biliary tract and brain tumors, sebaceous gland adenomas and keratoacanthomas, and carcinoma of the small bowel.

For the diagnostic approach in Belgium, we propose the following strategy (Lynch et al., 2007).



Notes

(1) One can also start with MSI

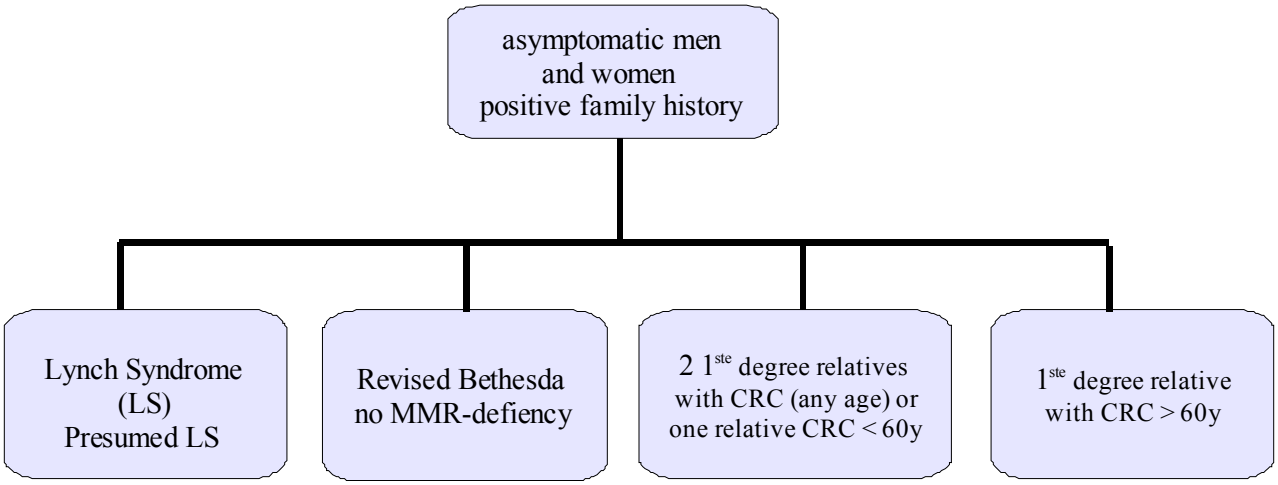
(2) hypermethylation of MLH1 should be excluded

Management of LS

A. Surveillance

For high-risk individuals, pre-symptomatic detection and treatment of precancerous adenomas or early cancers by screening is important since studies have shown that regular surveillance reduces morbidity and mortality from colorectal cancer.

When the diagnostic process has been completed, cancer risk assessment can be performed and recommendations for periodic surveillance can be formulated.



A.1. Lynch Syndrome

When a mutation in one of the MMR genes has been identified, presymptomatic testing can be offered to unaffected relatives. Carriers of a mutation are offered periodic surveillance (see table).

A.2. Presumed Lynch Syndrome

Presumed Lynch syndrome families are 1) families that meet the clinical Amsterdam II criteria (even in the absence of mismatch repair deficiency) or 2) families that meet the revised Bethesda criteria and demonstrate MSI but with no pathologic germline mutation found (yet). Since presymptomatic testing can not be offered, periodic surveillance is recommended to all high risk individuals in the family (see table).

Compared to the former group, cancer risks may be lower in Amsterdam-positive families that are MSI-negative and a less stringent surveillance protocol may be sufficient. However, until more data become available, these families are currently advised to have the same surveillance protocol as "proven" Lynch Syndrome families.

A.3. Familial colorectal cancer

Familial colorectal cancer (CRC) refers to 1) families that meet the revised Bethesda criteria without evidence of mismatch repair deficiency (by MSI/IHC) or 2) other families with familial clustering of colorectal cancer without evidence of mismatch repair deficiency (by MSI/IHC). Families in this category are also APC negative. First-degree relatives of CRC patients are offered periodic surveillance (see table).

Disorder	Lower age limit (y)	Examination	Interval (y)
Lynch Syndrome & Presumed LS	20-25	Colonoscopy	1-2
	30-35	Gynaecological examination	1-2
		Transvaginal ultrasound	
	30-35	Gastroduodenoscopy	1-2*
	30-35	Abdominal ultrasound	1-2*
		Urinalysis and cytology urine	
Revised Bethesda no MMR deficiency	20-40	Colonoscopy	To be discussed in view of fam.history
Familial CRC (2 1st degree relatives with CRC or one diagn. < 60 y)	40	Colonoscopy	5
Familial CRC (1st degree relative with CRC > 60 y)	40	Average risk method	

Note: In case of colonoscopy, it is essential to visualize the complete colon.

* only if gastric or urinary tract cancer runs in the family

B. Surgical management

B.1. colorectum

Studies have shown that patients with LS have an increased risk of developing multiple (synchronous and metachronous) CRCs. Therefore, apart from segmental resection, subtotal colectomy can be a treatment to consider in patients from families with LS with a primary tumour. In case of segmental resection, periodic surveillance remains essential.

B.2. endometrium / ovary

Prophylactic hysterectomy and bilateral salpingo-oophorectomy might be considered in female mutation carriers after menopause or after completion of family planning respectively.

C. Life style

Although there is evidence that the expression of LS is influenced by environmental factors, no sufficient data are available regarding which environmental factors play a significant role.

References

Lynch et al. (2007). Towards a consensus in molecular diagnosis of hereditary non-polyposis colorectal cancer (Lynch Syndrome). JNCI, 99 (4), 261-263.

Vasen et al. (2007). Guidelines for the clinical management of Lynch syndrome (Hereditary non-polyposis colorectal cancer). J. Med. Genet., 44, 353-362.