Protocols 9-12
MMR mutation carrier guidelines
Frequently asked questions

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Q: Where have the general population cancer risks been taken from?
The risk figures for the general population in UK have been calculated by the Cancer Research UK Statistical Information Team, and are based on UK cancer incidence data for 2010. The risk figures represent cancer risk up to the age of 64yrs.

Q: How accurate are the lifetime cancer risk figures?
These figures are risks for an 'average carrier' and do not represent a definitive risk for an individual carrier. The data provided are taken from retrospective studies reporting lifetime cancer risks in cohorts of mutation carriers selected and/or unselected for family history. Please note that 'lifetime risk' refers to the cancer risks up to 70 years and are therefore comparable to the population risks discussed above.

The figures include data from studies corrected and uncorrected for ascertainment bias. The figures have been condensed to present the data in a practical format for use in clinic, and represent the best approximation of lifetime cancer risks for an individual. The principal aim of the figures is for use during the genetic counselling process, where many carriers find more qualitative discussion most helpful.

Q: What cancer types are currently considered part of the LS tumour spectrum?
The LS tumour spectrum is defined by the Amsterdam I criteria (colorectal cancer), Amsterdam II criteria (addition of endometrium, small bowel, ureter or renal pelvis cancers), and the revised Bethesda guidelines (addition of stomach, ovarian, pancreas, bladder, biliary tract, brain, sebaceous gland adenomas and keratocanthoma). See background document Lynch Syndrome evaluation and investigation.

Q: Why is the range of lifetime risk of colorectal and endometrial cancer so broad?
The range for lifetime colorectal and endometrial cancer risk for MMR mutation carriers reflects the range of risk figures derived from retrospective studies which have been corrected (using statistical methods or by excluding index cases) and uncorrected for ascertainment bias.

The lower figure in the range is taken from studies corrected for ascertainment bias, in which MMR mutation carriers were identified in cases selected (clinic-based) and unselected (population-based) for family history.

The upper figure in the range is taken from uncorrected (clinic-based) studies of large, multiple case families identified through Lynch Syndrome registries. The majority of these carriers will have been referred to family cancer clinics on the basis of clinical criteria (e.g. Amsterdam criteria I/II).

Most families seen in Genetics have some family history. The most appropriate risk figure may be selected by assessing family history. The lower risk figures represent the best approximate risk for Amsterdam-negative families, and the upper risk figures represent the best approximate risk for Amsterdam-positive families.

Q: Why are the same cancer risks figures not used for all MMR mutation carriers?
Increasingly, multiple studies suggest that the phenotypic spectrum and cancer risks differ substantially between MMR carriers. From the data, *MLH1* and *MSH2* carriers generally

have higher lifetime risks of cancer compared to *MSH6* and *PMS2* carriers. The only inconsistency in the data is endometrial cancer risks, which has been demonstrated to be highest in *MSH6* carriers by some studies.
The data also suggest that *PMS2* and *MSH6* carriers are at low risk of minor LS-related cancers. But some caution is warranted, as cancer risks have been less well defined in these carriers, particularly *PMS2* carriers.

Q: How should I manage an *EPCAM* deletion carrier?
EPCAM deletion carriers should have equivalent management to *MSH2* mutation carriers, as *EPCAM* deletions cause Lynch syndrome 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 (although still above 10% threshold). This may be in part due to the tissue-specific MSH2 deficiency caused by *EPCAM* deletions, but there is still uncertainty regarding the risks of minor cancers in deletion carriers.

Q: Are prostate and breast cancer considered part of the tumour spectrum of MMR carriers?
Prostate and breast cancer are not currently considered part of the LS tumour spectrum. Both of these cancers are very common in the general population. Further studies are required to include these cancer types as part of the Lynch syndrome spectrum.

Q: Are tumours with an MMR-deficient phenotype part of the LS tumour spectrum?
Many rare cancer types have been reported in MMR carriers, with evidence of MMR deficiency (loss of MMR protein straining on IHC and/or MSI) being demonstrated for various sites such as adrenocortical adenocarcinoma, thyroid carcinoma, and sarcomas. However, there is insufficient data that MMR carriers have increased lifetime risk for these cancer types, and therefore they are not currently considered part of the LS tumour spectrum. Should a MMR-deficient phenotype be identified in a non-LS spectrum tumour, the family history should be evaluated for other evidence of a LS phenotype

Q: What is the clinical phenotype of Muir-Torre Syndrome?
Muir-Torre syndrome (MTS) is characterised by the coexistence of at least one sebaceous skin tumour (sebaceous adenomas and carcinomas) or keratocanthoma (neoplasm of the hair follicle) and one or more visceral malignancies (most commonly colorectal cancers). Most reported MTS diagnoses have been in *MSH2* carriers, with a few reported in *MLH1* mutation carriers.

Q: Why are lifetime risk figures for sebaceous tumours not given in the protocols?
There are no risk figures available for sebaceous tumours in MMR carriers. However, there is data available regarding the frequency of Muir-Torre syndrome among Lynch pedigrees. The frequency of MTS is estimated to range from 1 to 9%.

Q: What is the clinical phenotype of Turcot Syndrome?
Turcot syndrome is a clinical description characterised by the coexistence of colorectal cancer and brain tumours. This syndrome is genetically heterogeneous and can been seen in MMR carriers (associated with glioblastomas) or *APC* carriers (associated with medulloblastomas).

Q: What is Constitutional MMR Deficiency Syndrome?
This is the term given to individuals who carry biallelic germline mutations in the MMR genes. This syndrome is characterised by café au lait spots, early (in childhood and teenage years) onset of colorectal cancers or other LS-related cancers, oligopolyposis in the small bowel and/or colon, brain tumours, and haematological malignancies.

Q: What types of colorectal cancers do MMR carriers get?
Colorectal cancers can be of any histological subtype but there are several characterised associations. Colorectal cancers in MMR carriers are predominantly located in the proximal colon (60–70% in LS, 30% in sporadic CRC), and are often mucinous and poorly differentiated. Colorectal cancers in carriers have a reported MSI frequency of ~85 to 90%. Diploid tumours and signet-ring cancers also seem to be common in carriers.

Q: What types of colorectal adenomas do MMR carriers get?
Colonic adenomas in MMR carriers tend to be larger and more severely dysplastic than in sporadic cases and most show MSI or loss of immunohistochemical staining of the MMR proteins.

Q: What types of endometrial cancers do MMR carriers get?
There is no consistent evidence of a significant difference in histological subtypes of endometrial cancers between MMR carriers and the general population. Endometrial cancers in carriers and the general population are predominantly endometrioid subtype (~80%), with non-endometrioid subtypes (e.g. clear cell, serous) accounting for the remaining cases.

Q: What types of ovarian cancers do MMR carriers get?
Ovarian cancers in MMR carriers can be of any histological subtypes but there are some recognised patterns. Ovarian cancers in MMR carriers are predominantly epithelial non-serous cancer subtypes, particularly endometrioid carcinoma. An excess of clear cell histology subtypes may also be seen in carriers. Ovarian cancers in MMR carriers typically present at an earlier stage (FIGO I/II ~ 80%), compared to sporadic and BRCA-related ovarian cancers (FIGO I/II~33%).

Q: What types of gastric cancers do MMR carriers get?
Gastric cancers in MMR carriers are predominantly intestinal subtype (~ 80%) with diffuse subtype (13%) accounting for most of the remaining cases. Gastric cancers in carriers have a high degree of MSI. The frequency of BRAF-V600E mutations is low in sporadic and Lynch-related gastric cancers, and therefore this cannot be used to selected individuals for genetic testing.

Q: What types of small bowel cancers do MMR carriers get?
Small bowel cancers in carriers are predominantly located in the duodenum (~43%) and jejunum (~37%); and only ~7% are located in the ileum. Small bowel cancers in MMR carriers have been shown to have a high degree of MSI (95% compared to ~13% sporadic cases).

Q: What types of urinary tract cancers do MMR carriers get?
MMR carriers can get any type of urinary tract cancer, but there is a predominance of urothelial cancers (ureter and renal pelvis) in carriers. The histology of these urothelial cancers is similar to that of sporadic cancers. There is conflicting data in regards to the incidence of bladder cancers in carriers. Studies have reported high frequencies of MSI for urothelial tumours in LS that clearly exceed frequencies for corresponding sporadic tumours.

Q: Why do we recommend a later starting age of colonoscopic surveillance for *MSH6* and *PMS2* carriers? From the available data, the average age of CRC onset is somewhat later in *MSH6* and *PMS2* mutation carriers (54yrs and 59yrs) compared to *MLH1* and *MSH2* carriers (44yrs and 45yrs). By age 50yrs the cumulative risk of CRC was not reported to exceed 2% for *PMS2* carriers and 3% for *MSH6* carriers. Based on this evidence, and the risks associated with colonoscopy, it would seem appropriate to offer *MSH6* and *PMS2* mutation carriers, surveillance starting from the age of 30yrs. However, some *MSH6* and

PMS2 carriers may still wish to start colonoscopy at the age of 25yrs. This can be arranged, but the above should be articulated to mutation carriers.

Q: What ovarian screening is available to carriers?
Ovarian screening is not recommended for MMR carriers, as no ovarian screening modality (including trans-vaginal ultrasound or CA-125 measurement), has demonstrated improved survival for carriers.

Q: What endometrial screening is available to carriers?
Endometrial screening is not recommended for MMR carriers, as no endometrial screening modality (including trans-vaginal ultrasound or hysteroscopy, or endometrial sampling) has demonstrated improved survival for carriers.

Q: What urinary tract screening is available to carriers?
Urinary tract screening is not recommended for MMR carriers, as no urinary tract screening modality (including renal ultrasound or urine cytology) has demonstrated improved survival for carriers

Q: What gastric screening is available to MMR carriers?
Gastric screening is not recommended for MMR carriers, as no gastric screening modality (upper GI endoscopy), has demonstrated improved survival for MMR carriers. The available data also demonstrates that the lifetime risk of gastric cancer is relatively low (<10%) for MMR mutation carriers, with the incidence of gastric cancer now declining in Western countries.

Q: Why is *Helicobacter pylori* screening and eradication recommended?
Infection with *Helicobacter pylori* is an important risk factor for gastric cancer. It causes chronic gastritis, which may lead to gastric atrophy and intestinal metaplasia. These are the main histological precursors to gastric cancer. The available data suggests that searching for and eradicating *H pylori* reduces the incidence of gastric cancer in asymptomatic individuals.

Q: When should I discuss *Helicobacter pylori* screening and eradication with MMR *carriers*?
Helicobacter pylori screening and eradication can be discussed and offered to *MLH1* and *MSH2* carriers. *PSM2* and *MSH6* carriers have significantly lower lifetime risk of gastric cancer, and therefore should only be offered *Helicobacter pylori* screening and eradication if they have at least one first or second degree relative with gastric cancer.

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.

Q: Who will prescribe *Helicobacter pylori* eradication therapy?
Helicobacter pylori eradication therapy will be prescribed by the patient's GP if required. There are several treatment regimens. Typically regimens include one-week 'triple therapy' regimen with a proton pump inhibitor (e.g. omeprazole) plus two antibiotics (e.g. amoxicillin and clarithromycin).

Q: What symptoms should be discussed with 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 (post menopausally or in between cycles), back pain, and constipation.

Urinary tract: Blood in urine, mass in abdomen, weight loss, fatigue, persistent pain in side, urinary frequency or urgency.

Gastric: persistent indigestion, feeling full early, pain or difficulty with swallowing, fatigue, dark tarry stools, nausea.

Q: What is the risk of a metachronous colorectal cancer?
The risk of a second colorectal cancer remains substantial after a partial colectomy. The risk of developing a metachronous colorectal cancer in MMR carriers has been reported by a study to be 16% (95% CI 10% to 25%) at 10 years, 41% (95% CI 30% to 52%) at 20 years and 62% (95% CI 50% to 77%) at 30 years after segmental colectomy. This data does have some limitations, as detailed information about the surveillance protocol (e.g. interval and quality) was unavailable, which may result in upwardly biased metachronous cancer risks. It is also unclear what factors influenced the choice of surgery.

Q: What surgical options are there for colorectal cancer?
All carriers with a newly diagnosed colorectal cancer should be offered the opportunity to discuss different surgical options (partial vs. subtotal colectomy) with their surgical team, and should be aware that carriers whose first colon cancer is treated with more extensive colonic resection have a lower risk of metachronous colorectal cancer than those having less extensive colonic surgery.

However, there is no data that suggests a survival benefit in carriers having more extensive surgery, and there is good evidence that colonoscopy is effective at preventing deaths by colon cancer in carriers. Other important issues carriers may like to consider are functional results of subtotal vs. partial colectomy, age, and personal preference.

Q: When should I discuss aspirin chemoprevention with carriers?
All MMR carriers who do not wish to take part in the CAPP3 study should be offered the option of taking low dose aspirin (75mg OD) from the age of 25yrs.

Q: What benefits of aspirin chemoprevention should I discuss?
MMR carriers should be made aware that aspirin (600mg) chemoprevention has been shown to reduce the overall number of colorectal cancer cases, and incidence of LS-related cancers in carriers. However, aspirin chemoprevention has not been shown to have an impact on mortality.

Q: What side effects of chemoprevention should I discuss?
Regular aspirin use is associated with an increased risk of gastrointestinal bleeding, (which is probably dose-dependent), and intracranial haemorrhage (1 in 10,000 per annum). Aspirin can also exacerbate asthma in certain individuals.

Q: Are there any contraindications to chemoprevention?
- Aspirin should not be taken if pregnant or planning pregnancy in next 2 years
- Aspirin should not be taken by women who are breast feeding
- Aspirin should not be taken with other drugs that increase the risk of bleeding (e.g. NSAIDS, anticoagulant medication, steroids)

- Aspirin should not be taken if carriers have a history of bleeding disorder, active peptic ulcer disease within the last 3 months, liver impairment, renal impairment, or poorly controlled hypertension.
- Aspirin should not be taken if carriers have known aspirin intolerance or hypersensitivity, including aspirin-sensitive asthma.

Q: Why do we recommend risk-reducing hysterectomy for all MMR carriers?
All female MMR carriers have been demonstrated to have a high (at least 10%) lifetime risk of developing endometrial cancer. A significant proportion of carriers who develop endometrial cancer will eventually die from their disease and there is significant morbidity associated with cancer-related treatment. There is also no proven, efficacious form of screening.

Risk reduction hysterectomy has been demonstrated to reduce the endometrial cancer risk in MMR carriers by up to 100%. However, it has not been shown to improve survival in MMR carriers, which in part may be due to the relatively good prognosis associated with endometrial cancers in Lynch syndrome patients.

Q: Why do we recommend risk-reducing bilateral salpingo-oophorectomy for *MSH2* and *MLH1* carriers?
Data has consistently demonstrated a high (at least 10%) lifetime risk of ovarian cancers for *MSH2* and *MLH1* carriers. Risk reducing bilateral salpingo-oophorectomy is recommended for *MSH2* and *MLH1* carriers because the benefit/harm ratio is likely to be favourable. These carriers have a high lifetime risk of ovarian cancer, a significant proportion of carriers who develop ovarian cancer will eventually die of their disease, and there is significant morbidity associated with cancer-related treatment. There is also no proven, efficacious form of screening.

Risk reducing BSO has been demonstrated to reduce the ovarian cancer risk in MMR carriers by up to 100% (not statistically significant due to low numbers). However, it has not been shown to improve survival in MMR carriers, which in part may be due to the relatively good prognosis associated with LS-related ovarian cancers (in comparison to sporadic or BRCA-related cancers).

Q: Why do we not routinely recommend risk-reducing bilateral salpingo-oophorectomy for *MSH6* and *PMS2* carriers?
Although the data is limited, it would appear that the lifetime risk of ovarian cancer for *MSH6* and *PMS2* carriers is significantly lower than *MSH2* and *MLH1* carriers. To date no studies have demonstrated a 10% or greater lifetime risk of ovarian cancers for *MSH6* and *PMS2* carriers. Therefore, risk reducing BSO is not routinely recommended in premenopausal *MSH6* and *PMS2* carriers, as based on the current evidence available, the benefit/harm ratio is likely to be unfavourable.

Q: Are there any circumstances that we would discuss risk-reducing BSO with *MSH6* and *PMS2* carriers?
Similar to non-carrier females, BSO may be discussed in *MSH6* and *PMS2* carriers who have two or more first or second-degree relatives with ovarian cancer. At least one should be a first-degree relative of the carrier. BSO may also be discussed with carriers undergoing hysterectomies post-menopausally, as the benefit/harm ratio is likely to be more favourable in this situation.

Q: At what age should women undertake risk-reducing hysterectomy with or without BSO?
For *MLH1* and *MSH2* carriers who have completed their families, it is appropriate to consider hysterectomy with BSO from 40yrs onwards, as the risk of endometrial and ovarian cancer increases from the age of 40yrs.

For *MSH6* and *PMS2* carriers who have completed their families it is appropriate to consider hysterectomy from 40yrs onwards, as the risk of endometrial cancer is not clinically significant below this age. For *PMS2* carriers it may be reasonable to delay until the age of 45, as the risk of endometrial cancer does not increase until the age of 50.

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

Q: What are the disadvantages of risk-reducing hysterectomy and bilateral salpingo-oophorectomy?
The main adverse effects of prophylactic gynaecological surgery include colonoscopic surveillance becoming more difficult and painful, loss of fertility, and surgically-induced menopause (if surgery is performed pre-menopausally). Menopausal symptoms include hot flushes, vaginal dryness, sexual dysfunction, sleep and cognitive disturbances. Premature menopause may also be associated with increased risk of osteoporosis and heart disease in later life. HRT should be used to minimise these effects and should be started in women who have not had breast cancer from time of surgery until 50 years (the approximate time of the natural menopause). Carriers should be made aware of the small risk of peritoneal carcinoma that remains following BSO. Carriers should also be made aware that surgery is associated with a small risk of morbidity and mortality.

Q: What advice should be given to carriers regarding the investigation of urinary tract cancer symptoms?
All MMR carriers should be advised that if they develop symptoms suggestive of urinary tract cancer, such as haematuria (blood in urine), that they should contact their GPs immediately for further investigations. Although, it is appropriate to exclude other more common causes of urinary tract symptoms (e.g. infection), it is important that GP have a low threshold for referring carriers onward for a urological opinion. This should be clearly articulated to carriers.

Q: What lifestyle advice should be given to MMR carriers?
Smoking and a high BMI have been demonstrated to increase the risk of adenomas and colorectal cancer in MMR carriers. Therefore carriers should be advised to maintain a healthy weight and refrain from smoking.

Q: How should I manage an individual in whom a predictive test is negative?
A negative predictive test is when an individual is found to not carry the mutation that has been shown to be responsible for the LS-related cancers in their family. On the basis of current knowledge such individuals should be returned to population bowel screening. FOB kits are sent out biennially to individuals aged ≥60yrs. Individuals with abnormal results are offered colonoscopy. See http://www.cancerscreening.nhs.uk/bowel for more details. Risk reducing hysterectomy or BSO is not recommended.

Q: How do I manage a MMR negative family?
Please see Protocols 7-8.

Q: What should I do if there is a variant of unclear significance?
Email report to vus@icr.ac.uk and discuss case at multi-disciplinary team meeting.