Gene-specific management guidelines for Lynch Syndrome
Frequently asked questions

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This document has been developed to facilitate the use of the below management guidelines:

- Management guidelines for *MLH1* mutation carriers
- Management guidelines for *MSH2* mutation carriers
- Management guidelines for *MSH6* mutation carriers
- Management guidelines for *PMS2* mutation carriers

This document and the management guidelines were written by **Bianca DeSouza** and **Demetra Georgiou**. The management guidelines represent an update of the ICR/RMH Lynch syndrome management guidelines previously written by **Bianca DeSouza** and **Helen Hanson**. **The management guidelines were designed for the use of health professionals only.**

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Q: Where have the cancer risk estimates for *MLH1*, *MSH2*, and *MSH6* mutation carriers been taken form?
The cancer risk estimates for *MLH1*, *MSH2*, and *MSH6* mutation carriers have been taken from large international prospective cohorts, curated by the Prospective Lynch Syndrome Database (PLSD) (Dominguez-Valentin, et al. 2019). The PLSD dataset consist of a total of 6,350 MMR mutation carriers and 51, 646 follow-up years. The risk figures represent prospective cancer risks estimates stratified by age, MMR gene, and gender from age 30 to 75.

Q: Why were cancer risks estimates for *PMS2* mutation carriers not taken from PLSD?
The cancer risk estimates for *PMS2* were not taken from the PLSD as there are insufficient numbers of *PMS2* mutation carriers included in the dataset to make reliable conclusions. Instead, retrospective cancer risk estimates were taken from the largest published *PMS2* international dataset (284 *PMS2* families and 4,878 individuals) (Ten Broeke, et al. 2018). The cancer risk estimates have been corrected for ascertainment bias using modified segregation analysis. The risk figures represent retrospective cancer risks estimates stratified by age and gender from age 30 to 80.

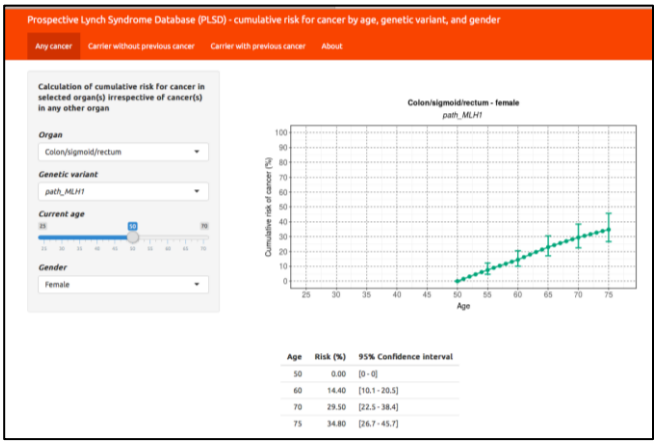
Q: Are the population cancer risks estimates directly comparable to the risks figures for MMR mutation carriers?
The population cancer risks estimates represent lifetime cancer risks, and act as a guide for comparison**, but are not directly comparable** with risks figures for MMR mutation carriers, which have been truncated at age 75 (*MLH1*, *MSH2*, and *MSH6*) or age 80 (*PMS2*). The risk estimates were Cancer Research UK and the Surveillance, Epidemiology, and End Results Program (risks for small bowel cancer and invasive brain tumour).

Q: What cancers are included in the upper gastrointestinal cancer risk estimates?
The upper gastrointestinal risk figures represent the combined risk estimates for stomach, small bowel, bile duct, gallbladder, and pancreatic cancer.

Q: How reliable are the cancer risks estimates for MMR mutation carriers?
The cancer risks figures for MMR mutation carriers are not definitive cancer risks, but aim to facilitate a genetic consultation. However, some caution is warranted with the use of risks estimates for *MLH1*, *MSH2*, and *MSH6* mutation carriers due to the relatively wide confidence intervals associated with the risk figures (Dominguez-Valentin, et al. 2019).

Q: Is it possible to obtain remaining lifetime risk for *MLH1*, *MSH2*, and *MSH6* mutation carriers?

Yes, you can obtain lifetime and remaining lifetime risks from the cancer risks algorithm on the PLSD website on line (www.plsd.eu). You need to select the organ, gene, gender, and the mutation carrier's current age (please see screen shot). Please note, it is not recommended that risk figures for *PMS2* mutation carriers are obtained from PLSD.



Q: How do the prospective cancer risks estimates for the *MLH1*, *MSH2*, and *MSH6* mutation carriers compared to previously reported retrospective cancer risk estimates?

The prospective cancer risks from the PLSD are generally in keeping with the previously published retrospective colorectal and endometrial cancer risks estimates (CRC risk ranged from 34% to 97.2% for *MLH1*, 37% to 77% for *MSH2*, and 10% to 69% for *MSH6* at age 70; EC risk ranged from 18% to 54% for *MLH1*, 21% to 51% for *MSH2*, and 16% to 71% for *MSH6* at age 70). However, the prospective CRC risks estimates may appear lower than retrospective studies subject to ascertainment bias, and the prospective risks represent the risk of developing CRC whilst undergoing regular bowel surveillance. Therefore, the risk of CRC is likely to be higher in carriers not undergoing bowel surveillance (Barrow, Hill and Gareth Evans 2013) (Dowty, et al. 2013).

A noteworthy difference between the prospective and retrospective risks estimates, is the lifetime risk of ovarian cancer for *MSH6* mutation carriers. This was **not** previously reported to be elevated (risk estimates ranged from 0- 1%; at age 70) (Barrow, Hill and Gareth Evans 2013) (Bonadona, et al. 2011), however the risk of ovarian cancer up to age 75 was reported to be 10.8% for *MSH6* mutation carriers (95%CI; 3.7 to 38.6) by the PLSD (Dominguez-Valentin, et al. 2019).

Q: Are male MMR mutation carriers at increased lifetime risk of developing prostate cancer?

A significantly increased risk of prostate cancer has only been reported for male *MSH2* mutation carriers, particularly at older age (RR 3.2; 95% CI; 1.2 to 5.2). Although an increased risk of prostate cancer has been reported for male *MLH1* (RR 1.7; 95%CI; 0.9 to 2.7) and *MSH6* mutation carriers (RR 1.8; 95%CI; 0 to 4.4) this did not reach statistical significance (P. Møller, T. Seppälä, et al. 2018). Male *PMS2* mutation carrier were not reported to have an increased relative risk of prostate cancer in the Ten Broeke et al (2018) study.

Q: Why do we recommend that colonoscopy surveillance commences at a later age for *MSH6* and *PMS2* mutation carriers?

Gene-specific colonoscopy surveillance protocols are justified by lower age-dependent risks and later mean onset of CRC reported for *MSH6* and *PMS2* mutation carriers. Moreover, the

risk of CRC at age 30 was reported to be <0.1% for *MSH6* and *PMS2* mutation carriers, compared to 4.5% for *MLH1* and 2.6% for *MSH2* mutation carriers (Dominguez-Valentin, et al. 2019). Based on this evidence we recommend that surveillance begins at the age of 25 for *MLH1* and *MSH2* mutation carriers, and at the later age of 35 for *MSH6* and *PMS2* mutation carriers. There is currently no strong evidence to support different surveillance intervals for the MMR genes.

Q: Should colonoscopic surveillance be started earlier in families with very young-onset CRC cases?
We note that published guidelines for LS had previously recommended that colonoscopic surveillance should commence 2-5 years before the youngest CRC case in the family, if diagnosed before the age of 25 (Giardiello, et al. 2014). However, we would not currently recommend this approach, as the evidence does not strongly support this. Phenotypic variation in age of CRC onset has been reported within LS families (Geary J 2008), with an earlier age of onset often seen in probands. This was illustrated by ten Broeke et al (2015), who reported a large difference in mean age of CRC (10 years) between probands and PMS2-mutation positive family members (Ten Broeke, et al. 2015). It is important however, that presence of other CRC predisposition mutations and constitutional mismatch repair deficiency (CMMRD) is considered in very young-onset CRC cases. Furthermore, all very young CRC cases (<30) are now eligible to undergo multigene panel gene testing in accordance with the National Genomic Test Directory.

Q. Should colonoscopy surveillance cease after the age of 75?
Colonoscopy can still be offered to individuals after the age of 75, following a review of their physical health and comorbidities. This assessment can be performed jointly by patient's GP and gastroenterology team.

Q: Why is cervical cancer screening recommended for female MMR mutation carriers?
Female MMR mutation carriers are **not** at increased risk of cervical cancer, which are typically of squamous cell histology and associated with the human papilloma virus (HPV). However, some endometrial cancers, particularly of the lower uterine segment, may be detected by a Pap smear test (Westin, et al. 2008). Moreover, in the UK, it is recommended that all women (including those vaccinated against HPV) take part in the NHS cervical screening programme from age 25 to 64.

Q: What gynaecological risk management options should I discuss with female *MLH1*, *MSH2*, and *MSH6* mutation carriers?
The benefit of surveillance protocols for endometrial and ovarian cancer in Lynch syndrome is currently unproven. The risk of endometrial and ovarian cancer rises rapidly from the age of 40 and the risk of endometrial and ovarian cancer was reported to be relatively low below this age in female *MLH1*, *MSH2*, and *MSH6* mutation carriers (<3%) (Dominguez-Valentin, et al. 2019). Therefore, we recommend that the option of risk-reducing total hysterectomy and bilateral salpingo-oophorectomy (BSO) should be offered to female *MLH1*, *MSH2*, and *MSH6* mutation carriers no earlier than the age of 35-40 years following completion of childbearing (Crosbie, et al. 2019).

Obviously there are also many personal factors that may influence this decision, which should be taken into consideration. For example, some women may wish to consider surgery earlier because there have been early-onset cases within their family.

Q: What gynaecological risk management options should I discuss with female *PMS2* mutation carriers?
Female *PMS2* mutation carriers have a significantly lower cumulative lifetime risk of endometrial cancer (13% at age 80) compared to other female MMR mutation carriers and have also not been shown to have a clinically relevant increase in ovarian cancer risk (Ten

Broeke, et al. 2018). In addition to this, the good survival rates for endometrial cancer in Lynch syndrome (10- year survival=89%) means that there is insufficient evidence to support risk-reducing gynaecological surgery in *PMS2* carriers. Nevertheless, endometrial cancer is often the sole or most frequent cancer type seen in *PMS2* families and therefore we recommend that risks and benefits of risk-reducing total hysterectomy **ALONE** be discussed with female carriers following completion of childbearing from the age of 45 (<1.2% risk below age 50).

Are there any circumstances that we would discuss risk-reducing BSO with *MSH6* and *PMS2* carriers?
Similar to non-carrier females, BSO should be discussed with *PMS2* carriers who have a first-degree relative with ovarian cancer and at least one other first- or second-degree relative with ovarian cancer (affected relatives should be first-degree kinship and family should be considered for further genetic investigations to exclude ovarian cancer susceptibility). BSO may also be discussed with *PMS2* carriers undergoing risk-reducing hysterectomies post-menopausally, as the benefit/harm ratio is likely to be more favourable in this situation. However, for *PMS2* carriers undergoing risk-reducing hysterectomies pre-menopausally, the Gynae-Oncologist should discuss the pros and cons of hysterectomy with or without ovarian preservation in a similar fashion to women who are having hysterectomies for benign indications.

Q: What information should I discuss with female MMR mutation carriers considering risk-reducing gynaecological surgery?
Risk-reducing total hysterectomy and BSO have been demonstrated to prevent endometrial and ovarian cancer in females with LS and will prevent the morbidity associated to cancer treatment. Although, the 10-year survival rates are high for LS-associated endometrial (89%, 95%CI; 82–94) and ovarian cancer (84%, 95%CI; 68-93), some women will eventually die from their disease (Dominguez-Valentin, et al. 2019). The pre-operative counselling of female carriers should also include the risks associated with surgery, the very small of primary peritoneal cancer following BSO, possible unnecessary removal, premature surgical menopause, and the possibility of more difficult colonoscopies following surgery. We would recommend that female mutation carriers have multi-disciplinary (e.g. gynaecological oncology surgeon and genetics clinician) pre-operative counselling and are offered surgery (preferably by the laparoscopy approach) at a specialist surgical centre (Crosbie, et al. 2019).

Q: Which females MMR mutation carriers should be offered HRT following risk-reducing surgery?
Female MMR mutation carriers who undergo premenopausal risk-reducing BSO and have not previously had ER-positive breast cancer should be offered oestrogen only HRT (preferably via transdermal route) until the average age of menopause in the UK (51 years). We would recommend that routine referral to a regional menopause clinic also be considered.

Q: What contraceptive methods should be offered to female MMR mutation carriers?
The combined oral contraceptive pill (OCP) should be considered for female MMR mutation carriers who wish have contraception because it has been demonstrated to reduce the risk of endometrial and ovarian cancer (Crosbie, et al. 2019).

Q: Why is Helicobacter pylori screening recommended for *PMS2* mutation carriers who are not reported to be at high risk of gastric cancer?
Although *PMS2* mutation carriers are not reported to be at increased risk of gastric cancer, eradication of Helicobacter pylori can reduce the potential side effects associated with long aspirin chemoprevention and is therefore still recommended.

Q: Who will organise Helicobacter pylori screening?
A letter should be sent to the patient's GP to organise H pylori screening. NICE recommends that the C urea breath or stool antigen tests be used to screen for H pylori in general practice.

Both tests are highly reliable for diagnosis and can be used to assess the success of eradication therapy in positive individuals. Eradication therapy (short course antibiotics and proton pump inhibitors) should be prescribed by the patient's GP if required.

Q: What dose of aspirin chemoprevention should be offered to MMR mutation carriers?
The optimal dose and duration of aspirin chemoprevention is currently unknown (Burn, et al. 2011). The CaPP3 aspirin chemoprevention study is now closed in the UK. It is important that MMR mutation carriers already enrolled in the CaPP3 study should maintain their assigned dose until the end of the study period. In the interim for carriers not enrolled in CaPP3, expert opinion suggests a daily intake of 150mg aspirin be considered for small and average size MMR mutation carriers and 300mg for mutation carriers over 70kg (John Burn).

Q: When should aspirin chemoprevention be considered in MMR mutation carriers?
Expert opinion on aspirin chemoprevention be considered for MMR mutation carriers between the ages of 25 and 65.

Q: Why should extended colectomy be discussed with *MLH1* and *MSH2* mutation carriers with colon cancer requiring surgical management?
MLH1 and *MSH2* mutation carriers who undergo segmental colectomy following a diagnosis of colon cancer have a high risk of developing a metachronous colon cancer (16% at 10y, 41% at 20y, and 62% at 30y) (Parry, et al. 2011). Therefore, we recommend that the option of extensive colectomy versus segmented colectomy be discussed with *MLH1* and *MSH2* mutation carriers (particularly) who require surgical management for colon cancer. The metachronous colon cancer risk, the good prognosis of metachronous colon cancers (10y survival = 91%) (P. Møller, T. Seppälä, et al. 2017), functional consequences of extensive surgery (e.g. increased stool frequency), patient's age and wishes, desire to continue with colonoscopy (and requirement for full bowel prep), and should be considered in the decision-making process. We do not recommend that extensive colectomy should be offered to *MSH6* and *PMS2* mutation carriers.

Q: Should MMR mutation carriers who develop cancer have tailored oncological management?
Yes, MMR mutation carriers with stage II (Dukes' B) CRC may not receive any benefit from adjuvant 5-FU chemotherapy. MMR deficient CRC have been demonstrated to have a very good prognosis and a very small chance of recurrence. As such, the risks of chemotherapy are likely to outweigh risks of recurrence (Schmoll, et al. 2012). These matters need to be discussed by the oncology team. Furthermore, emerging evidence regarding use of PD1 inhibitor therapies in advanced MMR deficient tumours have shown to be beneficial in LS. While this is not currently a NICE approved treatment, there are several research trials available throughout the UK. Patients can discuss their trial eligibility with their oncology teams.

Q: What symptoms should be discussed with MMR mutation carriers?
The importance of symptom awareness should be discussed with all MMR carriers. The following symptoms should be discussed:

Colorectal	Bleeding from the back passage (rectum), blood in stools, change in normal bowel habits to diarrhoea or looser stools (lasting longer than 4 to 6 weeks), unexplained weight loss, abdominal pain, and fatigue.
Endometrial	Vaginal bleeding after the menopause, heavy periods, bleeding between menstrual cycles, and vaginal discharge.

Ovarian	Symptoms can be quite vague, but include pain in the lower abdomen or side, feeling bloated, abdominal swelling, abdominal pain, abnormal vaginal bleeding (postmenopausal or in between cycles), back pain, and constipation.
Urinary tract	Blood in urine, mass in abdomen, weight loss, fatigue, persistent pain in side, and urinary frequency or urgency.
Upper GI tract	Persistent indigestion, feeling full early, pain or difficulty with swallowing, fatigue, dark tarry stools, nausea, pain in the back/stomach, unexpected weight loss, and yellowing of the skin and whites of the eyes.

We recommend that there is low threshold for further investigations in MMR mutation carriers presenting with any unexplained and persistent symptoms.

Q: What lifestyle advice should I offer to MMR mutation carriers?
MMR mutation carriers should be advised to have a healthy diet (i.e. at least five portions of fruit and vegetables, limit red and process meat consumption), maintain a healthy body weight, take regular exercise, only drink alcohol in moderation, and not smoke (Van Duijnhoven, et al. 2013).

Q: Should dermatology screening be offered for MMR mutation carriers with a personal or family history of a LS-associated skin tumour?
Yes, a baseline dermatology skin review may be offered to MMR mutation carriers who have a personal or family history of a sebaceous skin tumour (sebaceous adenomas and carcinomas) or keratoacanthoma (neoplasm of the hair follicle). The term, Muir Torre syndrome (MTS) is often used to LS families who develop these characteristic skin tumours, and most cases have been reported in *MSH2* mutation carriers. The frequency of MTS is estimated ln LS families have been reported to range from 1 to 9% (Ponti, et al. 2005) (South, et al. 2008).

Q: How should I manage an *EPCAM* deletion carrier?
We currently recommend that *EPCAM* deletion carriers have equivalent management to *MSH2* mutation carriers, as *EPCAM* deletions cause LS through epigenetic silencing of *MSH2* in EPCAM-expressing tissues. From the limited data, *EPCAM* deletion carriers have similar lifetime risks of colorectal cancer to *MSH2* carriers, but the risk of endometrial cancer has been reported to be significantly lower, and the actual risk of endometrial cancer may be dependent on the deletion size and location (Kempers, et al. 2011). There is still uncertainty regarding the risks of minor LS- associated cancers in *EPCAM* deletion carriers.

Q: What is Constitutional MMR Deficiency (CMMRD) Syndrome and when should this diagnosis be considered?
CMMRD syndrome is a distinct childhood cancer syndrome caused by biallelic germline mutations in the MMR genes. This syndrome is characterised by multiple hyperpigmented and hypopigmented skin areas, immune deficiency, brain malformations, pilomatricomas, early onset colorectal cancers or other LS-related cancers (i.e. in childhood and teenage years), oligopolyposis in the small bowel and/or colon, brain tumours, and haematological malignancies (Wimmer, et al. 2014). The diagnosis should be considered is LS patients that are diagnosed with LS-related cancers in childhood, adolescence, or early adulthood (<25y for *MLH1* and *MSH2* and <30y for *MSH6* and *PMS2*).

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