Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts

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ABSTRACT
Lynch syndrome (LS) is characterised by the development of colorectal cancer, endometrial cancer and various other cancers, and is caused by a mutation in one of the mismatch repair genes: MLH1, MSH2, MSH6 or PMS2. In 2007, a group of European experts (the Mallorca group) published guidelines for the clinical management of LS. Since then substantial new information has become available necessitating an update of the guidelines. In 2011 and 2012 workshops were organised in Palma de Mallorca. A total of 35 specialists from 13 countries participated in the meetings. The first step was to formulate important clinical questions. Then a systematic literature search was performed using the Pubmed database and manual searches of relevant articles. During the workshops the outcome of the literature search was discussed in detail. Table 1 shows the criteria that were used for evaluation of studies, for the categorisation of evidence that they represented and for the strength of the recommendations that were made.

SHORT UPDATE ON LS
LS was first described by Aldred Warthin in 1913.4 In 1956, Henry Lynch reported two large families with hereditary CRC from the midwest.5 Since then, many hundreds of families with the same pattern of cancer occurrence have been identified throughout the world. In the early 1990s the underlying gene defect was discovered, that is, a mutation in one of the MMR genes MLH1, MSH2, MSH6 or PMS2. Recently, two groups reported that a constitutional 3′ end deletion of EPCAM, which is immediately upstream of the MSH2 gene, may cause LS through epigenetic silencing of MSH2.6,7

An MMR gene defect leads through loss of the corresponding normal alleles in the tumours of carriers to loss of MMR function and results in an accumulation of mutations in (coding and non-coding) microsatellites in such tumours (so-called microsatellites instability; MSI). Carriers of an MMR gene mutation have a very high risk of developing CRC (25–70%) and EC (30–70%) and an increased risk of developing other tumours. The main clinical features are an early age of onset and the occurrence of multiple tumours.
Since 2007, many studies have been published on the risk of developing non-CRC, non-EC cancers in carriers of an MLH1 gene mutation, MSH2 gene mutation and MSH6 gene mutation.8–21 Such studies are not yet available for carriers of a PMS2 gene mutation. A summary of the findings is shown in table 2. Those new studies also reported increased risks for pancreatic, bladder and breast cancer and possibly prostate cancer. Notably, carriers of MSH6 mutations appear to be particularly at risk of gastrointestinal cancer and EC, whereas carriers of an MSH2 gene mutation have the highest cancer risks across the spectrum, especially for the development of urinary tract cancer. The risks for MLH1 gene mutation carriers are between the cancer risks reported for MSH6 carriers and those for MSH2 carriers.8–21 Moreover, a recent study reported on increased cancer risks for individuals with an EPCAM deletion.22 The investigators compared the cancer risks between 194 carriers of an EPCAM deletion and 473 carriers of a mutation in MLH1, MSH2, MSH6 or a combined EPCAM–MSH2 deletion. The risk of developing CRC for EPCAM deletion carriers was similar (75% by age 70 years) to the risks in carriers of an MLH1 or MSH2 mutation or a combined EPCAM–MSH2 deletion but was higher than the risk in MSH6 mutation carriers. By contrast, the risk of EC (12% by age 70 years) was significantly lower in female carriers of an EPCAM deletion compared to the risk in carriers of an MSH2 or MSH6 mutation or a combined EPCAM–MSH2 deletion. The EC risk in EPCAM deletion carriers was also lower than the risk in MLH1 carriers but this difference was not statistically significant.

The wide variation in cancer risk within and between families is direct evidence that the risk is influenced by environmental and genetic factors. In the past 5 years many genome-wide association studies in CRC patients have identified a total of 20 variants that are associated with an increased risk of sporadic CRC.23 A Dutch study evaluated whether six of these variants act as modifiers of the CRC risk in 675 gene mutation carriers.24 Two variants (rs16892766 and rs3802842) were reported to increase the CRC risk in LS, the latter only in female carriers. An Australian group evaluated the effect of nine variants on the CRC risk in 684 MMR gene mutation carriers.25 They confirmed the association of the previously reported variants with CRC risk but only for MLH1 carriers. A French group did not find an association between these and other variants in 748 mutation carriers.26 In summary, more studies are needed to define the role of these variants in clinical practice.

**QUESTION NO 1**
How can we improve the identification of LS?
Relevant literature
Identification of individuals with LS is extremely important because they can benefit from life-saving intensive-cancer surveillance. However, it is the experience of most physicians specialising in familial cancer that LS is underdiagnosed.28 There are many ways to improve the identification of this syndrome that have been described in a previous report from our group.2 For example, efforts should be aimed at increasing the awareness of hereditary CRC in the general population and at promoting the taking of an adequate family history in all patients visiting a physician. However, probably the most effective way to identify LS is via patients who are diagnosed with CRC or EC. Many criteria have been proposed to identify LS and carcinomas led to the detection of LS in a substantial proportion of cases (14%).11
An alternative approach to the identification of LS is by testing unselected cases of EC for MSI and/or immunohistochemistry. Two studies revealed that such an approach led to the identification of LS in a proportion of patients (1.8–3.9%) comparable with CRC testing (1.8–3.9%) (table 3). Molecular screening of EC has also been found to be cost effective.11
A recent study of molecular screening of sebaceous adenomas and carcinomas led to the detection of LS in a substantial proportion of cases (14%).12
Due to the cascade effect, the identification of index cases by molecular screening leads on average to the detection of three additional relatives with LS, which demonstrates the utility of this approach and indicates its cost effectiveness.

Table 3
Outcome of prospective molecular screening of CRC or LS-associated cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>No of (%) mutation carriers fulfilling revised Bethesda guidelines</th>
<th>Type of mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hampel et al (2008)</td>
<td>13/18 (72%)</td>
<td>4 MLH1 10 MSH2 3 MSH6 1 PMS2</td>
</tr>
<tr>
<td>Julie et al (2008)</td>
<td>6/8 (75%)</td>
<td>2 MLH1 5 MSH2 1 MSH6</td>
</tr>
<tr>
<td>van Lier et al (2012)</td>
<td>20/27 (74%)</td>
<td>5 MLH1 11 MSH6 5 PMS2 1 EPCAM</td>
</tr>
<tr>
<td>Moreira et al (2012)</td>
<td>78/82 (88%)</td>
<td>34 MLH1 33 MSH2 9 MSH6 6 PMS2</td>
</tr>
<tr>
<td>Canard et al (2012)</td>
<td>22/25 (88%)</td>
<td>4 MLH1 19 MSH2 2 MSH6</td>
</tr>
<tr>
<td>Hampel et al (2006)</td>
<td>N.A.</td>
<td>1 MSH1 2 MSH2 6 MSH6 2 PMS2</td>
</tr>
<tr>
<td>Leenen et al (2012)</td>
<td>N.A.</td>
<td>1 MLH1 2 MSH2 6 MSH6 2 PMS2</td>
</tr>
</tbody>
</table>

*LS-like: loss of expression of MMR proteins compatible with presence of MMR gene mutation.
CRC, colorectal cancer; IHC, immunohistochemistry; LS, Lynch syndrome; MMR, mismatch repair; MSI, microsatellites instability; NA, not applicable.
Conclusion and recommendation
Testing all CRC (or individuals with CRC<70 years) and all EC (or individuals with EC<70 years) by immunohistochemistry or MSI is useful for the identification of patients with LS (category of evidence IIb). The Mallorca group recommends investigation of all CRC (or individuals with CRC<70 years) by immunohistochemistry of the four MMR proteins or MSI (grade of recommendation C). These tests should be accompanied by methods that identify MLH1 promoter methylation. Investigation of all EC in individuals less than 70 years by immunohistochemistry or MSI can be considered to improve identification (grade of recommendation C).

QUESTION NO 2
What is the optimal colorectal surveillance protocol for LS?

Relevant literature
Colorectal surveillance is the only surveillance protocol in LS proved to be effective.\textsuperscript{43} Regular colonoscopy leads to a reduction of CRC-related mortality and also to a significant reduction of overall mortality in contrast with CRC screening in the general population.\textsuperscript{27}

However, there is an ongoing discussion about the optimal interval between colonoscopic examinations. Although a 3-year interval between colonoscopies has been proved to be effective,\textsuperscript{43} there are no studies that have compared the effectiveness between different intervals. Since 2007, three prospective studies and one retrospective study analysing the effectiveness of colonoscopic surveillance have been published.\textsuperscript{44–47} The characteristics of the study populations, the intervals that were recommended and the outcomes are summarised in table 4.

Unfortunately, it is difficult to compare the risks of developing an interval cancer (defined as a cancer that develops after a negative screening examination) between the studies due to the different methodologies used. The proportion of interval cancers with a local tumour (stages I and II) varied from 78% to 95%. Most tumours (57–62%) were located in the right colon, which emphasises the importance of careful investigation of this part of the colon. In the Dutch, German and Canadian series, most interval cancers were diagnosed in individuals older than 40 years. However, in the Finnish series a substantial proportion (20–30%) were diagnosed between the age of 30 and 40 years. In one study, the influence of the type of MMR gene defect on the risk of developing interval cancers was evaluated. That study demonstrated that the risk was lower for carriers of an MSH6 gene mutation, although the difference was not statistically significant.

In the Finnish series, it was found that mortality due to CRC was associated with a lack of participation in the surveillance programme. This is concerning given that the lack of compliance with the recommended surveillance interval in the German and Canadian studies was 20% and 42%. To guarantee the continuity of surveillance and improve compliance with the surveillance recommendations patients should be registered at a regional or national hereditary cancer registry. Such registries can improve participation in surveillance by using reminder systems.\textsuperscript{48}

Conclusion
A 3-year interval between colonoscopies has been proved to be effective (category of evidence IIb). In view of the observation of (advanced) CRC detected between 2 and 3 years after surveillance colonoscopy, the recommended interval for mutation carriers is 1–2 years (grade of recommendation C).

QUESTION NO 3
How effective is surveillance for endometrial and ovarian cancer?

Relevant literature
In LS, the risk of developing EC is very high and equals or even exceeds the risk of CRC in female gene carriers.\textsuperscript{49} The overall prognosis of patients diagnosed with EC is relatively good, with a 10-year survival of approximately 80%. However, 20% of the patients will ultimately die from the disease. Moreover, a substantial proportion of patients need treatment with radiation and/or chemotherapy.

The main goal of surveillance for EC is detection and treatment of premalignant lesions (ie, endometrial hyperplasia) or EC at an early stage and thereby improving the prognosis for the patients. The World Health Organization classifies endometrial hyperplasia as simple or complex determined by the degree of architectural abnormality, and as having or not having atypia. Nieminen et al\textsuperscript{40} studied serial specimens of normal endometrium, simple hyperplasia and complex hyperplasia with and without atypia during 10 years of surveillance. MMR deficiency was observed in 7% of normal endometrium, 40% of simple hyperplasia, 100% of complex hyperplasia without atypia and 92% of complex hyperplasia with atypia, suggesting that in LS, contrary to the traditional view, complex hyperplasia with and without atypia was equally important as precursor lesions of EC.

In 2011, Auranen and Joustiniemi\textsuperscript{41} performed a systematic review of all studies that addressed gynaecological cancer surveillance in women who belonged to LS families. The authors

<table>
<thead>
<tr>
<th>Table 4 Outcome of colonooscopy surveillance in LS</th>
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<tbody>
<tr>
<td><strong>Author/year</strong></td>
</tr>
<tr>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Mecklin et al (2007)\textsuperscript{44}</td>
</tr>
<tr>
<td>Engel et al (2010)\textsuperscript{46}</td>
</tr>
<tr>
<td>Vasen et al (2010)\textsuperscript{45}</td>
</tr>
<tr>
<td>Stuckless et al (2011)\textsuperscript{47}</td>
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</table>

*Defined as CRC that develops after a negative screening colonoscopy.
CRC, colorectal cancer; LS, Lynch syndrome.
identified five studies in the literature that included a total of 647 women. The screening methods applied in the studies varied from only transvaginal (or transabdominal) ultrasound (two studies) to a combination of transvaginal ultrasound and endometrial biopsy (two studies) and hysteroscopic endometrial biopsy (one study). The intervals between examinations varied between 1 year in three studies, 1–2 years in one study and 2–3 years in another study. In the studies that used only ultrasound as the screening tool, no EC were detected and only interval cancers occurred. However, in the studies with a protocol that also included endometrial biopsies, the detection of premalignant lesions and EC was improved.

Renkonen-Sinisalo et al compared the Federation of Gynecology and Obstetrics (FIGO) stages of the screen-detected cancers with those of EC diagnosed after presentation of signs or symptoms. Although less advanced cancers were observed in the screen-detected group, the difference was not statistically significant. The main advantage of the surveillance programme seems to be the identification of precursor lesions. No benefit was shown for ovarian cancer surveillance. Auronen and Joutsiniemi concluded that the available studies do not adequately allow for evidence-based clinical decisions.

Since that review, another retrospective study was published on the impact of gynaecological screening in MSH2 carriers (n=54). Nine women were diagnosed with EC, five of which were within 1 year of the previous negative screening test (transvaginal ultrasound and/or endometrial biopsy) and two were at initial screening. Of the nine EC, seven were localised cancers (stage I), and one was at an advanced stage (stage III). There were no deaths due to EC. Six women had ovarian cancer, three of which were within 1 year of a previous normal screening. Two died from ovarian cancer. The authors concluded that gynaecological screening did not result in earlier detection of gynaecological cancer.

In view of the uncertain benefit of the surveillance programme, it is important to consider possible disadvantages of the programme. Elmasry et al assessed the patient acceptability of the available screening modalities. Transvaginal ultrasound was associated with less discomfort than hysterectomy or Pipelle biopsy. There was no significant difference between the pain scores for hysterectomy and Pipelle biopsy. Huang et al compared a new patient-centered approach by combining endometrial biopsies and colonoscopy under sedation. This approach was much more acceptable than an endometrial biopsy as a single procedure without sedation.

Wood et al evaluated the effect of gynaecological screening in LS families on psychological morbidity. The authors did not demonstrate any adverse psychological effect in the screened population, even in those with false positive screening results.

Conclusion
The value of surveillance for EC is still unknown. Surveillance of the endometrium by gynaecological examination, transvaginal ultrasound and aspiration biopsy starting from the age of 35–40 years may lead to the detection of premalignant disease and early cancers (category of evidence III) and should be offered to mutation carriers (grade of recommendation C). The pros and cons should be discussed (table 5). Given the lack of evidence of any benefit, gynaecological surveillance should preferably be performed as part of a clinical trial.

**QUESTION NO 4**
What is the role of prophylactic hysterectomy with or without oophorectomy?

**Table 5 Pros and cons of surveillance for gynaecological cancer**

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
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<tbody>
<tr>
<td>Identification of precursor lesions of endometrial cancer</td>
<td>Small risk of death</td>
</tr>
<tr>
<td>Identification of early stage endometrial cancer (not proved)</td>
<td>Physical burden of surveillance examination especially Pipelle biopsy</td>
</tr>
<tr>
<td></td>
<td>No evidence of efficacy for early stage ovarian cancer detection</td>
</tr>
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<td></td>
<td>Psychological burden</td>
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</table>

**Relevant literature**
Schmeler et al have shown in a retrospective study that prophylactic hysterectomy and oophorectomy is very effective in LS: none of the patients who underwent prophylactic surgery (61 out of 313) developed endometrial or ovarian cancer, whereas 33% of patients who did not have surgery developed EC and 5.5% developed ovarian cancer.

A recent study documented two cases of LS patients who developed primary peritoneal cancers after prophylactic surgery. A cost-effectiveness analysis of prophylactic surgery versus gynaecological screening showed that risk-reducing surgery was associated with both the lowest costs and highest number of quality-adjusted life years.

In view of the very high risk of EC, the substantial proportion of women who will die from the disease, the morbidity associated with treatment and the effectiveness of prophylactic surgery, there is agreement that the option of prophylactic hysterectomy should be discussed with mutation carriers who have completed their family. However, there are still some important questions that should be addressed.

First, should prophylactic surgery include salpingo-oophorectomy? The risk of developing ovarian cancer in mutation carriers is approximately 9% with the highest risks in MLH1 and MSH2 mutation carriers and the lowest risk in MSH6 mutation carriers. Although the prognosis of unselected patients with ovarian cancer (and also of patients with ovarian cancer associated with BRCA1 and BRCA2 mutations) is very poor, recent studies suggested that the biology of ovarian cancer associated with LS may be different. Three studies showed that the majority of symptomatic ovarian cancers (77–81%) in LS are diagnosed at an early stage (FIGO stages I and II). In a multicentre study, Grinedal et al collected a large number (n=144) of prospectively diagnosed cases of ovarian cancer and demonstrated a very good prognosis with a 10-year survival of 81%.

Prophylactic surgery in postmenopausal women should include salpingo-oophorectomy. However, salpingo-oophorectomy in premenopausal women is associated with various adverse effects such as an immediate onset of menopause as a result of oestrogen deprivation potentially resulting in vasomotor symptoms and possible sexual dysfunction. Oestrogen deprivation may also lead to a higher risk of osteoporosis. A large study by Madalinska et al in 846 carriers of a BRCA1 and BRCA2 mutations reported significantly more endocrine symptoms in the patients who underwent prophylactic oophorectomy compared to women who underwent surveillance of the ovaries. No significant differences were observed in the level of sexual activities between the two groups, but women in the prophylactic surgery group reported significantly more discomfort (vaginal dryness and dyspareunia), less pleasure and less satisfaction during sexual activities. Despite this, the study did not...
In LS, the cumulative risk of developing gastric cancer by the age of 40 years is approximately 5%. Recent studies have shown that there is no evidence for the clustering of gastric cancer in specific LS families. In parts of the world with a high background incidence of gastric cancer in the population (Korea, Japan), the risk of developing gastric cancer in LS families is also higher, suggesting the role of environmental factors. Although not proved, the impression exists that the incidence of gastric cancer in LS in the western world seems to be decreasing in parallel to the declining incidence of gastric cancer in the general population.

The prognosis in unselected patients with cases of gastric cancer is poor, with an average 5-year survival rate of 20–25%. According to the Lauren’s classification, tumours are separated into ‘diffuse’, ‘intestinal’ and ‘mixed’ types. In ‘high incidence’ areas, patients with *Helicobacter pylori*-associated chronic gastritis may develop atrophy followed by intestinal metaplasia over time. This may culminate in neoplastic changes, especially adenocarcinoma of ‘intestinal’ type. Two studies showed that the majority of gastric cancer associated with LS is of the intestinal type (73–79%). The goal of surveillance for gastric cancer would be the detection of precursor lesions and gastric cancer at an early curable stage. It is well known that early detection of diffuse gastric cancer is extremely difficult, and for this reason prophylactic gastrectomy is recommended in carriers of a *CDH1* mutation. However, as most cancers in LS are of the intestinal type, regular upper gastrointestinal endoscopy may lead to the early detection of precursor lesions and early cancer. Indeed, a Finnish study reported potential precursor lesions in a substantial proportion of 73 MMR gene mutation carriers: *H pylori* infection was observed in 26%, atrophy in 14% and intestinal metaplasia also in 14%. There are no (other) studies in the literature that have evaluated the effectiveness of surveillance for gastric cancer. In view of the relatively low risk of gastric cancer and the lack of established benefit, the Mallorca group does not advise surveillance for gastric cancer. On the other hand, the Mallorca group recommends screening mutation carriers for the presence of an *H pylori* infection and subsequent eradication if detected. In countries with a high incidence of gastric cancer in LS, surveillance might be performed in a research setting.

**Cancer of the small bowel**

The risk of developing this cancer in carriers of an *MLH1* or *MSH2* mutation is approximately 5%. In carriers of a *MSH6* mutation, small bowel cancer is relatively rare. There is no evidence for the clustering of small bowel cancer in specific families. The tumours in LS families are mainly located in the proximal small bowel (43%) and the jejunum (33%); 7% are located in the ileum. Patients with small bowel cancer have a poor prognosis. The 5-year survival rate is 30–35%.

A French study recently compared the use of CT enteroclysis and video-capsule endoscopy in 35 mutation carriers. Video-capsule endoscopy detected three (10%) lesions of which two were missed by CT enteroclysis. The lesions included two adenomas and one jejunal cancer. Although the yield of this small study is noteworthy, more studies are needed to confirm the findings and to assess the cost effectiveness. Currently, the Mallorca group does not recommend surveillance for this cancer. As small bowel cancer is frequently located in the duodenum and ileum, we suggest inspection of the distal duodenum during upper gastrointestinal endoscopy (if performed) and also of the ileum during colonoscopy.

**Cancer of the urinary tract**

Many studies have reported an increased risk of urothelial cancers of the upper urinary tract in LS. Recent studies have also demonstrated an increased risk of bladder cancer. The estimated risk varies from 5% to 20%, with the highest risk

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**Guidelines**

**Table 6 Pros and cons of prophylactic hysterectomy with and without salpingo-oophorectomy**

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of endometrial and ovarian cancer</td>
<td>Small risk of death</td>
</tr>
<tr>
<td>Prevention of morbidity related to treatment</td>
<td>Mortality surgery (0.1%)</td>
</tr>
<tr>
<td></td>
<td>Morbidity surgery (5–9%)</td>
</tr>
<tr>
<td></td>
<td>Pelvic surgery makes colonoscopy more difficult and painful and may reduce chance of full colonoscopy</td>
</tr>
<tr>
<td></td>
<td>Psychosocial problems (10–20%)</td>
</tr>
<tr>
<td></td>
<td>Early menopause depending of age at surgery</td>
</tr>
<tr>
<td></td>
<td>Sexual problems related to hysterectomy and early menopause</td>
</tr>
<tr>
<td></td>
<td>Probably very small risk of developing primary peritoneal carcinoma after oophorectomy</td>
</tr>
<tr>
<td></td>
<td>Unnecessary removal</td>
</tr>
</tbody>
</table>

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reveal any other differences in quality of life. Usually, hormone replacement therapy is prescribed in premenopausal women after salpingo-oophorectomy, which may partly reduce the vaso-motor symptoms but has no effect on sexual discomfort.

In view of the recent study that suggests a relatively good prognosis of ovarian cancer in LS, it is questionable whether the possible small gain in life expectancy outweighs the adverse effects of prophylactic salpingo-oophorectomy at a young age.

The second question is how these issues should be discussed with the patient and how the patient can be supported in their decision-making? The best approach is to inform the patient fully about all pros and cons of prophylactic surgery. As a basis for this discussion, the pros and cons are summarised in table 6. Depending on the type of information, a gynaecologist, geneticist, clinical psychologist or other specialists should be involved. Ideally, this information should also be available in written form.

The third question is from which age surgery should be recommended. The risk of endometrial and ovarian cancer increases from the age of 40 years. The optimal timing of prophylactic surgery, therefore, would be around the age of 40 years.

**Conclusion**

Hysterectomy and bilateral oophorectomy largely prevents the development of endometrial and ovarian cancer (category of evidence III) and is an option to be discussed with mutation carriers who have completed their families especially after the age of 40 years (grade of recommendation C). Also, if CRC surgery is scheduled, the option of prophylactic surgery at the same time should be considered. All pros and cons of prophylactic surgery should be discussed.

**QUESTION NO 5**

What is the effectiveness of surveillance for other cancers?

**Gastric cancer**

In LS, the cumulative risk of developing gastric cancer by the age of 70 years is approximately 5%. Recent studies have shown that there is no evidence for the clustering of gastric cancer in specific LS families.

In parts of the world with a high background incidence of gastric cancer in the population (Korea, Japan), the risk of
in male carriers and those with an MSH2 mutation. The risk for non-urothelial tumours was not increased.

The classic presenting sign of urothelial tumours is haematuria without pain. The prognosis of patients with urothelial tumours depends on the stage and grade of the tumours. The 5-year survival of non-invasive, low grade cancers is over 90%, while for those with high grade cancers, it is 60–70%. Periodic examination may lead to the detection of cancers at earlier stages.

Options for urinary tract cancer screening include dipstick testing of the urine for microscopic haematuria, urine cytology, screening for tumour-specific molecular markers in the urine and abdominal ultrasound. Cystoscopy is the gold standard for bladder cancer detection. However, although flexible cystoscopy has a high sensitivity and positive predictive value, it is not considered appropriate for screening in the general population or high-risk groups due to its cost, procedural nature, and (small) risks.

Urothelial carcinoma in the sporadic setting is known to be associated with tobacco, aryl amines and other chemical carcinogens. Urine cytology and cystoscopy have been used to screen workers who are at extremely high risk of developing bladder cancer through occupational exposure to known urothelial carcinogens. Although several non-randomised studies have documented a high incidence of bladder cancer in populations with heavy exposure to such carcinogens, they have not demonstrated that active screening alters the natural history of the disease in those who do develop bladder cancer.76–79

One Danish study has evaluated the effectiveness of surveillance of the urinary tract in LS.80 The study reviewed records of 3411 relatives from LS families (n=263), or families that met the Amsterdam criteria I or II (n=426) or that had been suspected of LS (n=288).

The authors collected results of urine cytology from the National Danish Pathology Database. A total of 977 patients had 1868 screening procedures involving a total of 3213 person years (median 2.8 years, range 0–11.5). In two patients (0.1%), the screening led to the identification of asymptomatic urinary tumours (two small non-invasive bladder cancers). During the study 14 patients (of the 997) developed a urinary cancer, including five interval cancers. The tumours consisted of seven bladder cancers without invasion, four bladder cancers with invasion, one renal pelvis tumour with invasion and one renal pelvis tumour without invasion and one renal cell carcinoma. The sensitivity of urine cytology was 29% in diagnosing asymptomatic tumours. The corresponding specificity was 96%. Eleven out of the 14 tumours were diagnosed in MSH2 families.

The authors concluded that urine cytology is not an appropriate screening method of screening for urinary tract cancer in LS. The study does not allow any conclusion to be made about the benefit of surveillance in subgroups of families (eg, those with the MSH2 mutation). Although abdominal ultrasound has been recommended as a surveillance tool in LS, there are no reports on its effectiveness.

In view of the lack of evidence for the benefit of surveillance for urinary tract cancer, the Mallorca group does not recommend surveillance for urinary tract cancer in LS outside the setting of a research project.

Prostate cancer

Prostate cancer is the most common cancer in men. The prognosis of these tumours is relatively good, with a 10-year survival of all men with prostate cancer of 72%. Previous studies did not show a (significantly) increased risk of prostate cancer in men with LS11, 75 However, three recent studies did reveal an increased risk of developing this cancer in LS. A study by Engel et al19 reported a significantly increased risk of prostate cancer in LS (17 cases in 1011 male mutation carriers; standardised incidence ratio (SIR) 2.5 (1.4–4)). The highest risk was found in carriers of a MSH2 mutation (cumulative risk by the age of 70 years: MSH2: 18%; MLH1: 0%; MSH6: 4%). Another study reported a tenfold increased risk of prostate cancer in carriers of a MSH2 mutation (four cases in 130 male mutation carriers) but the cumulative risk by the age of 70 years was only 6%.21 In the third study from Norway, out of 106 male carriers or obligate carriers of MMR mutations, nine had developed prostate cancer16 (six in MSH2 carriers). Immunohistochemical analysis showed the absence of the corresponding MMR gene product in seven of eight available tumours. The number of men with a Gleason score between eight and 10 was significantly higher than expected. Kaplan–Meier analysis suggested that cumulative risk by 70 years in MMR mutation carriers may be 30% (SE 0.088) compared to 8.0% in the general population.

Prostate-specific antigen screening of the general population is generally not recommended due to the serious side-effects of treatment and the indolent course of most screen-detected cancers.

If the increased risk of prostate cancer and the development of aggressive tumours are confirmed in further studies of LS families, male gene carriers, especially of an MSH2 mutation might benefit from surveillance.

Until more studies are available, the Mallorca group does not recommend surveillance for prostate cancer in LS families outside of appropriate research studies (see http://impact-study.co.uk).

Pancreatic cancer

Recent studies have revealed an increased risk of developing pancreatic cancer in LS. Kastrinos et al20 reported a RR of 8 across 147 families with an MMR gene mutation, and calculated a cumulative risk of 3.7% by the age of 70 years. Win et al23 studied 446 MMR mutation carriers and reported a SIR of 11 for pancreatic cancer. The prognosis of patients with pancreatic cancer is very poor, with an average life expectancy of 6 months after diagnosis.

However, the benefit of surveillance for pancreatic cancer in high-risk groups is unknown and as the reported absolute risk is relatively low, the Mallorca group does not recommend surveillance for this cancer in LS families outside the setting of a research programme.

Breast cancer

Whether breast cancer is part of the tumour spectrum of LS is controversial.8 81 82 Loss of MMR function has been reported in a substantial proportion of breast cancers in LS.83 84 In a large study by Watson et al,12 the risk of breast cancer was not increased (5.4% by age 70 years). In contrast, two recent studies reported increased risks of developing breast cancer. Barrow et al11 reported an increased risk only in MLH1 carriers (18%). A large cohort study from the German and Dutch LS registry reported a significantly increased risk for developing breast cancer.19 The cumulative risk by the age of 70 years was 14% in all female carriers, with the highest risk in MLH1 carriers (MLH1: 17%; MSH2: 14.4%; MSH6: 11%). The risk of developing breast cancer started to increase after the age of 40 years. Win et al23 reported a SIR of 3.95 for breast cancer in the follow-up of a cohort of 446 unaffected carriers of a MMR gene mutation.
Further studies are needed to confirm these results and determine whether the increased risk is restricted to MLH1 mutation carriers. At present, female carriers of an MMR gene mutation should be advised to participate in population screening programmes for breast cancer (biannual mammography from the age of 45 or 50 years).

**General conclusion**

A recent analysis on the causes of deaths in LS revealed that a large proportion (61%) of the cancer deaths were now associated with non-CRC non-EC. Unfortunately, the benefit of surveillance for most extracolonic cancers is still unknown. Surveillance for these cancers should therefore only be performed in a research setting. The results of long-term surveillance should ideally be collected and evaluated at a regional or national or international LS registry.

To ensure informed decision-making about surveillance by patients, all pros and cons of such programmes should be discussed with the patient. If surveillance is offered, patients should understand that there is uncertainty about the potential benefits and harms. Table 7 shows the protocol recommended by the Mallorca group.

**QUESTION NO 6**

What is the appropriate surgical treatment for CRC?

**Relevant literature**

In LS, the risk of developing a second CRC after partial colectomy for primary CRC has been reported to be approximately 16% at 10 years follow-up despite close surveillance. In view of this risk, more extensive treatment (total or subtotal colectomy) of the primary CRC might be considered. However, for decision-making it is important to address the following questions to determine the benefit of the patient: what is the risk of developing a second cancer under appropriate (post-operative) surveillance; and what is the effect of more extensive surgery on the functional outcome and quality of life.

Three recent studies reported the risk of developing an interval CRC under colonoscopic surveillance. In one study, a risk of 6% after 10 years of follow-up was reported. In the other studies, the risk of developing CRC by the age of 60 years was between 22% and 35% depending on sex and surveillance interval. One study especially evaluated the functional outcome and quality of life after limited and extensive surgery in LS patients. Although the functional outcome was significantly worse after extensive surgery, quality of life was similar in both groups.

**Conclusion**

In view of the substantial risk of a second CRC after partial colectomy (category of evidence III) and similar quality of life after partial and subtotal colectomy (category of evidence III), the option of subtotal colectomy including its pros and cons should be discussed with all LS patients with CRC, especially younger patients (grade of recommendation C).

**QUESTION NO 7**

What is the influence of environmental and lifestyle factors on the development of adenoma or CRC in LS?

**Relevant literature**

There is ample evidence that the risk of developing cancer in LS is influenced by environmental factors. The tumour spectrum observed in the first LS syndrome family published in 1913 by Warthin included mainly gastric cancers and EC. Follow-up reports of this well-known family showed that in the current generations CRC was now the most common tumour. The changes reflect the decrease of gastric cancer and increase of CRC in the general population in western countries.

In addition, the spectrum of cancers in LS reported in Japan and South Korea also differs from the spectrum found in LS families in western countries, with more gastric cancers reported in families from eastern Asia. An important question is which environmental and lifestyle factors influence the development of cancer in LS. In the past decade a large number of studies have been published that addressed this question. The studies are summarised in Table 8.

Four studies showed that smoking was associated with a higher risk of developing colorectal neoplasias. In addition, two studies demonstrated that a higher body mass index (BMI) was associated with an increased risk of colorectal neoplasia. Alcohol (two out of three studies) was not associated and fruit and fibre intake was possibly related to decreased risks. A recent large randomised controlled trial showed that resistant starch (a component of dietary fibre) had no effect on the development of CRC in LS. Another study investigated the effect of various dietary patterns on the development of adenomas in LS. A ‘snack’ dietary pattern was associated with a higher risk of adenoma development.

**Conclusion**

Smoking and a high BMI increase the risk of developing adenomas and CRC in LS (category of evidence Ib). Patients are advised to stay within the normal weight range and refrain from smoking (grade of recommendation B).

**QUESTION NO 8**

What is the role of aspirin in the management of LS?

**Relevant literature**

The CAPP2 trial randomly assigned 1009 LS carriers to two tablets (600 mg) of enteric-coated aspirin daily for 2–4 years. The overall burden of adenomas and carcinomas at the end of the intervention phase was unchanged, but re-analysis when the first recruits reached the planned long-term follow-up...
target of 10 years revealed a significant reduction in CRC and other cancers among those randomly assigned to aspirin versus those randomly assigned to placebo. The study remained double blind.\textsuperscript{102} Forty-eight participants developed 53 primary CRC cancers developed in the gastrointestinal tract and elsewhere. A dose of an initial aspirin treatment period of at least 4 years). Using cancer registry data the impact on subsequent cancer incidence and mortality was investigated. Among the eight trials, with a total of 25,570 patients and 674 cancer-related deaths, aspirin treatment using doses between 75 and 1200 mg per day was associated with a 21% lower risk of death from any cancer during the in-trial follow-up period. Among those with data on cancer site, the HR of 0.63 (95% CI 0.35 to 1.13, p=0.12). Poisson regression taking account of the multiple primary events gave an incidence rate ratio (IRR) of 0.56 (95% CI 0.32 to 0.99, p=0.05). The primary endpoint of the trial was the number, size and stage of CRC after 2 years aspirin treatment. This ‘per protocol’ analysis yielded a HR of 0.41 (95% CI 0.19 to 0.86, p=0.02) and an IRR of 0.37 (95% CI 0.18 to 0.78, p=0.008). Secondary analysis revealed fewer LS-related cancers in those on aspirin for at least 2 years (IRR 0.42, 95% CI 0.25 to 0.72, p=0.001). There was a negative association of LS cancer incidence with the numbers of aspirin taken (p=0.002). In other words, the more aspirin someone had taken, the greater was the reduction in cancers developed in the gastrointestinal tract and elsewhere.

A meta-analysis conducted by Rothwell \textit{et al}\textsuperscript{103} included a total of eight randomised trials on the prevention of vascular disease (seven placebo controlled) that examined daily aspirin use with an initial aspirin treatment period of at least 4 years). Using cancer registry data the impact on subsequent cancer incidence and mortality was investigated. Among the eight trials, with a total of 25,570 patients and 674 cancer-related deaths, aspirin treatment using doses between 75 and 1200 mg per day was associated with a 21% lower risk of death from any cancer during the in-trial follow-up period. Among those with data on cancer site, patients randomly assigned to aspirin had a reduced risk of CRC mortality that approached statistical significance (HR 0.41; 95% CI 0.17 to 1.00), an effect that became apparent 5 years after the initiation of aspirin treatment. The review suggested there was no greater benefit with doses higher than 75 mg per day, although adverse effects in the gut increased with higher doses. A dose inferiority trial, CaPP3, will start in 2013. Combining the available data, the recommendation is that all LS gene carriers should consider regular daily aspirin starting with their regular surveillance and that, when available, they should consider helping with studies to determine the optimal dose.

### Table 8 Outcome of studies on the effect of environmental factors on the risk of adenomas and CRC in LS

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Type of study</th>
<th>No of participants</th>
<th>Environmental factor</th>
<th>Endpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voskuil et al (2002)\textsuperscript{92}</td>
<td>Case–control</td>
<td>62 Cases 83 Controls</td>
<td>Meat</td>
<td>Adenomas</td>
<td>No association</td>
</tr>
<tr>
<td>Diergaard et al (2007)\textsuperscript{93}</td>
<td>Case–control</td>
<td>145 Cases 103 Controls</td>
<td>Alcohol/smoking</td>
<td>Adenomas</td>
<td>Increased risk</td>
</tr>
<tr>
<td>Wintet et al (2004)\textsuperscript{94}</td>
<td>Retrospective analysis</td>
<td>360 Carriers 271 Carriers</td>
<td>Smoking</td>
<td>CRC</td>
<td>Increased risk</td>
</tr>
<tr>
<td>Pande et al (2010)\textsuperscript{95}</td>
<td>Retrospective analysis</td>
<td>752 Carriers</td>
<td>Alcohol</td>
<td>CRC</td>
<td>No association</td>
</tr>
<tr>
<td>Botma et al (2010)\textsuperscript{96}</td>
<td>Prospective cohort study</td>
<td>468 Carriers</td>
<td>Smoking</td>
<td>CRC</td>
<td>Increased risk</td>
</tr>
<tr>
<td>Watson et al (2011)\textsuperscript{97}</td>
<td>Retrospective analysis</td>
<td>1324 Carriers 1219 Non-carriers</td>
<td>BMI</td>
<td>Adenomas</td>
<td>Increased risk in males</td>
</tr>
<tr>
<td>Winkel et al (2012)\textsuperscript{98}</td>
<td>Prospective cohort study</td>
<td>468 Carriers</td>
<td>Smoking</td>
<td>Adenomas</td>
<td>Increased risk</td>
</tr>
<tr>
<td>Mathers et al (2012)\textsuperscript{99}</td>
<td>Randomised controlled trial</td>
<td>918 Carriers</td>
<td>Alcohol</td>
<td>Adenomas</td>
<td>No significant association</td>
</tr>
<tr>
<td>Botma et al (2012)\textsuperscript{100}</td>
<td>Prospective cohort study</td>
<td>468 Carriers</td>
<td>Resistant starch</td>
<td>CRC</td>
<td>No effect</td>
</tr>
<tr>
<td>Botma et al (2012)\textsuperscript{100}</td>
<td>Prospective cohort study</td>
<td>468 Carriers</td>
<td>Dietary patterns</td>
<td>Adenomas</td>
<td>With ‘snack’ dietary pattern* increased risk of adenomas</td>
</tr>
</tbody>
</table>

*‘Snack’ dietary pattern: high intake of chips, fried snacks, fast food snacks, spring rolls, mayonaised based sauces, cooking fat and butter, peanut sauce, ketchup, sweets and soda water. BMC, body mass index; CRC, colorectal cancer; LS, Lynch syndrome.

The importance of testing for \textit{H pylori} and subsequent eradication if detected has already been discussed in the section on surveillance for gastric cancer (see question 3). Before starting aspirin, eradication of \textit{H pylori} may also be beneficial because it may decrease the risk of upper gastrointestinal tract injury, especially in those carriers with a history of peptic ulcer or complications.\textsuperscript{104}

### Conclusion

Regular aspirin significantly reduces the incidence of cancer in LS (category of evidence Ib).

The optimal dose will be determined by further randomised studies. Given the lack of additional benefit revealed in the meta-analyses of follow-up data from former ‘vascular’ trials, a reasonable inference is that the option of taking low-dose aspirin should be discussed with gene carriers, including the risks, benefits and current limitations of available evidence (category of evidence Ib).

### QUESTION NO 9

What is the role of prenatal diagnosis (PND) and preimplantation genetic diagnosis (PGD) in LS?

### Relevant literature

For some individuals, learning that they have LS may have implications for reproductive decision-making. In some cases, this knowledge impacts on the timing of decisions about having children—for example, because of their desire to have children before pursuing prophylactic salpingo-oophorectomy. In addition, some men and women planning on having children in the future may have concerns about possibly passing the genetic risk of LS-related cancers to their children.

Individuals with LS should be adequately counselled about the risk of transmitting their hereditary predisposition to their future children and regarding their options for PND and PGD, including a complete discussion about the legal, practical and psychological aspects of these decisions and also the availability in various countries.\textsuperscript{105}

PGD is a technique that is performed in early pregnancy. If the family mutation is detected, abortion can be offered. PGD is a technique that always takes place in conjunction with assisted
reproduction (in-vitro fertilisation; IVF). Following a successful IVF procedure, one to two cells from the blastocyst can be tested for the family mutation. Only those embryos without the relevant mutation are selected for placement in the uterus.

Dewanwala et al. recently reported that of patients found to carry a gene mutation associated with LS, 42% would consider using prenatal testing and one in five women would consider having children earlier in order to proceed with prophylactic surgery to reduce their risk of developing gynaecological cancers. In addition, the majority of individuals undergoing genetic testing for LS felt that it would be ethical to offer prenatal genetic testing, either PND or PGD, to those with pathogenic MMR gene mutations. Interestingly, while most of the subjects in their study believed prenatal testing would be ethical, only a minority would consider it themselves. These facts reinforce the idea that decisions regarding childbearing are very personal ones and may be influenced by an individual’s personal and family history of cancer.

Conclusion and recommendation
Cancer geneticists and genetic counsellors should be prepared to discuss the option of PND and assisted reproductive technologies during genetic counselling of individuals with LS who are of childbearing age (grade of recommendation C).

QUESTION NO 10
What are the psychosocial implications of genetic testing and surveillance?

Relevant literature
Many studies have evaluated the psychological distress of genetic testing for LS. Most studies showed that immediately after disclosure of the test result, distress significantly increases, but decreases again after 6 months. Long-term studies have demonstrated that post-result increases in distress return to baseline by 1–3 years. However, a substantial subgroup may experience adjustment problems.

The psychological implications of surveillance for hereditary cancer has recently been reviewed by Gopie et al. In general, normal psychosocial functioning was reported in LS families, and a percentage comparable to the normal general population (10%) had clinically relevant distress levels. However, individuals with a higher cancer risk perception, decreased vitality, lower general mental health status and more anxiety are at risk of developing psychological problems.

In a Swedish study on 240 individuals at high risk of CRC (including MMR gene mutation carriers, HNPCC family members and individuals with familial CRC) evaluation of the quality of life using SF-36 (five of eight scales) showed generally normal levels but lower levels regarding mental health and vitality compared with the reference population. A study from the Danish HNPCC register demonstrated that living with the knowledge of LS has limited impact on self-concept.

Three studies evaluated the experience of patients undergoing colonoscopies. The studies showed that a substantial proportion of these patients (30–60%) considered undergoing colonoscopies as unpleasant, painful and frightening.

After being counselled about genetic test results, index patients play an important role in the communication of information regarding LS, the gene defect in the family and the preventive measures. Aktan-Collan et al. investigated how parents with LS share knowledge of genetic risk with their offspring. The study reported that out of 248 mutation carriers with children, 87% reported disclosure and 13% non-disclosure. Reasons for non-disclosure were mainly the young age of offspring, socially distant relationships, or a feeling of difficulty in discussing the topic. The most difficult communication aspect was discussing cancer risk with offspring. One third of the parents suggested that health professionals should be involved in passing on this information and that a family appointment at the genetic clinic should be organised at the time of disclosure. The authors concluded that it is a great challenge to improve the communication processes, so that all offspring get information that is important for their healthcare and parents get the professional support they desire at the time of disclosure to their children.

Recommendation
Professionals should be aware of the potential psychosocial problems before and after genetic testing and during follow-up and surveillance visits. People with increased psychological distress should be offered referral to a clinical psychologist. All efforts should be made to make colonoscopies as comfortable as possible by paying full attention to adequate pain control and sedation.

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**REFERENCES**

Guidelines


60 Wood NJ, Munot S, Sheridan E, et al. 'Does a 'one-stop' gynecology screening clinic for women in hereditary nonpolyposis colorectal cancer families have an impact on their psychological morbidity and perception of health?' *Int J Gynecol Cancer* 2008;18:279–84.


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