

European guidelines from the EHTG and ESCP for Lynch syndrome: an updated third edition of the Mallorca guidelines based on gene and gender.

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@Colores_ry, @me4_so, @SoMe4GenRisk) 5 2021 26 5 2021 108 5 441349 484 498 24 3 2020 16 5 2020 14 6 2020 30 6 2020 26 05 2021 31 07 2023 01 08 2023 © The Author(s) 2021.

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<https://creativecommons.org/licenses/by/4.0/> This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited. Abstract Background Lynch syndrome is the most common genetic predisposition for hereditary cancer but remains underdiagnosed. Large prospective observational studies have recently increased understanding of the effectiveness of colonoscopic surveillance and the heterogeneity of cancer risk between genotypes. The need for gene■ and gender■specific guidelines has been acknowledged.

The European Hereditary Tumour Group (EHTG) and European Society of Coloproctology (ESCP) developed a multidisciplinary working group consisting of surgeons, clinical and molecular geneticists, pathologists, epidemiologists, gastroenterologists, and patient representation to conduct a graded evidence review. The previous Mallorca guideline format was used to revise the clinical guidance. Consensus for the guidance statements was acquired by three Delphi voting rounds.

Recommendations for clinical and molecular identification of Lynch syndrome, surgical and endoscopic management of Lynch syndrome■associated colorectal cancer, and preventive measures for cancer were produced. The emphasis was on surgical and gastroenterological aspects of the cancer spectrum. Manchester consensus guidelines for gynaecological management were endorsed. Executive and layperson summaries were provided.

The recommendations from the EHTG and ESCP for identification of patients with Lynch syndrome, colorectal surveillance, surgical management of colorectal cancer, lifestyle and chemoprevention in Lynch syndrome that reached a consensus (at least 80 per cent) are presented.

El síndrome de Lynch (Lynch síndrome , LS) es la predisposición genética más frecuente para el cáncer hereditario, pero es una patología que sigue siendo infradiagnosticada. Recientemente, grandes estudios prospectivos observacionales han permitido comprender mejor la efectividad de la vigilancia mediante colonoscopia y la heterogeneidad del riesgo de cáncer entre genotipos. Se ha reconocido la necesidad de pautas específicas en función de los genes y del género.

El Grupo Europeo de Tumores Hereditarios (European Hereditary Tumour Group , EHTG) y la Sociedad Europea de Coloproctología (European Society of Coloproctology , ESCP) desarrollaron un grupo de trabajo multidisciplinar formado por cirujanos, genetistas clínicos y moleculares, patólogos, epidemiólogos, gastroenterólogos y una representación de pacientes para llevar a cabo una revisión para establecer los grados de evidencia. Se utilizó el formato anterior de las “Guías de Mallorca” para revisar las recomendaciones clínicas. El consenso para las declaraciones de la guía se alcanzó tras tres rondas de votación según el método Delphi.

Se elaboraron recomendaciones para la identificación clínica y molecular del LS, manejo quirúrgico y endoscópico del cáncer colorrectal asociado con el LS y medidas preventivas para el cáncer. Se hizo hincapié en los aspectos quirúrgicos y gastroenterológicos del espectro del cáncer. Se aprobaron las recomendaciones de consenso de Manchester para el manejo ginecológico. Se distribuyeron resúmenes para profesionales y el público en general.

Se presentan las recomendaciones de la EHTG y ESCP para la identificación de pacientes con LS, vigilancia colorrectal, manejo quirúrgico del cáncer colorrectal, estilo de vida y quimioprevención en LS en las que se obtuvo consenso (> 80%).

Recommendations for clinical and molecular identification of LS, surgical and endoscopic management of LS■associated colorectal cancer and preventive measures for cancer were

produced. The emphasis was on surgical and gastroenterological aspects of the cancer spectrum.

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pmc-prop-preprint no pmc-prop-in-epmc yes pmc-license-ref CC BY Definitions used in these
guidelines Consensus: at least 80 per cent agreement

Subtotal colectomy: anastomosis is ileosigmoidal

Total colectomy: anastomosis is ileorectal

Extended surgery: refers either to subtotal colectomy with ileosigmoidal anastomosis or total colectomy with ileorectal anastomosis, when used to replace an operation that would be oncological standard practice for a sporadic colorectal cancer, because of a pathogenic germline variant

Amsterdam criteria: these criteria were introduced for uniform classification based on family history and require at least three affected members on the same side of the family in two or more generations, with one being a first-degree relative of the other two and at least one individual diagnosed before 50 years of age. The Amsterdam I criteria apply to families with three or more colorectal cancers, and the Amsterdam II criteria also include extracolonic tumours: endometrial cancer, cancer of the upper urinary tract and cancer of the small bowel

Carrier: a person with a germline path _ MMR variant

Lynch syndrome (LS): the dominantly inherited cancer syndrome caused by the presence of a pathogenic mismatch repair gene variant

Revised Bethesda guidelines: guidance developed for testing colorectal tumours for microsatellite instability (MSI), when: colorectal or uterine cancer is diagnosed in a patient who is less than 50 years of age; synchronous, metachronous colorectal, or other hereditary non-polypoid colorectal cancer (HNPCC)-associated tumours (regardless of age) are present; colorectal cancer with MSI-high is diagnosed in a patient who is aged less than 60 years; colorectal cancer is diagnosed in one or more first-degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed under age 50 years; colorectal cancer is diagnosed in two or more first- or second-degree relatives with HNPCC-related tumours, regardless of age

Path_MMR : the pathogenic (disease-causing) variants of the specified mismatch repair (MMR) gene associated with cancer, including all structural or epigenetic variants of these

Recommendations for the identification of patients with Lynch syndrome (LS), colorectal surveillance, surgical management of colorectal cancer, lifestyle and chemoprevention that reached a consensus (at least 80 per cent) by a combined expert working group from the European Hereditary Tumour Group (EHTG; former Mallorca Group) and the European Society of Coloproctology (ESCP) are presented in Table 1 . In addition, there was agreement to endorse the Manchester consensus statement for gynaecological cancer in LS 1 . The summary of recommendations for healthcare professionals is as follows.

Recommendations that achieved consensus based on GRADE

*Based on moderate-quality evidence; † based on low-quality evidence. ‡ Consensus not reached between 2- and 3-year interval. GRADE, Grading of Recommendations, Assessment, Development and Evaluation; LS, Lynch syndrome; MMR, mismatch repair; MSI, microsatellite

instability; CRC, colorectal cancer; dMMR, deficient mismatch repair; APR, abdominoperineal resection; ECCO, European CanCer Organisation.

Overview of chromoendoscopy studies in Lynch syndrome

CE, chromoendoscopy; OR, odds ratio; NBI, narrow-band imaging; iSCAN, postprocessing software filter technology; LS, Lynch syndrome.

LS is caused by inherited malfunction in one of the four MMR genes named MLH1, MSH2, MSH6 and PMS2. The malfunctioning variants are referred to as path_MLH1, path_MSH2, path_MSH6 and path_PMS2. People carrying inherited path_MMR or inherited epigenetically silenced variants of these genes are referred to as carriers.

Carriers have an increased risk of developing colorectal, endometrial, ovarian, urinary tract, prostate and other cancers, depending on which gene is malfunctioning. Therefore, consideration to the responsible gene and gender should be given where a pathogenic variant has been identified.

The average risk for cancer stratified by gene, organ, gender and age is available at <http://www.PLSD.eu>. This resource allows personalized genetic counselling to support decision-making.

The guidelines presented here are designed to empower patients and clinicians to enable informed and individualized decision-making; the authors recognize that there is no universal approach to the care of those who carry path_MMR and have LS, and therefore personalized care is critical.

All colorectal and endometrial cancer should be tested for evidence of MMR deficiency to screen for LS. If not limited by resources, all those with colorectal or endometrial cancer can undergo direct germline testing for path_MMR.

The established clinical criteria may be used for selecting people without cancer to be genetically tested.

Colonoscopy is recommended every 2 or 3 years for path_MLH1, path_MSH2 and path_MSH6 carriers, unless they have had colorectal cancer before, after which biennial colonoscopy is recommended.

Path_PMS2 carriers may be considered for 5-yearly colonoscopy.

Colonoscopy surveillance is recommended starting at age 25 years for path_MLH1 and path_MSH2 carriers, and at age 35 years for path_MSH6 and path_PMS2 carriers.

The recommended surveillance for colorectal cancer does not differ between men and women.

The Manchester International Consensus Group 1 recommendations for the surveillance, management and prevention of gynaecological cancers in LS are endorsed.

Extended surgery is recommended for path_MLH1 and path_MSH2 carriers at the time of first diagnosis of a colonic cancer.

Removing part of the colon or rectum in the absence of cancer or endoscopically non-removable polyps is not generally recommended for path_MSH6 and path_PMS2 carriers.

Summary of core content of the recommendations

MMR, mismatch repair; IHC, immunohistochemical; MSI, microsatellite instability; CRC, colorectal cancer; EHTG, European Hereditary Tumour Group; ESCP, European Society of Coloproctology.

Smoking and obesity increase the risk of colorectal cancer in carriers.

Alcohol consumption increases the risk of colorectal cancer in carriers.

Physical activity reduces colorectal cancer risk in carriers.

Daily acetylsalicylic acid of at least 75 mg reduces cancer risk in carriers.

Recommendations for professionals have been summarized in Fig . 1 and Table S1 (supporting information). Universal laboratory screening for upper urinary tract carcinomas to identify LS was approved by a majority (73 per cent) but did not reach consensus. A summary of recommendations for patients (layperson summary) is presented in Table S2 (supporting information).

LS (OMIM #120435) is the most common dominantly inherited cancer syndrome but is often not recognized 2 , 3 . The prevalence of path_MMR carriers has been estimated to be around one in 300, that is 2.5 million people in Europe alone 4 .

Carriers are at increased risk of developing cancers, including colorectal, endometrial, ovarian, stomach, pancreatic, small bowel, biliary tract, urinary tract, brain and skin cancer. In LS, these cancers may occur much earlier in life than their sporadic counterparts, but older age of onset is not infrequent, and penetrance and expression vary by gene and gender from very high to immeasurable. The International Society for Gastrointestinal Hereditary Tumours (InSiGHT), through the use of its international database (<http://insightdatabase.org/>) and expertise, categorizes MMR gene variants as being pathogenic (class 5) or likely to be pathogenic (class 4) (or as being of uncertain significance, likely not pathogenic or not pathogenic). This information can then be used to inform patient-centred counselling in consultation with the Prospective Lynch Syndrome Database (PLSD) (<http://www.plsd.eu>). Potentially modifiable factors include acetylsalicylic acid (aspirin) prophylaxis and lifestyle. Typically, LS-associated cancers have significantly better prognoses than sporadic cancers affecting the same organs, reflecting biological differences, including the marked immune responses that characterize LS cancers 5 . Patients with LS who are within cancer surveillance programmes benefit from a stage shift and earlier cancer diagnosis and usually survive their first cancers. Despite surveillance, those with LS can go on to develop metachronous cancers, with service planning implications 6 .

Carriers are identified by demonstration of a class 5 or 4 germline path_MMR variant. HNPCC refers to a family history indicating dominantly inherited colorectal cancer, which was later divided to specify several distinct, inherited, cancer syndromes that include colorectal cancer and other cancers (Fig . 2) 7 . Previously published guidelines 8 , 9 , for clinical management of LS were based on retrospective studies and made uniform management recommendations, regardless of which gene was involved.

Clinical classification of hereditary non-polyposis colorectal cancer and causal genes 7

HNPCC, hereditary non-polyposis colorectal cancer; MMR, mismatch repair.

In 2007, a group of European experts (the Mallorca Group) published guidelines for the clinical management of LS 10 that were revised in 2013 8 . The present second revision was conducted by a combined expert working group from the EHTG (former Mallorca Group) and ESCP, and was based on previously selected clinical questions. The group consisted of surgeons, clinical and molecular geneticists, pathologists, epidemiologists, gastroenterologists and a patient representative. If a particular specialty was not represented, specialists outside the group were consulted. It was decided that the update format of the manuscript would be via a continuous

update process to be undertaken by the EHTG (living guidance).

This update is based on the results from new prospective studies that reported the average risk of cancer in carriers by organ, by age, by gene and by gender. It covers the screening, diagnosis and management of LS, and is targeted for patients with this condition. Its aim is to gather the most up-to-date evidence on the management of LS. Furthermore, this guideline addresses the clinical questions raised in previous versions, and updates recommendations for the clinical management of carriers. Specifically, the guideline details the treatment and prevention of cancers based on gene and gender, and identifies areas requiring more research. This document is directed to patients of both genders and all age groups in which the diagnosis of LS is suspected or confirmed. The recommendations are directed to all patients with the condition, irrespective of severity or comorbidities.

A PICO (Patients, Intervention, Comparison, Outcome) model structure was created for each area of interest, based on previously published template questions 8 . A systematic literature search was performed using the PubMed database and the Cochrane Database of Systematic Reviews, and manual searches of relevant articles up until November 2018. The following Medical Subject Heading (MeSH) terms were used: 'hereditary nonpolyposis colorectal cancer'[All Fields] OR 'Lynch syndrome'[All Fields]; 3893 articles were identified. The titles were screened and relevant articles written in English were reviewed, and the level of evidence was graded as high, moderate, low or very low, according to GRADE (Grading of Recommendations, Assessment, Development and Evaluation) criteria (<http://www.gradeworkinggroup.org/>) (Table S3 , supporting information).

During the working group meetings (3 meetings and several teleconferences), the outcomes of the literature search were discussed in detail. PICOs are available in Appendix S1 (supporting information) and Delphi round results in Table S4 (supporting information).

Suggestions for guidance statements emerging from the literature review were formulated and tested through Delphi model-based voting rounds. The first Delphi round took place as an online questionnaire on SurveyMonkey® (<https://www.surveymonkey.co.uk>) in week 38 of 2018. The stakeholders were identified from the membership of the EHTG to provide multidisciplinary expertise. The statements were thereby revised for a second Delphi round via live voting which took place in week 39 of 2018, among participants at the Third Annual Meeting of the EHTG in Nice, France. The statements were revised again, and a third Delphi round was conducted by SurveyMonkey® with voting in weeks 32–34 of 2019, again among multidisciplinary stakeholders identified by the EHTG. The most recent results from the PLSD studies were disclosed to all participants before voting, but were only published later 11 . The threshold for reaching consensus in the Delphi votes was set at 80 per cent.

The AGREE reporting checklist was used to guide the reporting of the process (Appendix S1 , supporting information). An external review of the statements was undertaken before the third Delphi round, focusing mainly on the language of the statements communicating the strength of the recommendation based on the quality of evidence.

LS carcinomas of the large bowel are associated with a highly cellular, medullary or mucinous appearance, with a marked increase in the number of intratumoral and peritumoral lymphocytes, a pushing border with a low frequency of budding and low stromal content. They have a lower rate of nodal spread. Although these phenotypic features are in keeping with aberrant MMR protein expression, they are not specific for LS.

The clinical criteria for preselection of people for genetic testing (Amsterdam II 12 and revised Bethesda 13 criteria) are insensitive and lack specificity in identifying carriers (Table S5 , supporting information); testing of incident colorectal cancer cases has been recommended for over a decade. In parallel with the present work, a consensus guideline meeting on gynaecological cancer in LS recommended screening for LS in patients with endometrial and ovarian cancer (and

also BRCA1/2 screening in ovarian cancer). Furthermore, identification of carriers provides the opportunity for cascade testing of relatives, which has the benefit of identifying healthy carriers. These approaches have been shown to be cost-effective 14 , 15 .

Laboratory screening of patients with upper urinary tract cancer to identify LS was agreed by a majority (73 per cent) but did not reach consensus.

All colorectal cancers should be tested by MMR (MLH1, MSH2, MSH6, PMS2) immunohistochemistry or MSI testing (followed by possible MLH1 hypermethylation testing) to screen for LS.

Patients with endometrial or ovarian cancer should be screened by immunohistochemistry or DNA testing as described in the Manchester consensus statement.

Data from largely observational studies conducted since the 1990s have supported the role of colonoscopic surveillance in patients with LS. Järvinen and colleagues 16 , 17 reported on the outcomes of a cohort of patients with LS who underwent colonoscopic surveillance and compared them with a group who did not, and observed a 62 per cent reduction in colorectal cancer in the surveillance group. Similar observations were made in other studies 18–20 . Altogether, colonoscopic surveillance seems to lead to a 60–72 per cent decrease in colorectal cancer mortality. More recent data from prospective observational studies have questioned the previously reported benefits in earlier studies 16,17,20 of comparative colorectal cancer incidence. Specifically, nearly half of path_MLH1 and path_MSH2 carriers develop colorectal cancer under surveillance 6,21–23 , and the benefits of colonoscopic surveillance are mainly to improve survival by earlier detection compared with no surveillance.

There was consensus agreement that for all path_MMR carriers colonoscopic surveillance should be performed to reduce mortality and incidence of colorectal cancer.

Chromoendoscopy (CE) uses contrast dyes (usually indigocarmine) to highlight the mucosal surface contours and enhance visualization. In virtual CE, filtering technology is built into the colonoscope system, which alters the white-light image to highlight mucosal surface architecture and capillary pattern. Results with use of CE and virtual CE are summarized in Table 2 24–33 . These studies are largely methodologically flawed, which limits the conclusions that can be drawn. CE may be equivalent to high-quality white-light examination with prolonged withdrawal. However, given the conflicting results of studies, and the methodological flaws of most published studies, CE may still be a helpful adjunct to be considered in colonoscopic surveillance in LS.

Chromoendoscopy is equivalent to high-definition white-light endoscopy in specialist centres. It may be an adjunct to be considered in the absence of high-definition endoscopy or in centres with lower adenoma detection rates.

In studies from the PLSD published by Møller and colleagues 21 , the interval between last surveillance colonoscopy and colorectal cancer was analysed. Of 145 colorectal cancers, 100 were diagnosed more 2 years after the last colonoscopy (interval after colonoscopy range 0–125 months). On the other hand, the high incidence of colorectal cancers in the PLSD despite colonoscopic surveillance was not due to the inclusion of a large cohort of Finnish path_MLH1 carriers for whom a 2–3-year interval between colonoscopies had been recommended 34 . The cumulative incidence of colorectal cancer or stage at detection did not differ between 1-yearly, 2-yearly and 2–3-yearly colonoscopic surveillance strategies in a study of 2747 path_MLH1 , path_MSH2 and path_MSH6 carriers who were followed up for a total of 23 309 years by 16 327 colonoscopies 23 .

Gathering evidence suggests that carcinogenesis in path_PMS2 is predominantly via the adenomatous pathway 35 , and that the cancer risk is substantially lower than that for other LS

genotypes, especially under colonoscopic surveillance 6 .

There is no reported substantial difference in lifetime incidence of colorectal cancer between that estimated by retrospective segregation analyses over three generations 36–38 and that in the PLSD report 6 on the effects of colonoscopy in preventing colorectal cancer as advocated by recent international guidelines (Table 3).

Studies describing the cumulative incidence of colorectal cancer in patients with Lynch syndrome

*Cumulative risk at 80 years. PLSD, Prospective Lynch Syndrome Database.

For path_MLH1 , path_MSH2 and path_MSH6 carriers, 2■ or 3■yearly colonoscopic surveillance is recommended (consensus not reached between 2 and 3 years).

For path_PMS2 carriers, 5■yearly surveillance may be considered.

For patients with LS with a history of colorectal cancer and segmental or subtotal colectomy, biennial colonoscopies should be performed.

There is no evidence at the moment to support different surveillance colonoscopy intervals for men and women.

If bowel preparation is not entirely adequate, a repeat procedure at 1 year is recommended.

If the bowel preparation is completely inadequate or the examination incomplete, an immediate repeat colorectal surveillance procedure should be requested (within next 6 weeks).

A number of studies have confirmed that the risk of developing colorectal cancer before the age of 25 years is very low (Table 4) 6 , 8 , 21 , 22 , 37–48 .

Overview of studies about age and risk of developing colorectal cancer in Lynch syndrome

The study described a series of 377 patients with path_PMS2 and the observed median age at first CRC was 52 (range 26–86) years. The authors also noted gender differences in CRC risk. The cumulative risk in men aged <40, 40–49, 50–59 and 60–69 years was 1·3, 4·6, 7·1 and 18·8% respectively. The corresponding cumulative risks by age in women were 0·5, 0·9, 4·7 and 10·5%. It was recommended that starting colonoscopy surveillance could be deferred until age 30 years for both genders.

ten Broeke et al . also published a large series of patients with path_PMS2, and reported only a 2–3 times increased cumulative incidence of CRC under surveillance compared with the general population. This is about the same level of CRC risk as when there is a positive family history of the disease but genetic testing for LS (and other hereditary CRC syndromes) proves negative

LS, Lynch syndrome; CRC, colorectal cancer; PLSD, Prospective Lynch Syndrome Database.

The risk of a path_PMS2 carrier developing cancer at young age is low, and the median age for path_PMS2 ■related first colorectal cancers is 52 years 47 . Based on PLSD studies, path_MSH6 carriers also have a lower risk of early■onset cancer; the cumulative colorectal cancer risk at age 40 years was 12 per cent for path_MLH1 , 9 per cent for path_MSH2 and 0 per cent for path_MSH6 . There is no convincing evidence to show that the age of onset is different between men and women.

For path_MLH1 or path_MSH2 carriers, surveillance colonoscopies should be initiated at the age of 25 years.

For path_MSH6 or path_PMS2 carriers, surveillance colonoscopies should be initiated at the age of 35 years.

Age at onset of surveillance should not be stratified by gender.

The individual cumulative risk of cancer in any organ for the remaining lifetime of a patient with LS may be obtained by indicating their age, gender and genetic variant using <http://www.plsd.eu/>. There is no demonstrated benefit of surveillance for incidence or survival of gastric cancer, small bowel cancer, pancreatic cancer, urinary tract cancer, prostate cancer or breast cancer in path_MMR carriers (Table 5) 6 , 49–56 .

Studies describing cumulative risk and surveillance outcome for gastric, small bowel, pancreatic, urinary tract, prostate and breast cancer in Lynch syndrome

LS, Lynch syndrome; HNPCC, hereditary non-adenomatous polyposis colorectal cancer; PLSD, Prospective Lynch Syndrome Database.

Consensus was not achieved for the statement 'Surveillance for other cancers (than colorectal, endometrial and ovarian) should not be offered'.

The risk of metachronous colorectal cancer after primary colonic cancer depends on which variant a carrier has and on the extent of surgery performed in managing the primary colonic cancer (how much colon is left to be at risk). There are no good data describing the risk of a second colonic cancer by gene and treatment of first cancer. Analyses in the PLSD 22 suggested that the risk of a second colorectal cancer was determined stochastically: the risk of a second cancer was not substantially different from the risk of a first cancer by age, gene and gender. Without stratifying by gene and treatment of first colonic cancer (because numbers in the study did not allow substrata for analysis), a PLSD study 22 reported that the risk of metachronous colorectal cancer by 70 years (starting from 40 years) after an earlier colonic cancer and despite regular colonoscopies was 36 (95 per cent c.i. 29 to 43.8) per cent. The numbers were likely to be conservative estimates for metachronous cancer, because a substantial proportion of these patients were treated at specialized centres and will have had extended colonic surgery. Three recent meta-analyses and several independent studies evaluated the risk of metachronous colorectal cancer after colectomy for colonic cancer (Table 6) 57–65 . No studies have reported the risk of a third colorectal cancer after subsequent colonic cancer. However, third metachronous colorectal cancers have been described, as has survival after these subsequent cancers 22 . There are no studies addressing the more invasive surgical option of extending colorectal surgery to a proctocolectomy at the occurrence of a first or metachronous colonic or rectal cancer. It is essential to evaluate the role of extended surgery prospectively and provide recommendations stratified by MMR gene in order to reduce the incidence of metachronous colorectal cancer occurring in path_MMR carriers.

Studies describing surgical treatment for colorectal cancer in Lynch syndrome

LS, Lynch syndrome; CRC, colorectal cancer; HNPCC, hereditary non-adenomatous polyposis colorectal cancer; RR, relative risk; STC, subtotal colectomy; ISA, ileosigmoidal anastomosis; IRA, ileorectal anastomosis; TC, total colectomy.

Extended surgery, either subtotal colectomy with ileosigmoidal anastomosis or total colectomy with ileorectal anastomosis, for primary colonic cancer in path_MLH1 and path_MSH2 carriers is preferable to reduce the risk of subsequent colorectal cancer, even though extended surgery has not been shown to improve overall survival. There is no substantial evidence to support extended surgery for path_MSH6 and path_PMS2 carriers. All surgical decision-making should be

personalized, based on the patient's age, gender, and expected functional outcome and priorities.

A largely retrospective body of evidence supports the extension of surgical resection in path_MLH1 and path_MSH2 carriers, but the risk of metachronous colorectal cancer in path_MSH6 and path_PMS2 carriers is not high enough to warrant an extended approach (Table 6).

For a path_MLH1 or path_MSH2 carrier with a first colonic cancer, extended surgery with ileosigmoidal/ileorectal anastomosis is preferable to standard resection to reduce the risk of metachronous colorectal cancer.

For a path_MSH6 or path_PMS2 pathogenic variant carrier with a first colonic cancer, standard/segmental colonic resection should be offered.

For a path_MMR carrier with a metachronous colonic cancer, the surgical treatment can be extended surgery with ileorectal/ileosigmoidal anastomosis.

A decision on extended surgery for colorectal cancer should not be based on deficient MMR immunohistochemistry (loss of MLH1, MSH2, MSH6 or PMS2) and BRAF staining/ MLH1 hypermethylation from the preoperative endoscopic biopsy only.

Studies have reported metachronous cancer after rectal cancer in carriers 66 , 67 . Because the cumulative risk of a subsequent colonic cancer developing during surveillance is significant, extended surgery may be a personal preference, considering the higher degree of surgical morbidity associated with the procedure. Quality of life of patients with an ileoanal pouch may be comparable to that of patients with familial adenomatous polyposis rather than those with inflammatory bowel disease (IBD), because the worse overall outcome in the latter group is due to the underlying inflammatory condition. There is clear evidence that surgeons performing a high volume of procedures in high-volume units (over 10 per year) achieve lower pouch failure rates as well as better pouch salvage than those with a lower throughput of these procedures 68 , 69 . Preferred surgical options by gene are shown in Table 7 .

Surgical options for colorectal cancer in path_MMR carriers

Adenoma formation in a colonic segment other than the segment affected by colonic cancer

Extended surgery such as colectomy with ileosigmoidal or ileorectal anastomosis.

For young patients, consider more extensive surgery

LS, Lynch syndrome; APR, abdominoperineal resection.

For a path_MMR carrier, the surgical treatment of a primary rectal cancer (occurring as the first colorectal cancer) should be standard resection (anterior resection or abdominoperineal resection).

In a young path_MMR carrier with a synchronous colorectal neoplasm or a personal preference, extended surgery can be considered.

Ileoanal pouch surgery (in agreement with European CanCer Organisation guidelines for pouch surgery in ulcerative colitis) should be performed in highly specialized colorectal surgical units.

It is acknowledged that, even with the more favourable stage at diagnosis in patients under surveillance, there is a 9 per cent overall mortality rate among patients with LS in the 10 years after diagnosis of colorectal cancer. There is no documented procedure to identify and separate carriers at higher risk of colorectal cancer than the average by using age, gene and gender, nor those who

might be at risk of not surviving a future colorectal cancer. There is no evidence base to support prophylactic colorectal surgery in path_MMR carriers.

In a study 70 of patients with high-grade dysplasia in endoscopic biopsies and a polyp that was not amenable to endoscopic removal, 22 of 165 polyps (13.3 per cent) had an invasive cancer on final pathology. In another study at the Mayo Clinic 71, 133 of 750 unresectable polyps (17.7 per cent) harboured a malignancy, of which 23 per cent were lymph node-positive. Although these studies were conducted without knowledge of the MMR status of the tumours, they indicate that high-grade dysplasia on biopsy is a strong predictor of tumours harbouring invasive malignancy.

In patients with LS and concurrent IBD, it is unclear whether colorectal cancer risks are sufficiently increased for prophylactic colectomy to be indicated. In a small series 72 of 12 patients with LS and concurrent IBD, four developed colorectal cancer in an early age. However, the series did not demonstrate a sufficiently increased risk of colorectal cancer to recommend prophylactic surgery.

For endoscopically non-removable polyps with advanced histology, an oncological approach is recommended, as for gene-specific treatment for carcinoma.

Prophylactic colorectal surgery in the absence of neoplastic lesions in the colorectum is not recommended for path_MMR carriers based on their pathogenic variant-related risk only.

The majority of studies showed positive associations between BMI and smoking and colorectal cancer, whereas some studies reported that alcohol consumption was positively associated with colorectal cancer. One study reported an inverse association between physical activity and colorectal cancer in path_MMR carriers (Table 8) 73–89 . No lifestyle factor has been demonstrated to increase the risk of cancer specifically for one gender, or for carriers of pathogenic variants in a specific gene.

Association studies between BMI, smoking, alcohol consumption, physical activity and colorectal cancer in Lynch syndrome

Path_MMR carriers should be advised that smoking and obesity increase the risk of colorectal cancer.

Path_MMR carriers should be advised that alcohol consumption increases the risk of colorectal cancer.

Path_MMR carriers should be advised that physical activity reduces the risk of colorectal cancer.

An RCT 76,85,90 showed that 600 mg acetylsalicylic acid daily for 2–4 years was well tolerated and reduced colorectal cancer incidence after 5 years following initiation of the treatment. A recently published study 91 has shown that the benefit of prevention with acetylsalicylic acid persists into the second decade. Observational data in the general population suggest that lower doses may also be effective 92, 93 . For bodyweight above average (70 kg), a higher dose than currently in clinical use for other indications may be required 94 .

Path_MMR carriers should be advised that daily acetylsalicylic acid intake will reduce colorectal cancer risk.

The recommended acetylsalicylic acid dose should be a minimum of 75–100 mg daily. This dose should be increased for people with above-average body mass.

The recommendations from the EHTG and ESCP for identification of patients with LS, colorectal surveillance, surgical management of colorectal cancer, lifestyle and chemoprevention in LS that

reached a consensus (at least 80 per cent) are presented here. The joint statement also endorsed the Manchester International Consensus Group recommendations for the management of gynaecological cancers in LS.

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Additional supporting information can be found online in the Supporting Information section at the end of the article.