UK CANCER GENETICS GROUP

FAQ for Management Guidelines for *MLH1, MSH2, MSH6*, and *PMS2* Germline Pathogenic Variant Carriers for Healthcare Professionals

Referral to Clinical Genetics

- It is recommended that all patients identified as carriers of a germline pathogenic variant (GPV – i.e. class 4 – likely pathogenic variant, or class 5 -pathogenic variant as determined by ACMG/AMP guidelines) in *MLH1, MSH2* (including *EPCAM* deletions), *MSH6*, or *PMS2* are referred to clinical genetics to receive advice on cancer risks, management of cancer risks, reproductive options and to facilitate cascade testing of at-risk relatives.

EPCAM deletions

- We currently recommend that patients identified as carriers of a germline 3'end *EPCAM* deletion have equivalent management to *MSH2* GPV carriers, as *EPCAM* deletions cause LS through epigenetic silencing of *MSH2*.

General population cancer risk estimates

- The estimates presented are from Cancer Research UK (personal communication, October 2023)

Cancer type	Gender	ICD-10 Code	Cumulative risk to age 74	Method used	Method reference
Bowel	Female	C18-C20	2.22%	AMP	Sasieni et al. 2011
Bowel	Male	C18-C20	2.87%	AMP	Sasieni et al. 2011
Uterus	Female	C54-C55	1.57%	CP	Esteve et al. 1994
Ovary	Female	C56-C57.4	1.13%	AMP	Sasieni et al. 2011
Bladder	Female	C67	0.25%	AMP	Sasieni et al. 2011
Bladder	Male	C67	0.66%	AMP	Sasieni et al. 2011
Kidney	Female	C64-C66, C68	0.69%	AMP	Sasieni et al. 2011
Kidney	Male	C64-C66, C68	1.30%	AMP	Sasieni et al. 2011
Stomach	Female	C16	0.24%	AMP	Sasieni et al. 2011
Stomach	Male	C16	0.49%	AMP	Sasieni et al. 2011
Small Intestine	Female	C17	0.15%	AMP	Sasieni et al. 2011
Small Intestine	Male	C17	0.18%	AMP	Sasieni et al. 2011
Pancreas	Female	C25	0.62%	CP	Esteve et al. 1994
Pancreas	Male	C25	0.75%	CP	Esteve et al. 1994
Gallbladder	Female	C23	0.13%	CP	Esteve et al. 1994
Gallbladder	Male	C23	0.05%	CP	Esteve et al. 1994
Brain, Other CNS and Intracranial Tumours	Female	C70-C72, C75.1-C75.3, D32-D33, D35.2-D35.4, D42-D43, D44.3-D44.5	0.94%	AMP	Sasieni et al. 2011
Brain, Other CNS and Intracranial Tumours	Male	C70-C72, C75.1-C75.3, D32-D33, D35.2-D35.4, D42-D43, D44.3-D44.5	0.92%	AMP	Sasieni et al. 2011
Prostate	Male	C61	9.02%	CP	Esteve et al. 1994

Method key/Notes:

- CP - “Current Probability”
- AMP - “Adjusted for Multiple Primaries”
- These age-specific cumulative risk estimates were calculated for males and females separately and by five-year age-band (e.g. 70-74), based on the methodology stated. These are therefore likely to be conservative estimates for risk in those aged 74.
- These numbers reflect the risk of cancer for people born in 1961.
- For more information on the methodology behind these calculations, please see: https://www.cancerresearchuk.org/health-professional/cancer-statistics/cancer-stats-explained/our-calculations-explained#heading-Eight
- Population risk figures for some LS-related cancers were not available and the closest alternative was used.

MLH1, MSH2**, and *****MSH6*** **cancer risk estimates**

- Cancer risk estimates are from the most recent report from the Prospective Lynch Syndrome Database: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(23)00086-X/fulltex
- The PLSD estimates are aimed at determining the risks of GPV carriers currently undergoing colorectal surveillance.
- The PLSD (www.plsd.eu) enables interactive calculation of remaining lifetime cancer risks, by age and gender and should be used during genetic counselling.

PMS2 **cancer risk estimates**

The PMS2-related colorectal and endometrial cancer risks have been obtained from two distinct sources:

1) Ten Broeke et al, 2018:

- A retrospective study of 284 families (n= 4,878 FDRs and SDRs) using modified segregation analysis. **The study attempted to estimate the cancer risk for *PMS2* carriers NOT undergoing colorectal surveillance.** https://ascopubs.org/doi/pdf/10.1200/JCO.2018.78.4777
- The study reported no clear evidence of an increased risk of ovarian, gastric, hepatobiliary, bladder, renal, brain, breast, prostate, or small bowel cancer in *PMS2* GPV carriers.
- The age-specific colorectal and endometrial cancer estimates were obtained through direct communication with the first author (2023).

PMS2 **penetrance with data points_Figure 1A and 1B_ten Broeke et al JCO 2018**

CRC risk for men					
Age (years)	gen pop (male)	PMS2.m	carriers (male)	CI (male)	CI (male)
30	0	0.1 (0.03-0.4)	0.1	0.03	0.4
35	0	0.3 (0.08-0.8)	0.3	0.08	0.8
40	0.1	0.5 (0.2-1.8)	0.5	0.2	1.8
45	0.2	1.0 (0.3-3.3)	1	0.3	3.3
50	0.3	1.8 (0.7-5.4)	1.8	0.7	5.4
55	0.7	2.8 (1.3-7.9)	2.8	1.3	7.9
60	1.2	3.9 (2.1-9.6)	3.9	2.1	9.6
65	2	5.3 (3.2-11)	5.3	3.2	11
70	3.2	7.2 (4.5-13)	7.2	4.5	13
75	4.7	9.7 (6.0-17)	9.7	6	17
80	6.6	13 (7.9-22)	13	7.9	22

CRC risk for women				
gen pop (female)	carriers (female)	carriers (female)	CI (female)	CI (female)
0	0.1 (0.04-0.3)	0.1	0.04	0.3
0	0.2 (0.08-0.7)	0.2	0.08	0.7
0.1	0.5 (0.2-1.4)	0.5	0.2	1.4
0.2	0.9 (0.4-2.6)	0.9	0.4	2.6
0.3	1.6 (0.7-4.2)	1.6	0.7	4.2
0.5	2.5 (1.2-6.0)	2.5	1.2	6
0.9	3.4 (1.9-7.3)	3.4	1.9	7.3
1.5	4.6 (2.7-8.9)	4.6	2.7	8.9
2.3	6.4 (3.8-12)	6.4	3.8	12
3.3	8.6 (5.1-15)	8.6	5.1	15
4.7	12 (6.7-21)	12	6.7	21

EC risk

gen pop	carriers	carriers	CI	CI
0	0.04 (0.02-0.07)	0.04	0.02	0.07
0	0.1 (0.06-0.2)	0.1	0.06	0.2
0	0.2 (0.1-0.5)	0.2	0.1	0.5
0.1	0.5 (0.3-1.0)	0.5	0.3	1
0.2	1.2 (0.6-2.3)	1.2	0.6	2.3
0.4	2.5 (1.3-4.8)	2.5	1.3	4.8
0.8	4.4 (2.3-8.3)	4.4	2.3	8.3
1.2	6.6 (3.5-12)	6.6	3.5	12
1.6	8.8 (4.7-16)	8.8	4.7	16
2	11 (5.9-20)	11	5.9	20
2.4	13 (7.0-24)	13	7	24

2) Dominguez-Valentin et al, 2023:

- Most recent report from the Prospective Lynch Syndrome Database (PLSD: www.plsd.eu). **Risk estimates are aimed at determining the cancer risks for *PMS2* GPV carriers undergoing colorectal surveillance**. The point estimates have wide confidence intervals because of the low number of *PMS2* GPV carriers (n= 549) and follow-up years collated by the PLSD.
- The recent report has suggested that *PMS2* GPV carriers could be at slightly increased risk of ovarian (2.5% at 75y; CI 0.4-16.3), male ureter/kidney (5.1% at 75y; CI 0.7-30.9), male gastric (2.7% at 75y; CI 0.4-17.5), small bowel (male 3.3% at 75y; CI 0.5-21.3; female 2.1% at 75y; CI 0.3-14.0), and male brain (7.3% CI 1.1 -41.6). However, the *PMS2* cancer risks from the PLSD should be interpreted and used with caution given the wide confidence intervals. In addition, in the Ten Broeke et al study (2018), the *PMS2*-related cumulative risks for ovarian, gastric, hepatobiliary, bladder, renal, brain, prostate, and small bowel cancer did not significantly differ from risks in the general population. Given the conflicting data and wide confidence intervals, the PLSD *PMS2* point estimates for less frequent Lynch syndrome related cancers have not been used in the management guideline, but will be reviewed as more data becomes available.
  https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(23)00086-X/fulltext
  https://pubmed.ncbi.nlm.nih.gov/36895471/
  https://ascopubs.org/doi/pdf/10.1200/JCO.2018.78.4777

Colorectal surveillance recommendations

- *MLH1*, *MSH2*, *MSH6*, and *PMS2* are based on British Gastroenterology Society guidelines (Monahan et al 2019: https://www.bsg.org.uk/wp-content/uploads/2019/12/Guidelines-for-the-management-of-hereditary-colorectal-cancer.full_.pdf

Prostate Surveillance

- The benefits of annual PSA screening are unproven in the Lynch syndrome setting but, given the higher risk of prostate cancer for MLH1 and MSH2 P/LP variant carriers, PSA can be considered from age 40. The population testing threshold for onward investigation should be used. This may be particularly relevant for MSH2 carriers, or where there is a family history of prostate cancer.

Aspirin chemoprevention

- CAPP2 showed a 50% reduction in colorectal cancers in those who took 600 mg aspirin per day for 2 to 4 years, an effect that persisted for over a decade. CaPP3 has involved 1,879 LS carriers, randomised to receive 600, 300, or 100/75 mg daily for 2 years (blinded), followed by 3 years open label. Those on the lowest dose had the fewest cancers. CaPP3 data is reported to show that 75–100 mg aspirin is non-inferior to 600 mg and significantly less likely to cause a serious adverse event (communication from Sir John Burn).
- Given the rarity of cancers in younger people and the 4–5-year time lag in all observational data and in CAPP2 between commencement and impact on cancer rates, a reasonable policy would be to start aspirin at age 21 in *MSH2* and *MLH1* gene PV/LPV carriers. In *MSH6* and *PMS2* PV/LP carriers, starting at 30 would be reasonable (communication from Sir John Burn).
- **Strategic aspirin holiday(s):** The protective effects of aspirin were shown to persist for at least 10 years in the CAPP2 trial, but 5 years of treatment may not provide protection for a person's entire lifetime. Therefore, it would be reasonable to treat for 5 years after diagnosis, or until symptoms of gastric irritation and/or bruising become a deterrent, then take an "aspirin holiday" for, say, five years before restarting, with the final therapeutic stage being at age 65–70. This would reduce side effects while hopefully retaining the benefits (communication from Sir John Burn).
- **For individuals with BMI >30:** Aspirin efficacy may be weight-dependent, but it is currently unclear at what BMI the dose should change. Individuals with a BMI over 30 should be offered low dose aspirin as standard but may want to consider 150 mg daily if there are no contraindications (communication from Sir John Burn).
- **For pregnant women**: There is no good evidence that aspirin causes harm to the baby in early pregnancy when taken at lower doses, or at higher doses taken short term. There is not much evidence about taking aspirin at higher doses long term in pregnancy. Patients should talk to their healthcare team before taking aspirin after 30 weeks of pregnancy. Aspirin is not recommended whilst breastfeeding (NICE chemoprevention patient decision aid).

Helicobacter pylori (H. pylori)

- H. pylori infection is a gastric cancer risk factor in Lynch syndrome (LS) and increases the risk of ulceration in aspirin users. Hawkey et al in the HEAT trial (*Lancet* 2022) tested 30,166 people for H. pylori and randomised 5,352 infected aspirin users in 1208 primary care centres to either have continue usual care or receive a one-week course of clarithromycin, metronidazole and lansoprazole. Over the first 2.5 years there was a 65% reduction in peptic ulcer-related bleeds in the treated group (17/1000 versus 6/1000 patient-years), but the benefit was lost thereafter. The possibility of reinfection may be an issue though gastroenterologists insist reinfection is rare. Treatment of family members is advisable in LS cases to avoid cross-infection and there is a growing concern about antimicrobial resistant strains becoming an issue. In LS, a five-yearly repeat would seem reasonable but presents logistic issues (communication from Sir John Burn).

Dietary recommendations

- The CAPP2 trial investigated the long-term effects of aspirin and resistant starch on cancer incidence in patients with LS. Participants with LS were randomised double-blind to 30 g resistant starch (RS) daily (*n*= 463) or placebo (*n*= 455) for up to 4 years. After up to 20 years follow-up, there was no difference in colorectal cancer (CRC) incidence (52 and 53 participants developed CRC in the RS and

placebo groups, respectively). However, there were fewer non-colorectal LS cancers among the participants in the RS group (*n*= 27) compared with participants in placebo (*n* =48); intention-to-treat (ITT) analysis [HR, 0.54; 95% CI, 0.33–0.86; *P* = 0.010]). In ITT analysis, allowing for multiple primary cancer diagnoses among participants by calculating incidence rate ratios (IRR) confirmed the protective effect of RS against non–colorectal LS cancers (IRR, 0.52; 95% CI, 0.32–0.84; *P* = 0.0075). These effects were particularly pronounced for cancers of the upper GI tract (stomach, duodenal, bile duct, and pancreatic cancers). There were 5 cancers in 5 participants randomised to RS versus 21 cancers in 17 participants randomised to placebo. The reduction in non–colorectal LS cancers was detectable in the first 10 years and continued in the next decade. The authors concluded that 30 g daily RS appears to have a substantial protective effect against non–colorectal cancers for patients with LS.
https://aacrjournals.org/cancerpreventionresearch/article/15/9/623/708166/Cancer-Prevention-with-Resistant-Starch-in-Lynch

- Dietary recommendations and practical information about increasing dietary intake is based on expert opinion (personal communications with Prof. John C. Mathers and Prof. Sir John Burn 2023).

Risk-reducing gynaecological recommendations

- *MLH1, MSH2*, and *MSH6* gynaecological management recommendations are based on the Manchester International Consensus Group recommendations for the management of gynaecological cancers in Lynch syndrome (Crosbie et al, 2019). The consensus group stated that the strength of evidence was insufficient to strongly recommend risk-reducing surgery in *PMS2* GPV carriers, however, patient representatives with a *PMS2* GPV felt strongly that they should be offered risk-reducing surgery alongside other women with Lynch syndrome.
https://www.nature.com/articles/s41436-019-0489-y#Sec10
- Dominguez-Valentin et al (2021): Used the PLSD to investigate the impact of risk-reducing hysterectomy and bilateral salpingo-oophorectomy (BSO) at different ages on gynaecological cancer incidence and death in MMR GPV carriers. Risk-reducing hysterectomy at 40 years was estimated to prevent endometrial cancer by 50 years in 13%, 16%, 11%, and 0% of *MLH1, MSH2, MSH6,* and *PMS2* GPV carriers and death in 1%, 2%, 1%, and 0%, respectively. Similarly BSO at 40 years was estimated to prevent ovarian cancer before 50 years in 4%, 8%, 0%, and 0% of *MLH1, MSH2, MSH6,* and *PMS2* GPV carriers and death in 1%, 1%, 0%, and 0%, respectively. The authors concluded that little benefit is gained by performing RRS before 40 years of age and premenopausal BSO in *MSH6* and *PMS2* GPV carriers has no measurable benefit for mortality. These findings may aid decision making for women with LS who are considering RRS.
https://diposit.ub.edu/dspace/bitstream/2445/195173/1/706835.pdf

Obesity and cancer risk in LS

- Movahedi et al (2015): Analysed the data from the CAPP2 study, in which patients with LS were randomly assigned to receive aspirin 600 mg per day or aspirin placebo, plus resistant starch 30 g per day or starch placebo (2 × 2 factorial design). Mean intervention period was 25.0 months, and mean follow-up was 55.7 months. Obese participants had significantly higher CRC risk compared with those who were underweight or had a normal weight (reference group): HR, 2.34; 95% CI, 1.17 to 4.67, *P*=.02). Obese patients with *MLH1* GPVs had a significantly higher CRC risk compared with the reference group (HR, 3.72; 95% CI, 1.41 to 9.81; *P* = .008). In contrast, CRC was not significantly raised in obese participants with *MSH2* GPVs (HR, 1.59; 95% CI, 0.47 to 5.44). The obesity-related excess CRC risk was confined to those randomly assigned to the aspirin placebo group (HR, 2.75; 95% CI, 1.12 to 6.75; *P* = .03). The authors concluded that obesity is associated with substantially increased CRC risk in patients with LS, but this risk is abrogated in those taking aspirin.

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