

Protocols 9-12

Background information for MMR mutation carrier (Lynch Syndrome) Management

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This document corresponds to:

MMR mutation carrier guideline- frequently asked questions (FAQ)

Protocol 9- *MLH1* mutation carrier guidelines

Protocol 10- *MSH2* and *EPCAM* mutation carrier guidelines

Protocol 11- *MSH6* mutation carrier guidelines

Protocol 12- *PMS2* mutation carrier guidelines

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Reason for guidelines development

Guidelines for MMR carrier management for RMH were proposed for the following reasons:

1. To ensure consistency within the Clinical Genetics unit
2. To ensure evidence-based management of MMR mutation carriers in the absence of UK specific guidelines covering this area
3. To ensure gene-specific management of MMR mutation carriers
4. To provide gene-specific approximate cancer risks for MMR mutation carriers selected and unselected for family history
5. To ensure cancer surveillance and risk-reducing intervention is directed appropriately and consistently

Current guidelines for MMR mutation carriers

Guidelines have been developed to facilitate the clinical management of MMR mutation carriers, providing recommendations on:

- Cancer surveillance protocols
- Risk-reducing interventions (surgical and chemoprevention)

Four clinical guidelines developed using a systematic approach were identified:

1. Mallorca Group European guidelines, Vasen et al (2013)[1]
2. British Society of Gastroenterology guidelines, Cairns et al (2010)[2]
3. National Comprehensive Cancer Network, (2014)[3]
4. The American Journal of Medicine, Lindor (2006)[4]

Cancer surveillance recommendations

Colorectal: The European guidelines [1, 2] recommend colonoscopy, at 1-2 yearly intervals, starting from 20-25yrs for all MMR carriers. However, the North American guidelines [3, 4] have gene-specific protocols. Colonoscopy at 1-2 yearly intervals, starting from 20-25yrs is recommended for *MLH1*, *MSH2*, and *EPCAM* carriers, and colonoscopy at 1-2 yearly intervals, starting from 25-30yrs is recommended for *MSH6* and *PMS2* carriers.

Gynaecology: Three guidelines covered gynaecological surveillance [1, 3, 4] Surveillance was recommended by a single guideline [4], at 1-2 yearly intervals, between in ages of 35-40yrs for all MMR carriers. The other guidelines recommended that this be offered in a research setting [1] or at the clinician's discretion[3].

Urinary tract: Three guidelines covered urinary tract surveillance [1, 3, 4] Urinary cytology was recommended by two guidelines [3, 4], at 1-2 yearly intervals, starting from 25-35yrs. The other guideline [1] recommended annual surveillance within a research setting for *MSH2* carriers only, from 30-35yrs.

Gastric: Two guidelines [1, 3] recommended endoscopy only in MMR carriers from high incidence countries, and a single guideline [2] recommended 2- yearly endoscopy from 50yrs.

Risk reducing interventions recommendations

Surgery: Three guidelines [1, 3, 4] addressed prophylactic hysterectomy and bilateral salpingo-oophorectomy, and all three recommended this intervention for all female MMR carriers from 40yrs, once childbearing was complete.

Chemoprevention: Two guidelines addressed [1, 3] addressed aspirin chemoprevention in carriers, and this intervention was recommended for all MMR carriers by a single guideline[1].

Cancer management recommendations

Surgical management of colorectal cancer in MMR carriers was addressed by two guidelines [1, 4, 5]. Both guidelines recommended that the pros and cons of subtotal versus partial colectomy be discussed with MMR carriers, especially younger patients.

Difficulties with current recommendations

There are various disparities across the clinical guidelines regarding the management of MMR mutation carriers. We have also demonstrated evidence of variation in practice via a national survey of Genetic Centres in the UK. Some guidelines recommend gene-specific management, whilst others recommend equivalent carrier management. There is inconsistency regarding whether surveillance protocols should be influenced by the family phenotype, with some guidelines advocating that screening should start between 2-10 years earlier than the youngest colorectal cancer case within the family.

Despite the recognition of the absence of evidence to support surveillance for extra-colonic cancers, some guidelines still advocate such practices within a clinical setting or at the clinician's discretion. Furthermore, differences in cancer penetrance and phenotypic spectrum of MMR mutations selected and unselected for family history are not addressed.

Curating lifetime risks from the literature

We conducted a systematic literature search using PubMed to identify relevant risk studies. Reference lists of retrieved articles were reviewed and manual searches of relevant articles undertaken. Search terms included:

Population: *Lynch syndrome, hereditary non-polyposis colon cancer, MMR mutation, MSH2 mutation, MLH1 mutation, MSH6 mutation, PMS2 mutation, EPCAM mutation, and EPCAM deletion.*

Outcome: *cumulative risk, penetrance, lifetime risk, and cancer risks*

Articles selected for consideration, included risk data on MMR carriers and/or individuals from HNPCC pedigrees. Only peer-reviewed, retrospective studies, reporting lifetime risks (up to 70yrs), published in the English language until 20th October 2013 were included. Case reports, and prospective studies were excluded. We developed criteria to assess

the quality of evidence and to assign quality grades (high, moderate, and low) for each study. Areas assessed included recruitment of pedigrees (clinic- vs. population based), adjustment for ascertainment, sample size, proportion of pedigrees/individuals with confirmed mutations, evidence of significant founder effect, and study population similarity to the UK.

Lifetime cancer risks – the upper range

It was important to define cancer risk estimates that were appropriate for MMR carriers selected for family history. To achieve this objective, we selected clinic-based studies (uncorrected for ascertainment bias) from the literature, which ascertained carriers through Lynch syndrome registries. Carriers identified from Lynch syndrome registries typically come from high-risk pedigrees (i.e. multiple case and early-onset phenotype).

Our upper risk ranges have been selected from (uncorrected) clinic-based studies with the largest sample size, highest proportion of Amsterdam criteria (AC) positive pedigrees, and with truncating mutation (PTV) carriers only. Please see table 1.

Table 1: Lifetime risk of cancer in uncorrected studies of MMR carriers selected for family history

MMR Carrier	Study	Characteristics	Lifetime risk, up to 70yrs (95% CI)			
			Male CRC	Female CRC	EC	OC
<i>MLH1</i>	Vasen (2001) [6]	Largest study (34 <i>MLH1</i> pedigrees, 917 carriers), all PTV mutations, 60% met AC (I/II)	65% (NA)	54% (NA)	25% (NA)	3.4% (NA)
<i>MSH2</i>	Vasen (2001) [6]	Largest study (40 <i>MLH1</i> pedigrees, 925 carriers), all PTV mutations, 60% met AC (I/II)	73% (NA)	55% (NA)	37% (NA)	10.4% (NA)
<i>MSH6</i>	Hendriks (2006) [7]	Largest study (20 <i>MSH6</i> pedigrees, 146 carriers, all PTV mutations, 30% met AC (II)	69% (42-83)	30% (12-44)	71% (50-83)	-
<i>PMS2</i>	-	-	-	-	-	-
<i>EPCAM</i>	Kemper* (2011)[8] *only study identified	Only study (194 <i>EPCAM</i> 3' deletion carriers, clinic-based pedigrees, only confirmed deletion carriers or obligate carriers included.	75% (65-85)	74% (56-92)	12% (0-27)	-

Lifetime cancer risks – the lower range

It was important to define cancer risk estimates that were appropriate for MMR carriers unselected for family history. To achieve this objective, we selected studies corrected for ascertainment bias, which recruited carriers via population cancer registries (population-based) and also from multiple-case families referred to family history clinics (clinic-based).

Our lower cancer risk ranges have been selected from studies corrected for ascertainment bias (using modified segregation analysis conditioned on ascertainment criteria), which have been assessed to be of sufficient quality given, a larger sample size, focus on families (or individuals) with confirmed pathogenic mutations, and inclusion of population-based pedigrees. Age-dependent cumulative cancer risks estimates were also derived from the selected studies. Please see tables 2-6.

Table 2: Lifetime risk of cancer in corrected studies of MMR carriers selected and/or unselected for family history

MMR Carrier	Study	Characteristics	Lifetime risk, up to 70yrs (95% CI)			
			Male CRC	Female CRC	EC	OC
<i>MLH1</i>	Dowty (2013) [9]	Large cohort (166 <i>MLH1</i> , 244 <i>MSH2</i> pedigree), 17,576 informative relatives used in penetrance analysis	34% (25-50)	36% (25-52)	18% (9.1-34)	13% (6.1-26)
<i>MSH2</i>			47% (36-60)	37% (27-50)	30% (18-45)	9.5% (4.2-21)
<i>MSH6</i>	Baglietto (2010) [10]	Largest cohort of <i>MSH6</i> pedigrees (n=133), 1,043 informative relatives used in penetrance analysis	22% (14-32)	10% (5-17)	26% (18-36)	-
<i>PMS2</i>	Senter (2008) [11]	Only cohort study of <i>PMS2</i> pedigrees (n=39), 634 informative relatives used in penetrance analysis	20% (11-34)	15% (8-26)	15% (6-35)	-

Table 3: Age-dependent cumulative cancer risks for *MLH1* mutation carriers [9]

Age (yrs)	Age-dependent cumulative risks (95% CI)			
	Male CRC	Female CRC	EC	OC
30	2.8% (1.6-4.7)	0.7% (0.3-1.6)	0.5% (0.2-1.4)	0.6% (0.3-1.2)
40	11% (6.6-17)	3.2% (1.4-6.8)	2.8% (1.0-7.9)	1.2% (0.6-2.7)
50	23% (16-33)	12% (7.1-21)	6.9% (3.5-16)	3.3% (1.5-7.0)
60	31% (22-44)	24% (16-37)	12% (6.3-23)	7.2% (3.4-15)
70	34% (25-50)	36% (25-51)	18% (9.1-34)	13% (6.1-26)
80	39% (28-58)	48% (34-65)	23% (11-43)	20% (9.5-38)

Table 4: Age-dependent cumulative cancer risks for *MSH2* mutation carriers [9]

Age (yrs)	Age-dependent cumulative risks (95% CI)			
	Male CRC	Female CRC	EC	OC
30	2.2% (1.3-3.6)	1.8% (1.0-3.3)	0.8% (0.3-1.7)	0.4% (0.2-.09)
40	8.9% (5.6-14)	7.3% (4.3-12)	4.2% (2.0-8.6)	0.9% (0.4-2.1)
50	23% (17-32)	21% (15-30)	15% (8.7-24)	2.4% (1.0-5.4)
60	37% (28-49)	32% (23-44)	26% (15-39)	5.3% (2.3-12)
70	47% (36-60)	37% (27-50)	30% (18-45)	9.5% (4.2-21)
80	57% (44-72)	44% (32-60)	34% (20-52)	15% (6.5-31)

Table 5: Age-dependent cumulative cancer risks for MSH6 mutation carriers [10]

Age (yrs)	Age-dependent cumulative risks (95% CI)			
	Male CRC	Female CRC	EC	OC
50	3% (1-7)	2% (1-5)	7% (4-11)	-
60	9% (5-14)	5% (2-9)	14% (9-20)	-
70	22% (14-32)	10% (5-17)	26% (18-36)	-
80	44% (28-62)	20% (11-35)	44% (30-58)	-

Table 6: Age-dependent cumulative cancer risks for PMS2 mutation carriers [11]

Age (yrs)	Age-dependent cumulative risks (95% CI)			
	Male CRC	Female CRC	EC	OC
50	2% (1-4)	2% (1-4)	3% (1-8)	-
60	8% (4-14)	6% (3-10)	9% (3-21)	-
70	20% (11-34)	15% (8-26)	15% (6-35)	-

Minor cancer risks for MLH1 and MSH2 carriers

Gastric: Risk figures were identified from corrected, uncorrected, and cancer site specific-study, see table 7. From the data male carriers, and carriers from high incidence countries (e.g. Korea) have the highest lifetime risks. There is no significant difference in lifetime risk for *MLH1* and *MSH2* carriers. The incidence of gastric cancer is also declining in carriers (and general population) in Western countries [12, 13]. Family history of gastric cancer is a poor indicator for individual risks, and most gastric cancers occur in carriers with no family history of gastric cancer. Given the above, risk figures were selected the Capelle et al study [12] for the protocol, which provides combined risk estimates for males (6%) and female (2%) carriers, see table 7.

Urinary tract: Risk figures were identified from corrected, uncorrected, and cancer site specific-studies, see table 8. The risk data is limited as not all studies clearly distinguish between urothelial cancers (renal pelvis and ureter) and renal cancers, making comparisons between the studies difficult. From the data the lifetime risks of urinary tract cancer are higher in males, and *MSH2* mutation carriers. Risk figures were taken from the Watson et al study (see table 8), as this study had the most precise risk estimates, and was consistent with the above evidence [14].

Pancreatic: Risk figures were identified from corrected, uncorrected, and cancer site specific-studies. From the data, there is no significant difference of pancreatic cancer risks between different genders, or *MLH1* and *MSH2* carriers. Our pancreatic risk figures have been derived by from the Kastrinos et al study, see table 9[15].

Small bowel: Risk figures were identified from corrected, uncorrected, and cancer site specific-studies, see table 10. From the data there is no significant difference of small bowel cancer risks between different genders, or *MLH1* and *MSH2* carriers. We used the combined risk data from the Watson et al study in our protocols, see table 10 [14].

Brain: Risk figures were identified from corrected and uncorrected study, see table 11. From the limited data, the risk of brain cancers seems to be highest for male carriers, although a statistically significant difference has not been demonstrated. Risk figures were taken from the Watson et al study (see table 11), as this study had the most precise risk estimates [14].

Hepatobiliary: Risk figures were identified from a corrected study. Lifetime risk of 3% (95% CI; 1.2-4.9) for *MLH1* and 0.4% (95% CI; 0-0.8) for *MSH2* carriers [13].

Sebaceous: No risk figures were identified. However, the overall frequency of Muir Torre syndrome (constituting sebaceous skin tumour or keratocanthoma and at least one visceral malignancy) has been estimated within the literature, and ranges from 1-9.2% in HNPCC pedigrees with *MSH2* or *MLH1* mutations [16, 17].

Table 7: Gastric cancer risk for *MLH1* and *MSH2* mutation carriers

Study	Lifetime risk, up to 70yrs (%95 CI)		
	<i>MLH1</i>	<i>MSH2</i>	Combined MMR genes
Dowty (2013)[9]	Male: 20% (10-35) Female: 7.5%(2.6-20)	Male: 2.2% (0.4-12) Female: 9.3% (4.1-21)	-
Capelle (2010)[12]	-	-	Male: 6.2% (3.2-9.2) Female: 2.0% (0.6-3.3)
Watson (2008)[14]	6.1% (4.3-8.7)	5.2% (3.3-8.2)	5.8% (3.4-12.5)

Table 8: Urinary tract cancer risk for *MLH1* and *MSH2* mutation carriers

Study	Lifetime risk, up to 70yrs (%95 CI)		
	<i>MLH1</i>	<i>MSH2</i>	Combined MMR genes
Dowty (2013)[9]	Male: 1.2% (0.1-9.8) Female: 2.9% (0.7-13)	Male: 7.8% (3.2-19) Female: 10% (4.2-23)	-
Van der Post (2010)[18]	Male: 15.6% (0-39.2) Female: 2.2% (0-7.2)	Male: 18.2% (5-31.4) Female: 8.4% (0-15.4)	-
Watson (2008)[14]	Male: 3.7% (1.7-8.1) Female: 1.1% (0.4-3.1)	Male: 27.7% (19.7-38.3) Female: 11.8% (7.8-17)	-

Table 9: Pancreatic cancer risk for *MLH1* and *MSH2* mutation carriers

Study	Lifetime risk, up to 70yrs (%95 CI)		
	<i>MLH1</i>	<i>MSH2</i>	Combined MMR genes
Kastrinos (2009) [15]	-	-	3.68% (1.45-5.88)
Watson (2008) [14] - biliary/pancreatic	-	-	4.1%, (2.8-5.9)
Barrow (2009) [13]	0%	0.7% (0-1.4)	-

Table 10: Small bowel cancer risk for *MLH1* and *MSH2* mutation carriers

Study	Lifetime risk, up to 70yrs (%95 CI)		
	<i>MLH1</i>	<i>MSH2</i>	Combined MMR genes
Barrow (2009) [13]	4.5% (2.7-6.4)	1.3% (0.5-2.1)	-
Watson (2008) [14]	-	-	Male: 6.1% (4.1-9.0) Female: 2.7% (1.5-4.8)
Ten Kate (2007)[19]	4.4% (NA)	5.9% (NA)	4.2% (NA)

Table 11: *Brain cancer risk for MLH1 and MSH2 mutation carriers*

Study	Lifetime risk, up to 70yrs (%95 CI)		
	<i>MLH1</i>	<i>MSH2</i>	Combined MMR genes
Barrow (2009) [13]	0.3% (0-0.6)	2.5% (4-8.7)	-
Watson (2008) [14]	1.7% (1.0-2.8)	2.5% (2.6-3.8)	-

Minor cancer risks for *MSH6*, *PMS2*, and *EPCAM* carriers

***MSH6*:** Lifetime risks of minor Lynch-related cancers have not been well described in the literature. We identified three studies in the literature reporting lifetime risks for *MSH6* carriers [10, 13, 20]. We derived risk estimates from the Baglietto et al study, which combined age-dependent cumulative cancer risks of kidney, stomach, small bowel, ovary, ureter, and brain at 50yrs, 60yrs, 70yr, and 80yrs. The lifetime risk (up to 70yrs) of minor cancers was reported to be 3% (95% CI; 1-14), and 11% (95% CI; 7-16) for females. This study was selected as it had the largest population of *MSH6* carriers, and was the best designed. At present no studies in *MSH6* mutation carriers have reported a high (at least 10%) lifetime risk of ovarian cancer in *MSH6* studies, and reported risk estimates have ranged from 0-1% [13, 20]. From the data available it would appear that *MSH6* carriers have a significantly lower risk of minor-related cancers compared to *MSH2* and *MLH1* carriers. Furthermore, data suggests that lifetime risk of the minor-related cancers in *MSH6* carriers may be similar to the general population(see table 12).

***PMS2*:** Lifetime risks of minor Lynch-related cancers have been reported by a single study within the literature [11], and hence are largely undefined. The Senter et al study reported combined age-dependent cumulative cancer risk of kidney (renal pelvis), ureter, stomach, small bowel, ovary, and brain at 50yrs, 60yrs, and 70yrs. The lifetime risk (up to 70yrs) of minor cancers was reported to be 6% (95% CI;1-33) for males and 6%(95% CI; 1-25) for females. From the data is would appear that the lifetime risk of minor-related cancers in *PMS2* carriers may be similar to the general population (see table 12).

***EPCAM*:** There are no risk figures for minor-cancer types available in the literature. However, Lynch-related minor cancer types have been reported in *EPCAM* mutation carriers including duodenal, pancreas, urinary tract and brain. At present there is insufficient evidence to suggest that lifetime risk of minor cancers is significantly different to *MSH2* carriers.

Risk of Lynch-related cancers in the general population

The population risk figures used in this protocol were obtained from the Cancer Research UK Statistical Information Team, and have been derived from UK incidence 2010 data and have calculated using the 'adjusted for multiple primary' or 'current probability method' (pancreatic cancer) [21]. Cancer risks are reported up to age 64yrs, and over a lifetime for males and females in the UK. The lifetime risks have not been truncated at an arbitrary upper age (e.g. 70y), but represent the estimated risk of developing cancer over a lifetime in a hypothetical birth cohort. Lifetime risks have been modelled on the 1945 birth cohort (life expectancy of males and females is 83y and 85y respectively) and therefore represent lifetime risk up to the age of 85y. We have used cancer risks up to age 64yrs in the protocols, as this permits more direct comparison with cancer risks (up to age 70yrs) provided in protocols for mutation carriers. Please see table 12, please note the risk figures for small bowel cancer have been derived from the Surveillance, Epidemiology, and End Results Program [22], the urinary tract risk is the product of bladder and kidney cancer combined, the hepatobiliary risk includes liver, and intra-hepatic duct, and the brain cancer risk includes brain and CNS invasive cancer risks.

Table 12: General population risk of Lynch-related cancers

Cancer	Male		Female	
	Up to age 64yrs	Lifetime	Up to age 64yrs	Lifetime
Colorectal	1.58%	7.18%	1.10%	5.34%
Endometrial	-	-	0.89%	2.35%
Ovarian	-	-	0.78%	2%
Gastric	0.26%	1.57%	0.13%	0.84%
Urinary tract	0.91%	4.37%	0.45%	2.05%
Pancreatic	0.29%	1.38%	0.21%	1.36%
Small bowel	-	0.2%	-	0.2%
Brain	0.38%	0.81%	0.27%	0.59%
Hepatobiliary	0.22%	0.86%	0.09%	0.47%

Cancer Surveillance Guidelines

The primary objective of the surveillance guidelines is to ensure that only efficacious screening interventions are undertaken in MMR carriers. It is important that cancer surveillance recommendations are evidence-based and only undertaken in presence of evidence to support a reduction in cancer-related mortality or morbidity.

Colorectal surveillance

We conducted a literature review and identified eight studies addressing the efficacy of colorectal surveillance, please see table 13.

Recommendation for colorectal surveillance

There is good evidence that regular colonoscopy leads to a reduction CRC-related mortality and overall mortality in LS patients. There is still uncertainty regarding the optimal screening interval, as no studies have directly assessed this issue, and the available data is limited by heterogeneity in study design, which means outcome data cannot be directly compared.

However, from the available data it appears that colorectal cancers detected with screening intervals greater than 2 years are more commonly advanced staged, and based on this we recommend that colonoscopy be performed at 18 month intervals in MMR mutation carriers. It is important to note that there is a limited amount of data in regards to the effectiveness of colonoscopy screening in *MSH6* and *PMS2* carriers.

We recommend that colonoscopic surveillance commence from the age of 25yrs for *MLH1*, *MSH2*, and *EPCAM* mutation carriers. Based on the available risk data, the risk of CRC below the age of 30yrs has not been reported to exceed 3% in *MLH1* and *MSH2* mutation carriers [9].

However, we recommend that colonoscopic surveillance commence from the age of 30yrs for *MSH6* and *PMS2* mutation carriers. Based on the available risk data, the risk of CRC below the age of 50yrs has not been reported to exceed 3% in *MSH6* and *PMS2* mutation carriers [10, 20, 11]. In addition the the average age of CRC onset has been reported to be somewhat later in *MSH6* and *PMS2* mutation carriers (54yrs and 59yrs) compared to *MLH1* and *MSH2* carriers (44yrs and 45yrs).

These recommendations are consistent with recommendations by other groups [3,4].

Table 13: *Studies assessing the efficacy of colorectal surveillance in Lynch syndrome*

Study	Description	Intervention	Population	Findings	Comments
Jarvinen (2000) [23] [Finland]	Observational: At-risk individuals from LS pedigrees invited to participate in colorectal cancer surveillance	Colonoscopy every 3yrs (n=133) vs. no planned screening (n=119). Mean follow-up 15yrs	252 patients from LS pedigrees (20/22 pedigrees with known <i>MLH1</i> or <i>MSH2</i> mutations)	CRC incidence: 8 (6%) CRCs in screened group vs. 19 (16%) CRCs in unscreened group (p=0.014). Sub-analysis (mutation-positive only): 18 % cases vs. 41% in controls (p=0.02): CRC rate was reduced by 62% Interval cancers: Interval cancers; 26 months, 34, 36, 37, 59, and 60 (2 stage A and 4 with stage B) CRC-related deaths: No CRC deaths in screened and 9 deaths in unscreened	This study provides evidence that 3 yearly colonoscopy confers a survival benefit in LS patients and also decreased the incidence of CRC.
de Vos tot Nederveen (2002)[24] [Netherlands]	Observational: Examined stage of CRC in screen-detected tumors vs. screening interval	All participants had at least 1 screening exam or prior resection of CRC	114 LS pedigrees with MMR mutations/met AC; unaffected or previously affected (post colectomy) family members	CRC incidence: 35 new CRC identified Surveillance intervals of ≤ 2 yrs: CRCs were at Dukes Stage A (n = 4), B (n = 11), and C (n=1) Surveillance interval of > 2 yrs: CRCs were at Dukes Stage A (n = 3), B (n = 10), and C (n = 6) 10-year cumulative risk of developing CRC: was 10.5 (95 percent confidence interval, 3.8-17.2) percent in proven mutation carriers, 15.7 (95 percent confidence interval, 4.1-27.3) percent after partial colectomy, and 3.4 percent after subtotal colectomy	This study suggests that surveillance at intervals of 2yrs or less is more optimal than an interval >2yrs, as screened detected cancers are more likely to be early staged.
Dove-Edwin (2005) [25] [UK]	Observational: Investigating the efficacy of colonoscopy in high-risk families	Colonoscopy was initially offered at 5 year intervals or 3 year intervals if an adenoma was detected.	554 patients from 290 families with MMR mutations and/or fulfilled Amsterdam criteria	CRC incidence: 1% diagnosed with CRC and 5% with high-risk adenomas with median screening interval of 3.3 years Mortality: 72% reduction in mortality	This study provides further evidence to support the reduction in CRC-related mortality conferred by colonoscopy (~70% mortality reduction).
De Jong (2006) [26] [Netherlands]	Observational: Assessing CRC-specific mortality before (<1990) and after (>1990) the introduction of a large scale CRC surveillance in NL	Colonoscopy every 1-2 years, from the age of 20-25 yrs (n= 897) vs. no screening (n=1073)	2788 patients from LS pedigrees (<i>MLH1</i> , <i>MSH2</i> , and <i>MSH6</i>)	Standardised mortality Ratio (O/E cases): screened patients: SMR =6.5, unscreened patients: SMR=23.9 (p<0.09) A significant decrease in (70%) SMR for CRC (p<0.001) was observed with surveillance	This study provides evidence that 1-2 yearly colonoscopy confers a survival benefit in LS patients (70% reduction in SMR)

Table 13 (continued): *Studies assessing the efficacy of colorectal surveillance in Lynch syndrome*

Study	Description	Intervention	Population	Findings	Comments
Mecklin (2007) [27] [Finland]	Observational: Investigating the risk of interval cancers and adenomas with colonoscopy	Colonoscopy every 2-3yrs, 1252 colonoscopies, total follow-up was 3150yrs (mean 6.7yrs/patient)	Finnish HNPCC registry: 420 unaffected mutation carriers	Interval cancers: 26 (80% local stage) Risk of interval cancer by age 60: M (35%), F (22%) with interval of 2-3 yrs Cumulative risk of adenoma by age 60 yrs 68% in men and 48% in females CRC-related deaths: 5	This study demonstrates that there is a significant risk (22-33% by age 60) of interval cancers in patients undergoing 2-3 yearly colonoscopies.
Engel (2010) [28] [Germany]	Observational: Examining the efficacy of annual colonoscopy	Annual colonoscopy, NB: 81% completed within 15 months. Mean follow-up: 3.7yrs	German HNPCC registry: 1126 patients from LS pedigrees with confirmed MMR mutations or suspected LS pedigrees	Interval cancers: 25 (95% were local stage)	This study shows that there is still a risk of interval cancers with annual surveillance, but, most of these cancers can be expected to be early stage.
Vasen (2010) [29] [Netherlands]	Observational: Investigating the rate of interval cancers with screening.	Colonoscopy 1-2 yrs, Mean follow-up: 7.2 yrs	745 patients from 205 HNPCC pedigrees (with <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i>)	Interval cancer: 33 (83% local stage); ranging from 34 to 71 yrs, 4 cases <40; higher in carriers older than 40 years Risk of interval cancer over 10 years: 6%, Interval cancer risks and genotype: higher risk in carriers of <i>MLH1</i> and <i>MSH2</i> mutation; 1/127 <i>MSH6</i> carriers developed CRC, compared to 19/290 <i>MLH1</i> and 13/328 <i>MSH2</i> (p=0.08)	This study suggests that the risk of interval cancers with annual surveillance is highest for <i>MLH1</i> and <i>MSH2</i> carriers, and carriers
Stuckless (2011) [30] [Canada]	Observational: Assessing CRC incidence and survival in screened and non-screened carriers	Colonoscopy every 1-2 years (n=152) Vs. no screening (n=170)	322 <i>MSH2</i> mutation carriers (proven, obligate, and putative); Median follow-up: 9 yrs (m); 11 yrs (F)	Median age of CRC: In screened males was 58yrs (compared to the expected 47yrs p= 0.000) and in screened female was 79yrs (compared to 57yrs in the non-screened group, p= 0.000) Median survival: In screened males was 66yrs (compared to the expected 62yrs, p=0.0034), and 80yrs (compared to the expected 63yrs, p =0.001) Interval cancers: 11/41 (27%) males; median; 1.7 yrs; 4< 1yr, 10/68 (15%) females: at median interval of 2.1yrs; 1 <1yrs CRC-related deaths: 1	This study provides further evidence of the survival benefit conferred by colonoscopy in MMR carriers

Gynaecological surveillance

We conducted a literature review and identified the below studies addressing the efficacy of gynaecological surveillance:

Auranen (2011)[31]: Systematic review of all studies addressing the effectiveness of gynaecological cancer surveillance in females from HNPCC pedigrees [32-36] The authors identified 5 observational studies examining endometrial surveillance (with transvaginal USS +/- endometrial biopsy and hysteroscopic endometrial sampling), and 3 examining ovarian cancer surveillance (CA125 measurements). Most studies recommended starting surveillance between age 30 and 35, and the surveillance interval ranged from 1 to 3yrs.

From the data provided from this systematic review, transvaginal ultrasound scans without endometrial sampling is not an effective screening tool for endometrial cancer. Only interval endometrial cancers and no screen-detected cancers were reported in studies using this modality. The sensitivity of screening is significantly improved with routine endometrial sampling. In the 3 studies that performing endometrial sampling (with transvaginal ultrasound scan or using hysteroscopy) 17 screen-detected endometrial cancers and 24 endometrial hyperplasias were detected. In total 17 complex hyperplasias were detected without and with atypia. This has been shown to be important precursor lesions of endometrial cancer in Lynch Syndrome. The vast majority (>80%) of screen detected endometrial cancers were locally staged. However, no statistically significant difference in FIGO tumour stage or overall survival was been demonstrated between screened and unscreened women. It is also important to note, in one study all of the screen-detected endometrial cancers and hyperplasias occurred in women who were symptomatic at the time of screening. Five interval cancers were reported and 3 cancers occurred within a year of a negative screening visit; however it is unclear whether or not some of these cancers occurred in patients who had endometrial sampling.

Ovarian cancer screening is also ineffective in Lynch Syndrome. Five ovarian cancers were also reported and only one was screen detected. The screen-detected cancer was a FIGO IIIC cancer and the patient died 5 months after their diagnosis [36]. There was also a high false-positive rate reported for CA125 measurements and/or transvaginal ultrasound.

Since the systematic review, the below observational studies have been reported in the literature:

Manchanda (2012): Study reporting the outcome of annual office hysteroscopy-guided biopsies in 41 women with Lynch Syndrome attending the high-risk familial history clinic at University College London Hospital. Four women were found to have endometrial cancers or atypical hyperplasia, and no interval cancers occurred over a median follow-up of 22 months [37].

Stuckless (2013) Study compared gynaecological cancer incidence and overall survival in *MSH2* mutation carriers (n=54) undergoing gynaecological screening (annual transvaginal ultrasound scans and optional biopsy) and matched controls. A statistically significant difference was not demonstrated in mean survival (79yrs vs. 69yrs; p=0.11) or FIGO (Stage I/II 92% vs. 71%; p=0.17) between the groups. Five interval endometrial cancers were reported [38].

Recommendation for gynaecological surveillance

From the data available there is no evidence that endometrial surveillance confers a survival benefit or reduces the incidence of endometrial cancer in MMR carriers. There is no convincing evidence that endometrial screening detects cancers earlier, and a

statistically significant difference in FIGO tumour stage between screened detected and symptom detected endometrial cancers have not been demonstrated.

There is also no convincing evidence that ovarian cancer surveillance using transvaginal ultrasound scans and CA125 tumour marker measurements is beneficial female MMR mutation carriers.

Based on the current evidence we do not recommend ovarian and endometrial cancer surveillance for female MMR carriers. However, we note that there is a need for more research in this area, as the current data has been derived from small and single-centred studies, and has been limited by short follow-up times. Therefore, we would offer MMR carriers endometrial cancer surveillance in a research setting between the ages of 35 and 40, should this be available.

Prophylactic Hysterectomy and Bilateral Salpingo-oophorectomy

We identified a single study addressing the efficacy of prophylactic hysterectomy and BSO in MMR carriers:

Schmeler (2006)[39]: Retrospective cohort study of 315 female MMR mutation carriers in which 61 carriers (47 hysterectomy and BSO and 14 hysterectomy alone) had undergone gynaecological surgery, either for prophylaxis or for a benign disorder. During a follow-up period of approximately 10 years, no endometrial or ovarian cancers developed in those who had surgery, whereas 33% of those who did not have surgery developed endometrial cancer and 5.5% developed ovarian cancer. There were also 3 deaths due to endometrial cancer in the control group. This study demonstrated a 100% efficacy for prophylactic surgery in preventing endometrial and ovarian cancer in MMR mutation carriers; however this was not statistically significant for ovarian cancer due to small numbers. No primary peritoneal cancers were reported in the females who had undergone surgery. However, there was no difference in total cancer-specific mortality between the two groups (5% for both groups). A single surgical complication was reported in 1 of 61 (1.6%) carriers undergoing surgery. This is in keeping with the previously published complication rate of 1 to 9% associated hysterectomies and BSOs for benign conditions. The most common surgical complications include bleeding, infection, and injury to bowel, bladder, and ureter. Patients who have had previous surgery and radiotherapy to treat colorectal cancer may have a higher risk of developing surgical complications [1, 39].

Cost-effectiveness analyses of prophylactic surgery versus gynaecological screening have also been reported in the literature. Kwon et al conducted a cost-effectiveness analysis, which demonstrated that prophylactic surgery at 40 was associated with both the lowest cost (ICER \$5025) and the highest number of quality-adjusted life years (18.94 QALYs). Although, it is important to note that annual gynaecological screening (from 30 years) combined with prophylactic surgery at the age of 40 years was found to be the most effective risk reducing strategy (18.98 QALYs) [40].

Recommendation for Prophylactic Hysterectomy and BSO

From the data available there is evidence that prophylactic hysterectomy and bilateral salpingo-oophorectomy reduces the incidence of endometrial and ovarian cancer in MMR mutation carriers respectively. However, risk reducing gynaecological surgery has not been demonstrated to confer a survival advantage in MMR mutation carriers [39]. There also is a small, but undefined risk of primary peritoneal cancer after prophylactic gynaecological surgery [41].

Based on the available evidence we recommend that:

- *MLH1* and *MSH2* carriers consider **prophylactic hysterectomy and BSO**, once they have completed their families, from 40. The benefit-harm ratio favours this intervention, which has been shown to significantly reduce the incidence of endometrial and ovarian cancers in MMR carriers, as carriers are at high lifetime risk of these cancers, and have a significant risk of dying from these cancers over their lifetimes (4% risk for endometrial and a 2% risk for ovarian cancer). Given the risk data showing a low risk endometrial and ovarian cancer at 30, and the mean age of onset of endometrial (47-48yrs) and ovarian cancer (48yrs) it seems appropriate to offer this intervention from the age of 40yrs. Although, there is no data to suggest a survival benefit with prophylactic surgery (which may be in part due to the relatively good-prognosis of Lynch-related ovarian and endometrial cancers), we feel that benefit is also conferred by the avoidance of cancer treatment related morbidity.
- Premenopausal *MSH6* and *PMS2* carriers consider prophylactic hysterectomy alone, once they have completed their families, from 40. BSO may be recommended in the presence of a significant family history of ovarian cancer or if surgery is performed post-menopausally. Given the data available it is unlikely that the benefit-harm ratio would favour BSO in premenopausal carriers, as no data to suggest that these carriers have a high lifetime risk of ovarian cancer, and BSOs in premenopausal carriers will result in adverse side effects associated with the surgical menopause.

Surveillance for other cancer sites

We reviewed literature to determine the role of surveillance for the below cancer sites in MMR carriers:

Gastric: A single study assessing the effectiveness of gastric surveillance in MMR carriers was identified [42]. In this Finnish study, upper GI endoscopy was performed in 73 *MLH1/MSH2* carriers (median age, 47yrs), and no early gastric cancers or premalignant lesions were detected. There was only one screened detected cancer, which was an advanced duodenal cancer. **This study failed to show any benefit for gastric cancer surveillance in MMR carriers.**

Small bowel: A single study examining the effectiveness of small bowel surveillance in Lynch syndrome was identified [43]. Saurin et al performed a prospective, blinded, compared study of capsule endoscopy and CT enteroclysis in 35 MMR carriers. Three small bowel neoplasms (1 local jejunal cancer, and two adenomas with low grade-dysplasia) were detected with capsule endoscopy, and two cancers were missed by CT imaging. **This study provides some evidence that small bowel cancers and pre-invasive lesions can be detected using capsule endoscopy.** But this intervention is limited, and full images of the small bowel are not achieved in ~20% of patients. **There is no data that this intervention confers a survival benefit in MMR carriers.**

Urinary tract: We identified a single study in the literature that assessed the effectiveness of urinary tract surveillance in LS [44]. In this Danish study analysed the outcome of biennial urinary cytology in 977 individuals from HNPCC pedigrees or with a suspected LS diagnosis. There were 1868 screening procedures involving a total of 3213 person years (median 2.8 years, range 0–11.5). Two screened detected urinary tumours identified (0.1%), the tumours were small and non-invasive. During the follow-up period, a total of 14/997 patients (11/14 *MSH2* carriers) developed a urinary tract cancer (5 interval cancers); including 7 bladder cancers without invasion, 1 renal pelvis without invasion, and 1 renal cell carcinoma. The sensitivity of urine cytology was just 29%, and the specificity was 96%. **This study shows that urine cytology is an insensitive screening tool in MMR carriers, but also further supports of the increased risk of urinary tract cancers in *MSH2* carriers.**

Recommendation for surveillance for other cancer sites

From the limited data available surveillance for gastric, small bowel, or urinary tract cancers have not been shown to be beneficial in MMR carriers (with no demonstration of survival benefit or reduction in the incidence of cancer). The risk data (with the exception of urinary tract cancers and *MSH2* carriers) has generally also demonstrated that the lifetime risk of the other Lynch-related cancer is relatively low for *MLH1* and *MSH2*, and similar to the general population for *PMS2* and *MSH6* carriers. Therefore, based on the current data we do not recommend screening for these cancer types in MMR. However, urinary tract surveillance could be performed in *MSH2* carriers within the context of a research study, should this be available.

It is important that MMR carriers are educated about symptoms (e.g. haematuria in *MSH2* carrier) and encouraged to practice symptom awareness.

Aspirin chemoprevention

We reviewed literature to determine the role of aspirin chemoprevention in MMR carriers and identified a single study:

Burns (2008; 2011): The CAPP2 trial (double-blind) randomised Lynch syndrome MMR carriers (*MLH1*, *MSH2*, and *MSH6*) in a two-by-two factorial design to 600mg aspirin or aspirin placebo or 30g resistant starch or starch placebo, for up to 4 years. The primary outcome was the incidence of new primary colorectal cancers. At the end of the intervention phase the overall burden of adenomas and carcinomas unchanged. However, a re-analysis was performed at a mean follow-up of 55.7 months, and 48 participants had developed 53 primary colorectal cancers (18 of 427 randomly assigned to aspirin, 30 of 434 to aspirin placebo). Intention-to-treat analysis of time to first colorectal cancer showed a hazard ratio (HR) of 0.63 (95% CI; 0.35-1.13, p=0.12). Poisson regression taking account of multiple primary events gave an incidence rate ratio (IRR) of 0.56 (95% CI; 0.32-0.99, p=0.05). For participants completing 2 years of intervention (258 aspirin, 250 aspirin placebo), per-protocol analysis yielded an HR of 0.41 (0.19-0.86, p=0.02) and an IRR of 0.37 (0.18-0.78, p=0.008). No data for adverse events were available post-intervention; during the intervention, adverse events did not differ between aspirin and placebo groups. **This study shows that regular aspirin (600mg) dose reduced cancer incidence. The CAPP3 trial is now underway, aiming to establish the optimum dose of aspirin in MMR carriers.**

Recommendation for aspirin chemoprevention

From the data available regular aspirin has been beneficial in MMR carriers. We therefore recommend that carriers be recruited to the CAPP3 study, or consider taking regular low dose aspirin (100mg) from the age of 25, in the absence of contraindications to aspirin.

Glossary:

MMR- **M**ismatch **R**epair
PTV - **P**rotein **T**runcating **V**ariant
AC – **A**msterdam **C**riteria
CRC- **C**olorectal **C**ancer
EC- **E**ndometrial **C**ancer
BSO- **B**ilateral **S**alpingo-**o**ophorectomy
CNS- **C**entral **N**ervous **S**ystem

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