

# National consensus and clinical guidance for diagnosis and management of Lynch Syndrome

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## DEFINITIONS

**Lynch syndrome (LS)** is a hereditary condition found in ~3 % of all colorectal cancers and is defined by the identification of a germline mutation in one of the DNA mismatch repair (MMR) genes (hMSH2, hMLH1, hMSH6, hPMS2) or the EPCAM gene.

**Lynch-like syndrome families** are families that meet the revised Bethesda criteria (mean age of onset similar to Lynch syndrome patients (53.7 years of age vs. 48.5 years of age) and demonstrate MSI<sup>1</sup> within their cancers in absence of an identifiable DNA MMR gene germline mutation. Much of this group is now explained by somatic MMR mutations, and some tumours acquire somatic mutations in MMR genes due to underlying mutations in other genes such as POLD1. **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).

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<sup>1</sup> Microsatellite instability of related-LS tumors : Deficiency of MMR complex determines high rate of mutations in repetitive DNA sequences known as microsatellites. This condition is known as microsatellite instability (MSI) and is present in approximately 95% of all LS-associated cancers. The sporadic CRC also display an MSI phenotype in about 15%. In this case, the MSI may be result of somatic hypermethylation of the MLH1 gene promoter in the presence of a specific mutation in the BRAF oncogene, usually the V600E missense mutation (40–87% of all sporadic MSI tumors).

## IDENTIFICATION OF LYNCH SYNDROME

The clinical diagnosis of LS can be made by applying the Amsterdam Criteria II (see box 1). However, since these criteria are too stringent to identify all LS families, the revised Bethesda guidelines (see box 2) have been formulated to identify families who should be tested for MSI/IHC.

### Box 1

#### **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 tumor should be diagnosed before the age of 50 years,
- FAP should be excluded in the CRC case if any,
- tumors should be verified by histopathological examination

### Box 2

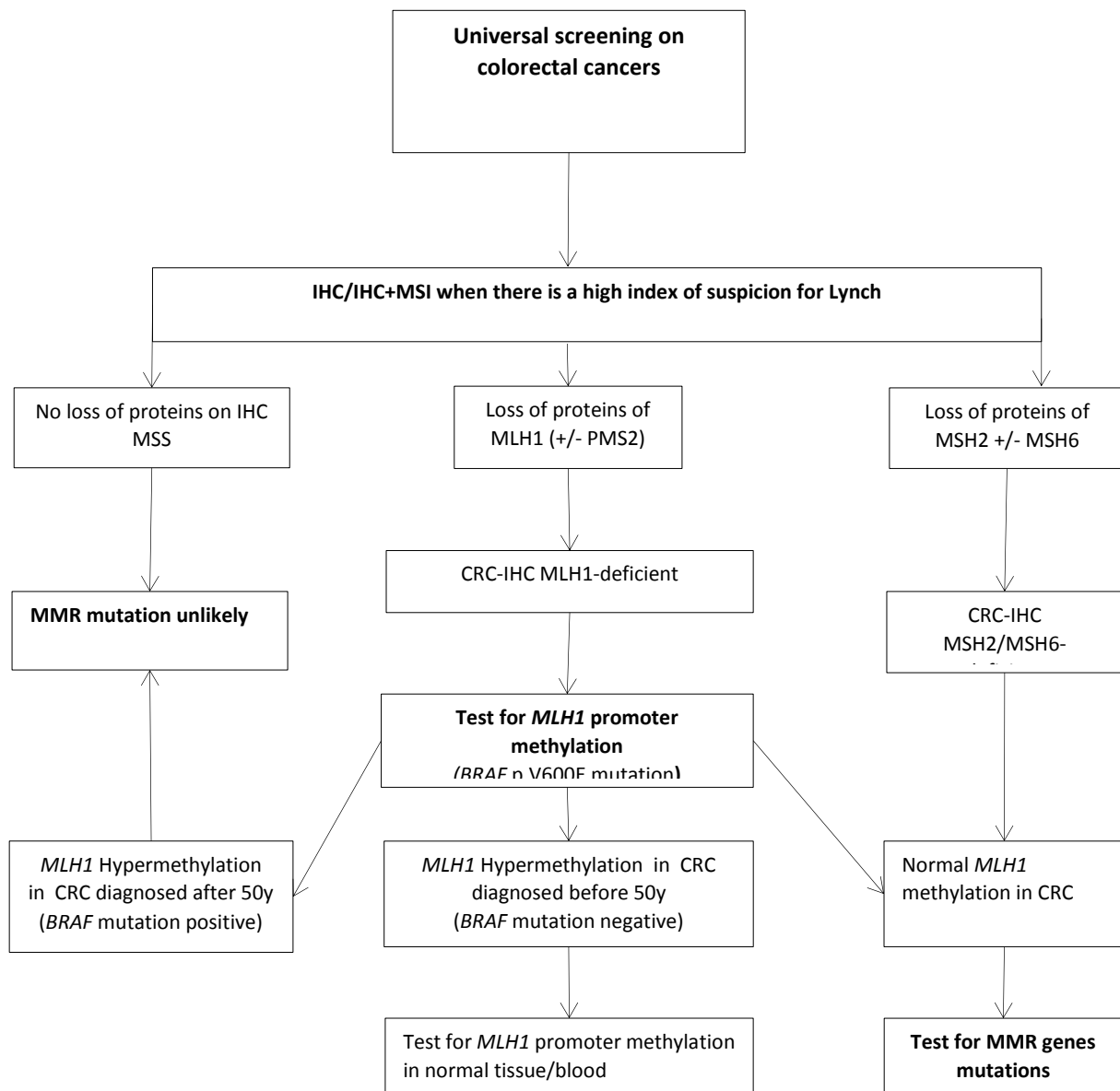
#### **Revised Bethesda guidelines**

- CRC diagnosed in a patient aged < 50 years
- presence of synchronous, metachronous colorectal or other Lynch Syndrome-related<sup>2</sup> tumors, 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 tumor, 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 tumor, regardless of age.

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<sup>2</sup> Lynch Syndrome-related tumors 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** (Ferber M, Mao R, Samowitz W, et al. *ACMG technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and MYH-associated polyposis)*. *Genetics in Medicine* 2014;16(1):101-16, Hébrant A, Jouret-Mourin A, Froyen G, et al. *Molecular test algorithms for digestive tumours*. *Belgian Journal of Medical Oncology* 2019,13:4-10).



- Immunohistochemical testing for DNA mismatch repair (MMR) protein expression (ie, MLH1, MSH2, MSH6, and PMS2 expression) is performed on formalin-fixed, paraffin embedded tissue on colorectal biopsy rather than resection specimen and can be considered if Lynch Syndrome-related tumors (endometrium, urinary tract, gastric) ([https://kce.fgov.be/sites/default/files/atoms/files/KCE\\_220\\_Oncogenetic%20testing.pdf](https://kce.fgov.be/sites/default/files/atoms/files/KCE_220_Oncogenetic%20testing.pdf)).

- MLH1 promoter methylation testing is indicated to rule out sporadic MLH1-deficient cancer (Newton K, Jorgensen NM, Wallace AJ, et al. *Tumour MLH1 promoter region methylation testing is an effective prescreen for Lynch Syndrome (HNPCC)*. *Journal of Medical Genetics* 2014;51:789-796). If MLH1 promoter assay is not available, BRAF testing can be proposed but is less specific.
- Previous studies have shown that the yield and cost-effectiveness of screening are significantly decreased in the elderly (Li D, Hoodfar E, Jiang S, et al. *Comparison of Universal Versus Age-Restricted Screening of Colorectal Tumors for Lynch Syndrome Using Mismatch Repair Immunohistochemistry: A Cohort Study*. *Ann Intern Med*. 2019;171:19–26).

**The diagnosis of Lynch syndrome is established by the detection of a germline causative variant** in MLH1, MSH2, MSH6, or PMS2 or an EPCAM deletion on molecular genetic testing (MMR testing).

In patients diagnosed with colorectal tumors younger than 50 years, the use of a broad multigene panel (including genes responsible for colonic adenomatous polyposis syndrome) may facilitate the diagnosis of hereditary cancer syndromes (Pearlman R, Frankel WL, Swanson B, et al. *Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations Among Patients With Early-Onset Colorectal Cancer*. *JAMA Oncol*. 2017;3(4):464–471).

Constitutional epimutation of *MLH1* (CEM) is a rare cause of Lynch syndrome. In 2-3% of MLH1-deficient tumors without germline *MLH1/PMS2* mutation, the cancer predisposition is associated with constitutional epimutation of *MLH1*, in which one allele of the CpG island promoter is aberrantly hypermethylated throughout normal tissues.

There are so far two distinct types of constitutional *MLH1* epimutation:

- Secondary type, which is linked in-cis to a genetic alteration and follow an autosomal dominant pattern of inheritance (Hitchins MP, Rapkins RW, Kwok CT, et al. *Dominantly inherited constitutional epigenetic silencing of MLH1 in a cancer-affected family is linked to a single nucleotide variant within the 5'UTR*. *Cancer Cell*. 2011;20(2):200-213);
- And primary type, which occurs in the absence of any apparent linked sequence change, typically arises de novo and demonstrates null (Suter, C. M., Martin, D. I. K. & Ward, R. L. *Germline epimutation of MLH1 in individuals with multiple cancers*. *Nat. Genet*. 2004; 36, 497–501) or non-Mendelian inheritance (Sloane, M. A., Nunez, A. C. & Packham, D. et al. *Mosaic epigenetic inheritance as a cause of early-onset colorectal cancer*. *JAMA Oncol*. 2015; 1, 953–957)

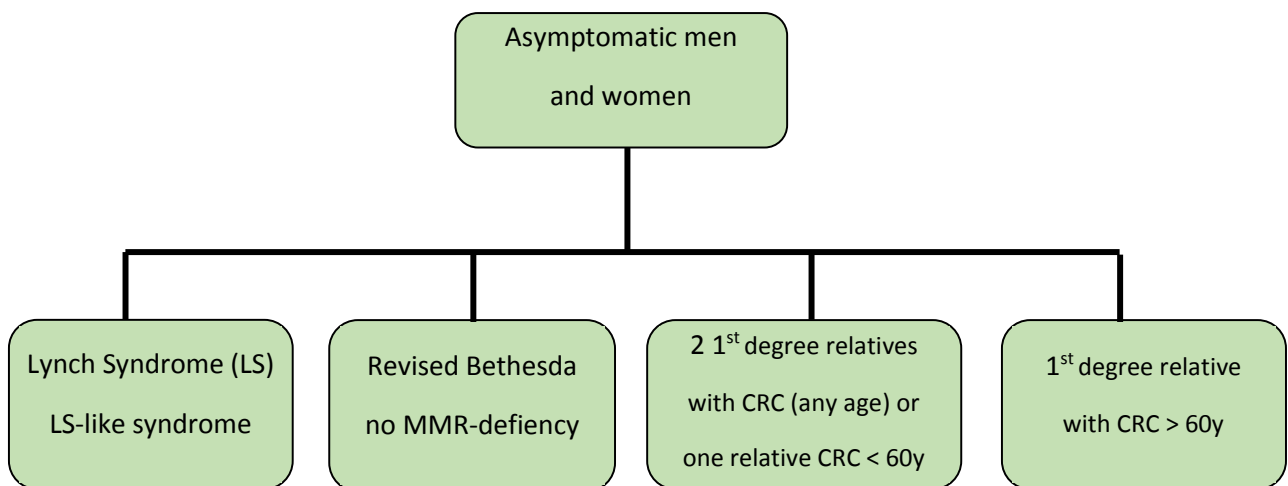
The available data in the literature strongly suggest that constitutional *MLH1* epimutations may cause severe LS phenotype, including a young age of cancer onset (<50y) and multiple primary tumors.

## MANAGEMENT OF LYNCH SYNDROME

### 1. 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. Lynch Syndrome

When a mutation in one of the MMR genes has been identified, pre-symptomatic testing can be offered to unaffected relatives. Carriers of a mutation are offered periodic surveillance (see tables for risk figures and surveillance guidelines)

Table 1: Cumulative incidence at age 75 (%)

	MLH1	MSH2	MSH6	PMS2	Population risk
Colorectal cancer	60-80	60-80	10-20	10-20	4-5
Endometrial cancer	35	50	40	10-15	1.5
Ovarian cancer	10	17	10 <sup>b</sup>	3 <sup>b</sup>	0.8
Upper GI cancer	10-20	10-20	4-8	4	
Ureter-bladder-kidney	10-12	25-30	6-9	/	
prostate	10-20	20-30	/	/	10

This table provides averaged risk estimates for cancers in path\_MMR carriers according two Prospective Lynch Syndrome Database (PLSD) studies <sup>a, b</sup>.

Colorectal cancer still occurs in prospectively followed population under surveillance. However with good 5-y survival rates.

For ovary cancer, the recent cohort <sup>b</sup> included 1423 women with *MLH1* mutation, 1350 with *MSH2* mutation, 474 with *MSH6* mutation and 233 with *PMS2* mutation. Among the groups of *MSH6* and *PMS2* carriers, the ovarian cancer risk is estimated on few ongoing diagnosis cases (3 in the *MSH6* carrier group and 1 in the *PMS2* carrier group).

<sup>a</sup>Moller P, Seppala TT, Bernstein I, et al. Cancer risk and survival in path\_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut*. 2018;67:1306–1316

<sup>b</sup>Dominguez-Valentin, M., Sampson, J.R., Seppälä, T.T. et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. *Genet Med*.2020;22, 15–25

## B. Lynch-like Syndrome

Cancers from Lynch-like syndrome (LLS) patients show MSI phenotype in absence of aberrant *MLH1* promoter methylation and detectable germline mutation of a MMR gene. A large majority of these MMR deficient tumors (60%) are now explained by biallelic somatic MMR gene mutations (*Haraldsdottir S, Hampel H, Tomsic J, et al. Colon and endometrial cancers with mismatch repair deficiency can arise from somatic, rather than germline, mutations. Gastroenterology. 2014;147(6):1308–1316.e1*).

The LLS clinical presentation is close similar than LS with a mean age of onset younger than sporadic CRC. The main distinguished feature between these two syndromes are the lower standardized incidence ratios for CRCs and non-CRC LS-associated tumors in LLS patients as compared with those in LS patients.

It remains prudent to continue to perform surveillance for cancer formation in these patients.

Since pre-symptomatic testing cannot be offered, periodic surveillance is recommended to all first degree relatives (see table surveillance)

## C. 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) or hereditary polyposis syndromes. First-degree relatives of CRC patients are offered periodic surveillance (see table surveillance).



## Surveillance table

Disorder	Lower age limit (y)	Examination	Interval (y)
Lynch Syndrome & Presumed LS  Colorectal cancer	(20-)25 <sup>A</sup> or 5y younger than the youngest age at diagnosis of CRC in family if diagnosed before 25y	Colonoscopy Essential to visualize the complete colon and the terminal ileum	1-2
Gastric cancer	(30-)35	Baseline Gastroduodenoscopy with gastric biopsy of the antrum Treating <i>Helicobacter pylori</i> infection when found  Subsequent surveillance can be considered every 3–5y based on individual patient risk factors ( <i>MLH1/MSH2</i> mutations) and/or family history of gastric and duodenal cancer <sup>B</sup>	
Gynecological cancer	(30-)35	Pelvic examination Transvaginal ultrasound and endometrial biopsy <sup>C</sup> Prevention options (use of oral contraceptives) <sup>D</sup>	1
Urinary tract cancer <sup>E</sup>	Age 40 or after completion of Childbearing (30-)35	Hysterectomy and bilateral salpingo-oophorectomy should be discussed with women who are known to be <i>MLH1/MSH2</i> carriers  Urinalysis for microscopic hematuria Urine cytology  based on individual patient risk factor ( <i>MSH2</i> mutation) and/or family history	1
Revised Bethesda no MMR deficiency	20-40	Colonoscopy (interval need to be discussed in view of fam. history)	
Familial CRC (2 FDR With CRC or one FDR diagnosed < 50 years)	40	Colonoscopy	5
Familial CRC One FDR with CRC > 50 years	40	Average risk method	

Note:

<sup>A</sup> Literature data support a move to commence colonoscopy surveillance in *MSH6/PMS2* heterozygous carriers at the older age of 30 years, unless an early onset cancer exists in a given family and extend the interval to 2 years. (Ryan NAJ, Morris J, Green K, et al. Association of Mismatch Repair Mutation With Age at Cancer Onset in Lynch Syndrome: Implications for Stratified Surveillance Strategies. *JAMA Oncol.* 2017;3(12):1702–1706).

<sup>B</sup> The lifetime risk of gastric cancer is estimated between 8.0% and 5.3% in males and females with *MLH1/MSH2* mutation, respectively, without notion of familial clustering. Majority of gastric cancers in LS patients appear to be histologically classified as intestinal type. (Capelle LG, Van Grieken NC, Lingsma HF et al. Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in the Netherlands. *Gastroenterology.* 2010; 138:487-92).

<sup>C, D</sup> Current guidelines are based on consensus opinion only and in general recommend annual endometrial biopsy starting at age 30–35 or 5–10 years prior to the earliest diagnosis of endometrial cancer in the family (Lindor NM, Petersen GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. *JAMA.* 2006;296:1507–17).

Women with LS should be counseled on symptoms related to endometrial cancer and on cancer chemoprevention using progestins (Lu KH, Daniels M. Endometrial and ovarian cancer in women with Lynch syndrome: update in screening and prevention. *Fam Cancer.* 2013;12(2):273–277).

<sup>E</sup> The benefit of urinary tract cancer surveillance program in LS setting remains unclear. The only large study on screening by annual urine cytology in high-risk LS individuals found that the test performed extremely poorly-sensitivity was 29% and false positive tests were ten times as common as true positives (Myrhøj T, Andersen MB, Bernstein I. Screening for urinary tract cancer with urine cytology in Lynch syndrome and familial colorectal cancer. *Fam Cancer.* 2008;7(4):303–307).

A minimum routine annual urinalysis could be recommended, using the American Urological Association guideline of 3 or more red blood cells per high power field as a trigger for further assessment (renal and bladder ultrasonography, CT urograms, MRI,..) (Mork M, Hubosky SG, Rouprêt M, et al. Lynch Syndrome: A Primer for Urologists and Panel Recommendations. *J Urol.* 2015;194(1):21–29).

Other tumors are managed as in the general population.

## 2. Surgical management

### A) colorectal

For individuals with LS who develop a colon cancer, a total colectomy is preferred for cancer risk reduction.

Consideration for less-extensive surgery should be given in patients >60–65 y and those with underlying sphincter dysfunction.

Annual colonoscopy should be performed after segmental resection of colon cancer in patients with LS

A recent meta-analysis including a total of 871 individuals pointed a significant increased rate of metachronous cancers (23% versus 6%) among individuals who had a segmental colectomy, compared to individuals who had subtotal colectomy (*Anele CC, Adegbola SO, Askari A, et al. Risk of metachronous colorectal cancer following colectomy in Lynch syndrome: a systematic review and meta-analysis. Colorectal Dis. 2017;19(6):528–536*). The difference was seen despite annual endoscopic surveillance in 88% of patients; median follow-up was 104 months (*Parry S, Win AK, Parry B, et al. Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery. Gut. 2011;60(7):950–957*).

### B) endometrium/ovary

Prophylactic hysterectomy and bilateral salpingo-oophorectomy should be recommended to women with LS who have finished childbearing or at age of 40–45 y (*Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med. 2006;354(3):261–269*). The lifetime risk for endometrial cancer is 40–50% compared with a risk of 3% in the general population. For ovarian carcinoma, the lifetime risk is 10–17% compared with the general population risk of 1.4%.

Unlike BRCA-associated ovarian cancers, which are usually high-grade serous tumours, Lynch-related ovarian carcinomas are often early stage and moderately or well differentiated. Women with Lynch syndrome also have a greater likelihood of synchronous endometrial cancer than other ovarian cancer patients (*Watson P, Bützow R, Lynch HT, et al. The clinical features of ovarian cancer in hereditary nonpolyposis colorectal cancer. Gynecol Oncol. 2001;82(2):223–228*).

Prescription of estrogen-only hormone replacement therapy (HRT) until at least natural menopause age (~ 51 years) is recommended.

### 3. 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, except for smoking.

A retrospective cohort analysis shown that individuals with LS who smoke regularly are at increased risk for colorectal cancer, providing first evidence to avoid smoking to reduce the colorectal cancer risk (*Pande M, Lynch P. M, Hopper J.L. et al: Smoking and Colorectal Cancer in Lynch Syndrome: Results from the Colon Cancer Family Registry and The University of Texas M.D. Anderson Cancer Center. Clin Cancer Res.2010;16(4):1331-1339*).

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Suter, C. M., Martin, D. I. K. & Ward, R. L. Germline epimutation of MLH1 in individuals with multiple cancers. Nat. Genet.2004; 36, 497–501

## WORKING GROUP

The guidelines were prepared by an ad hoc working group of FAPA constituted by the specialists mentioned below. The meetings took place between November 2018 and September 2019. The guidelines were approved by the board of FAPA on 12 November 2019. The guidelines are submitted for approval to the Belgian Dutch Genturis workgroup (date) and released during the annual meeting of FAPA on 24 March 2020.

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