Lynch syndrome Care pathway

*The Patient Clinical Pathway is "the whole care pathway from identification, diagnostics, and multidisciplinary case discussions to surveillance and preventive surgery", so indeed a pathway in time, focusing on **HOW***

Annual Review Recommended

Lynch syndrome (LS) is caused by germline mutations in the mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, *PMS2* or germline deletions in *EPCAM* that result in inactivation of *MSH2*. Carriers of pathogenic variants (PVs) in *MLH1* and *MSH2* have a > 50% lifetime risk of colorectal and endometrial cancer, as well as an increased lifetime risk of small intestine and ovarian cancer. Individuals with LS also have an increased risk of urinary tract, pancreato-biliary, gastric cancer and brain tumours. Some carriers of PVs in MMR genes develop multiple sebaceous adenomas, this phenotype is often denoted Muir-Torre syndrome. Carriers of PVs in *MSH6* have a lifetime risk of 20% for colorectal cancer and 50% for endometrial cancer. Carriers of PVs in *PMS2* have much lower risks compared to the other MMR genes.

Families with high clinical suspicion of having LS and patients with genetically confirmed LS and their (first degree) relatives should ALWAYS be offered genetic counselling by a medical genetic specialist.

Annual or biannual review should be undertaken by specialists in LS (gastroenterologist, oncologist, surgeon, gynaecologist). Intensive LS-specific surveillance measures should be continued throughout the person's life or until deemed appropriate based on individual assessment. In addition, preventive surgery might be appropriate. However, the details of surveillance and preventive measures in current national guidelines differ among EU countries and with European guidelines because of lack of evidence on surveillance outcome and different health care systems.

Review Checklist — Adults (25+)

	WHAT TO LOOK FOR	WHEN REFERRAL AND WHERE TO
COLON/RECTUM	Colonoscopy every 1-2 years from age (20-)25 y, ideally performed at a centre/ by gastroenterologists with experience in LS. Consider starting surveillance from 30 or 40 y of age for *PMS2* PV-carriers and for *MSH6* PV-carriers	In case of abnormal findings or in need of treatment, **REFER** to a specialised centre for discussion by a multidisciplinary team (MDT) to make the proper clinical decisions
UTERUS	Educate females to recognize the symptoms of endometrial cancers (e.g., abnormal uterine bleeding, postmenopausal bleeding). Consider gynaecological surveillance with transvaginal ultrasound and endometrial biopsy every 1-2 years from age 30-35 y. Information on the pros and cons of prophylactic hysterectomy after childbearing (not in *PMS2* PV-carriers)	In case of an abnormal ultrasound or biopsy, **REFER** to gynaecologist familiar with LS
OVARIES	For MLH1, MSH2, and MSH6 pathogenic variant carriers: Information on prophylactic bilateral salpingo-oophorectomy (BSO) between the age of 30-35 years including the pros (highly reduced cancer risk) and cons (long- and short-term side effects). The timing of BSO should be individualised. Mean age of diagnosis is 42-46 years. Post-surgery, hormone replacement therapy is given until the age of 45-50 years unless there is a contra-indication.	**REFER** to gynaecologist familiar with ovarian cancer between the age of 30-40 years **REFER** to diagnostic unit investigation if signs or symptoms associated with ovarian cancer

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UPPER GASTROINTESTINAL TRACT	Testing of *Helicobacter pylori* and if positive, eradicate. There is no demonstrated benefit of surveillance for survival of gastric cancer in MMR mutation carriers, although upper gastrointestinal tract endoscopy every 3-5 years if family history for gastric or duodenal cancer is present, or for all Lynch patients is recommended in most guidelines by means of esophagogastroduodenoscopy	Prevention according to the family history can be considered.
URINARY TRACT	There is no demonstrated benefit of surveillance for urinary tract cancers. Follow-up should be advised only under a research project.	Prevention according to the family history might be considered.
OTHER TUMOURS	If other symptoms develop, be generous with investigations as there is a (small) increased risk for other tumour types such as pancreatic cancer, brain tumours, small bowel cancer, skin cancer, hepatobiliary tract cancer, and probably breast cancer. However, there is yet no demonstrated benefit of surveillance for survival of these cancers in individuals who carry PVs in the MMR genes. In some individuals, multiple sebaceous adenomas develop (Muir-Torre phenotype). Consider skin exams yearly, also with mole check-up.	In case of suspicious skin tumours, **REFER** to dermatologist for extirpation and histopathological diagnosis. Prevention according to the family history might be considered.
PSYCHOLOGICAL BURDEN	Psychological problems are common but patients, both men and women, may be reluctant to talk about these issues and need encouragement.	Consider **REFERRAL** to an appropriate psycho-oncology counselling service
PREGNANCY	Pre-natal diagnosis is usually not requested, but pre-implantation testing (PGT) is available. PGT relies on pre-pregnancy genetic work up and that the family fulfils the requirements for IVF.	Women who are planning pregnancy should be **REFERRED** to a medical geneticist
OTHER	The possibility of chemoprophylaxis with acetylsalicylic acid (ASA) can be discussed, especially with young patients (e.g., <50 years), taking into account the advantages and disadvantages.	

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Lynch syndrome

Care pathway

Family name:

Given name(s)

Address:

Date of Birth: Sex: ☐ M ☐ F ☐ I

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Lynch syndrome Review Checklist

Clinical Presentation:
..... ☐
Other symptoms:
.....
Genetic counselling completed ☐
Date Completed: .....

Clinical diagnosis
.....
Genetic Test '+'ve ☐
Diagnosis Date: .....

General Health Check:
Please record the follow as soon as possible and then annually:
Height
.....

Weight
.....

Blood Pressure
.....

Notes:
.....
.....

Doctor:
.....
.....
Review date:
.....
.....

WHAT TO LOOK FOR	WHEN TO REFER
COLON/RECTUM : Colonoscopy every 1-2 years from age 20-25 years, ideally performed at a centre/by gastroenterologists with experience in LS. Consider starting surveillance from 30 or 40 y of age for *PMS2* PV-carriers and for *MSH6* PV-carriers.	In case of abnormal findings or in need of treatment, **REFER** to a specialised centre for discussion by a multidisciplinary team (MDT) to make the proper clinical decisions. ☐ **Date Referred**: .....
UTERUS: Educate females to recognize the symptoms of endometrial cancers (e.g. abnormal uterine bleeding, postmenopausal bleeding). Consider gynaecological surveillance with transvaginal ultrasound and endometrial biopsy every 1-2 years from age 30-35 y. Information on the pros and cons of prophylactic hysterectomy after childbearing (not in *PMS2* PV-carriers).	In case of an abnormal ultrasound or biopsy, **REFER** to gynaecologist familiar with LS ☐ **Date Referred**: .....
OVARIES : For MLH1, MSH2, and MSH6 pathogenic variant carriers: Information on prophylactic bilateral salpingo-oophorectomy (BSO) between the age of 30-35 years including the pros (highly reduced cancer risk) and cons (long- and short-term side effects). The timing of BSO should be individualised. Mean age of diagnosis is 42-46 years. Post-surgery, hormone replacement therapy is given until the age of 45-50 years unless there is a contra-indication.	**REFER** to gynaecologist familiar with ovarian cancer between the age of 30-40 years **REFER** to diagnostic unit investigation if signs or symptoms associated with ovarian cancer ☐ **Date Referred**: .....
UPPER GASTROINTESTINAL TRACT: Testing of Helicobacter pylori and if positive, eradicate. There is no demonstrated benefit of surveillance for survival of gastric cancer in MMR mutation carriers, although upper gastrointestinal tract endoscopy every 3-5 years if family history for gastric or duodenal cancer is present, or for all Lynch patients is recommended in most guidelines by means of esophagogastroduodenoscopy	Prevention according to the family history can be considered.
URINARY TRACT: There is no demonstrated benefit of surveillance for urinary tract cancers. Follow-up should be advised only under a research project.	Prevention according to the family history might be considered.
OTHER TUMOURS: If other symptoms develop, be generous with investigations as there is a small increased risk for other tumour types such as pancreatic cancer, brain tumours, small bowel cancer, skin cancer and hepatobiliary tract cancer. There is yet no demonstrated benefit of surveillance for survival of small bowel cancer, pancreatic cancer, prostate cancer, or breast cancer in individuals who carry PVs in the MMR genes. In some individuals, multiple sebaceous adenomas develop (Muir-Torre phenotype). Consider skin exams yearly, also with mole check-up.	**REFER** to appropriate specialist ☐ **Date Referred**: ..... Prevention according to the family history might be considered.
PSYCHOLOGICAL BURDEN: Psychological problems are common but patients, both men and women, may be reluctant to talk about these issues and need encouragement. Psychological problems are common but patients, both men and women, may be reluctant to talk about these issues and need encouragement.	Consider **REFERRAL** to an appropriate psycho-oncology counselling service ☐ **Date Referred**: .....
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OTHER: The possibility of chemoprophylaxis with acetylsalicylic acid (ASA) can be discussed, especially with young patients (e.g., <50 years), taking into account the advantages and disadvantages.	