



## European guidelines for the clinical management of Lynch syndrome (HNPCC)

Hans F.A. Vasen, Gabriele Möslein, Angel Alonso, Inge Bernstein, Lucio Bertario, Ignacio Blanco, John Burn, Gabriel Capella, Christoph Engel, Ian Frayling, Waltraut Friedl, Frederik J. Hes, Shirley Hodgson, Jukka-Pekka Mecklin, Pål Møller, Fokko N. Nagengast, Yann Parc, Laura Renkonen-Sinisalo, Julian R. Sampson, Astrid Stormorken and Juul Wijnen

*J. Med. Genet.* published online 2 Mar 2007;  
doi:10.1136/jmg.2007.048991

---

Updated information and services can be found at:  
<http://jmg.bmj.com/cgi/content/abstract/jmg.2007.048991v2>

---

*These include:*

### Rapid responses

You can respond to this article at:  
<http://jmg.bmj.com/cgi/eletter-submit/jmg.2007.048991v2>

### Email alerting service

Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

---

### Notes

---

**Online First** contains unedited articles in manuscript form that have been peer reviewed and accepted for publication but have not yet appeared in the paper journal (edited, typeset versions may be posted when available prior to final publication). Online First articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Online First articles must include the digital object identifier (DOIs) and date of initial publication.

---

To order reprints of this article go to:  
<http://www.bmjournals.com/cgi/reprintform>

To subscribe to *Journal of Medical Genetics* go to:  
<http://www.bmjournals.com/subscriptions/>

## European guidelines for the clinical management of Lynch syndrome (HNPCC)

H.F.A.Vasen<sup>1\*</sup>, G.Möslein<sup>2\*</sup>, A.Alonso<sup>3</sup>, I.Bernstein<sup>4</sup>, L.Bertario<sup>5</sup>, I.Blanco<sup>6</sup>, J.Burn<sup>7</sup>, G.Capella<sup>8</sup>, C.Engel<sup>9</sup>, I.Frayling<sup>10</sup>, W.Friedl<sup>11</sup>, F.J.Hes<sup>12</sup>, S.Hodgson<sup>13</sup>, J-P Mecklin<sup>14</sup>, P Møller<sup>15</sup>, F.Nagengast<sup>16</sup>, Y.Parc<sup>17</sup>, L.Renkonen-Sinisalo<sup>18</sup>, J.R.Sampson<sup>10</sup>, A.Stormorken<sup>19</sup>, J.Wijnen<sup>12</sup>

<sup>1</sup>Department of Gastroenterology, Leiden University Medical Centre, Leiden, The Netherlands

<sup>2</sup>Department of Surgery, St.Josefs Hospital Bochum-Linden (Helios), Bochum, Germany

<sup>3</sup>Department of Medical Genetics, Hospital Virgen del Camino, Pamplona, Spain

<sup>4</sup>Department of Gastroenterology, Hvidrove Hospital, Hvidrove, Denmark

<sup>5</sup>Department of Surgery, Hospital Tumori, Milan, Italy

<sup>6</sup>Department of Genetic Counselling, Prevention and Cancer, Catalanian Institute of Oncology, Barcelona, Spain

<sup>7</sup>Institute of Human Genetics, Newcastle upon Tyne, UK

<sup>8</sup>Translational Research Laboratory IDIBELL, Institut Catala D'Oncologia, Barcelona, Spain

<sup>9</sup>Institute of Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany

<sup>10</sup>Institute of Medical Genetics, Cardiff, UK

<sup>11</sup>Institute of Human Genetics, University Clinics, Bonn, Germany

<sup>12</sup>Department of Clinical Genetics, Leiden University Medical Centre, The Netherlands

<sup>13</sup>Department of Clinical Genetics, St. George's Hospital, London, UK

<sup>14</sup>Department of Surgery, Jyvaskyla Central Hospital, Jyvaskyla, Finland

<sup>15</sup>Department of Genetics, Norwegian Radium Hospital, Oslo Norway

<sup>16</sup>Department of Gastroenterology, University Medical Centre, Radboud, Nijmegen, The Netherlands

<sup>17</sup>Department of Digestive Surgery, Hospital Saint-Antoine, University Pierre et Marie, Paris, France

<sup>18</sup>Department of Surgery, Helsinki University Central Hospital, Helsinki, Finland

<sup>19</sup>Department of Medical Genetics, Ullevål University Hospital, Oslo, Norway

\* HFA Vasen and G Möslein contributed equally to the preparation of this manuscript

### Correspondence should be addressed to:

Hans FA Vasen MD

Department of Gastroenterology,

Leiden University Medical Centre &

The Netherlands Foundation for the Detection of Hereditary tumours

Rijnsburgerweg 10,

2333 AA Leiden, the Netherlands

Email address: [hfavasen@stoet.nl](mailto:hfavasen@stoet.nl)

### Abstract

The Lynch syndrome (HNPCC) is characterized by the development of colorectal cancer, endometrial cancer and various other cancers and is caused by a mutation in one of the mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6* or *PMS2*. The discovery of these genes 15 years ago, has led to the identification of large numbers of affected families. In April 2006, a workshop was organized by a group of European experts in Hereditary Gastrointestinal Cancer (the Mallorca-group) aiming to establish guidelines for the clinical management of Lynch syndrome. Twenty-one experts from nine European countries participated in this workshop. Prior to the meeting, various participants prepared the key management issues of debate according to the latest publications. A systematic literature search using Pubmed and the Cochrane Database of Systematic Reviews, reference lists of retrieved articles, and manual searches of relevant articles was performed. During the workshop all recommendations were discussed in detail. Because most of the studies that form the basis for the recommendations were descriptive and/or retrospective of nature, many of them were based on expert opinion. The guidelines described in this manuscript may be helpful to the appropriate management of Lynch syndrome families. In order to further improve the care of these families, prospective controlled studies should be undertaken.

Keywords: Lynch syndrome, HNPCC, guidelines, management, MSI, immunohistochemistry, surveillance, surgical treatment, chemotherapy

## Introduction

Environmental factors play a dominant role in the etiology of most colorectal cancers. However, in between 15 and 30% of cases, inherited genetic factors are also significant. In about 5% of all cases, CRC is associated with a highly penetrant dominant or recessive inherited syndrome. The most common of these is Lynch syndrome (hereditary non-polyposis colorectal cancer; HNPCC).[1] It is characterized by the development of colorectal cancer, endometrial cancer and various other cancers and is caused by a mutation in one of the mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6* or *PMS2*. Familial adenomatous polyposis (FAP) is another well-described inherited syndrome and is responsible for <1% of all CRC cases. It is characterized by the development of hundreds to thousands of adenomas in the colorectum. Almost all patients develop CRC if they are not identified and treated at an early stage. FAP is transmitted as an autosomal dominant trait and is caused by truncating mutations in the *APC*-gene. Recently the *MUTYH* gene has been identified as a further polyposis gene. The associated disorder has been termed *MUTYH*- associated polyposis or MAP and displays an autosomal recessive pattern of inheritance.[2]

In April 2006, a workshop was organized by a group of European experts in Hereditary GI-Cancer in Palma de Mallorca. The main purpose of this meeting was to establish guidelines for the clinical management of the most common inherited forms of CRC and to identify collaborative studies. Twenty-one experts from nine European countries participated in this workshop. Prior to the meeting, various participants were requested to prepare the key management issues of debate according to the latest publications. During the workshop all recommendations were discussed in detail. In this manuscript we report the outcome of the discussion with respect to Lynch syndrome.

A systematic literature search using Pubmed and the Cochrane Database of Systematic Reviews, reference lists of retrieved articles, and manual searches of relevant articles was performed. Search terms included HNPCC, Lynch syndrome, microsatellite instability, and mismatch repair genes. Only peer-reviewed English-language articles were included. The criteria that were used for evaluation of studies on management, for categorisation of evidence that they presented and for the strength of recommendations that we made are shown in Table 1.

## Characteristics of Lynch syndrome

Carriers of an MMR- gene mutation have a high risk of developing CRC, endometrial cancer and other associated cancers. The various types of cancers and the reported risks are summarised in Table 2.[3-10] The cancers observed in Lynch syndrome families are diagnosed at an unusual early age and may be multiple. The MMR-defect leads to instability at microsatellites of tumour-DNA that is called microsatellite instability (MSI). This feature can be found in >90% of colon cancers associated with Lynch syndrome whereas in sporadic CRC, it is found in about 15% of the cases. With immunohistochemical (IHC-) analysis using antibodies against the four MMR- proteins, loss of protein expression of the causative gene can be shown.

In 1989, the Amsterdam criteria were proposed in order to provide uniform family material required for international collaborative studies.[11] In 1999 these criteria were revised and now include various extra-colonic tumours.[12] In 1997 the Bethesda guidelines were developed to identify individuals with CRC that should be tested for MSI.[13;14] These guidelines were revised in 2004.[15] The revised Amsterdam criteria and Bethesda guidelines are shown in Table 3. After the discovery of mutations in the MMR-genes fourteen years ago, the syndrome finally received the attention in the medical community that it deserved. This has led to the identification of large numbers of affected families.

## Terminology

Various names for Lynch syndrome have been used in the past century. A workshop in Amsterdam in 1989 agreed upon the name *HNPCC*, because at that time the syndrome was unknown to most doctors. This name clarified that the syndrome described an inherited form of CRC. The appropriateness of the name was discussed again at an international meeting in Bethesda in 2004. Most participants considered the term HNPCC to be inappropriate, since the syndrome is also associated with many other tumours. It was proposed that the name *Lynch syndrome* should be reintroduced and that this name should be reserved for families with strong evidence of mismatch repair deficiency for example by the presence of an MMR defect or the presence of MSI in tumours.[15] The European group agreed that this name is the best available name for the syndrome. The group suggests that families that meet the original Amsterdam criteria but do not have evidence for MMR deficiency are referred to as having *familial colorectal cancer*.

### Identification

Identification of family members carrying a MMR-gene defect is important as colonoscopic surveillance may be restricted to these individuals while those without a gene defect may be reassured and spared intensified surveillance. Mutation analysis is rather expensive as four genes may have to be analysed. Moreover, comprehensive screening of these genes is required as their mutational spectra are wide.

Currently, the Amsterdam II/Revised Bethesda criteria are used to select patients with CRC for molecular genetic and/or immunohistochemical analysis of the tumour and those with evidence of MSI or loss of MMR expression are offered mutation analysis.

**QUESTION:** *Are the Amsterdam II criteria and the revised Bethesda guidelines appropriate to select families for molecular genetic analysis of tumours?*

One way to establish whether these criteria are appropriate is to determine the proportion of cases with inherited MMR-gene mutations that they would miss in a series of *unselected* CRC patients. We found six studies in which either MSI- or IHC-analysis or both tests were performed as the primary screening tool in prospective and unselected series of colorectal cancer patients (Table 4).[16-21] Previous studies have shown that the yield of mutation analysis (positive predictive value) in families that meet the Amsterdam criteria is approximately 50% and the yield in families that meet the Bethesda criteria between 10 and 20%.[22] The six studies showed that the sensitivity of the Amsterdam criteria for the detection of mutations was 40% and that of the Bethesda guidelines about 90% (Table 4). This means that if the revised Bethesda guidelines had been used about 10% of the mutation carriers would have been missed, mostly patients with CRC diagnosed between age 50 and 60. According to the revised Bethesda guidelines, in patients with CRC diagnosed in their fifties special attention should be given to the presence of pathological features that suggests Lynch syndrome (e.g., the presence of tumour infiltrating lymphocytes). If these features are found, the tumours should be tested for MSI. Unfortunately, the studies summarized in Table 4 did not present data on the pathological examination of the cancers in these cases.

In view of the high costs of testing all CRCs for MSI or loss of MMR-protein, the group felt that the revised Bethesda guidelines are appropriate tools to help in selecting patients for genetic testing. An alternative approach is to use computer models that are currently being evaluated.[23;24]

Because of the accumulating evidence that MSI is a predictive factor for response to 5FU-based chemotherapy, the group expects that these tests will be performed in an increasing number (if not all) of patients with CRC in the near future.

**CONCLUSION:** *The revised Bethesda guidelines are appropriate tools to help in selecting families for molecular genetic and/or immunohistochemical analysis of tumours (Category of evidence II)*

**QUESTION:** *Which test, MSI or IHC, has the best sensitivity for the detection of MMR-gene mutations?*

In the literature many studies have been published on the results of MSI or IHC analysis for the identification of MMR-gene mutations. However, most studies were retrospective and the methods that were used varied widely. The number of markers for MSI-analysis ranged from 1 to more than 10. For IHC-analysis, most studies used two antibodies (MLH1, MSH2) against the MMR proteins; other studies used three or four antibodies (MLH1, MSH2, MSH6, PMS2). In the studies in which both MSI-analysis and IHC-analysis have been used prospectively (Table 5), the sensitivity of MSI-analysis was slightly better than that of IHC-analysis.[17;19-21;24-28] The false negatives with IHC might be due to the fact that the antibody detects a fragment of the truncated protein. There is one large (German) study that evaluated the outcome of these tests prospectively in families that meet the Amsterdam, Bethesda or slightly modified criteria. In this study, MSI-analysis (using the Bethesda set of 5 markers) and IHC-analysis (2 antibodies) was performed in 1119 index patients.[26] Altogether 230 pathogenic MMR-gene mutations were identified. The sensitivity of MSI-analysis was 100% and that of IHC-analysis 94%. A Dutch study showed that by adding antibodies against PMS2 the sensitivity for the detection of MLH1 mutations increased.[29] Had the German investigators used all four antibodies the sensitivity of IHC might have been higher.

The advantage of IHC is that it may direct mutation analysis because the pattern of staining is suggestive for the underlying gene defect. This is the reason for most authors recommending the use of IHC as the first step in families with a high probability of carrying a mutation (e.g. families that meet the Amsterdam criteria or families with a high predicted probability based on calculations using computer models.[22-24;26] (see Figure 1) Because of the incomplete sensitivity of IHC-analysis, MSI is recommended for cases with a high prior probability of Lynch syndrome but with apparently normal expression of the MMR proteins. In families with a moderately increased probability of carrying a

mutation, depending on the experience of the centre either MSI- or IHC-analysis might be used as the first step to exclude the presence of MMR deficiency. Preferably, colon tumour tissue is used for MSI/IHC-analysis. However, if colon tumour tissue is not available other tumours, e.g. endometrial cancer or adenomatous polyp may be analyzed. Unfortunately, the few studies that are available showed that sensitivity of MSI/IHC for MMR mutations in these tumour tissues was lower than that of the same analysis of colon cancers[30;31].

Because interpretation of the pedigree information, the pathology of the tumour, and the outcome of MSI and IHC testing can be complex, our group advises that these data are discussed together by a multidisciplinary team.

**CONCLUSION:** *The sensitivity of MSI-analysis is slightly higher than that of IHC-analysis (Category of evidence II). In families with a high probability of having a mutation (Amsterdam II criteria, computer models), IHC is the best first step because it may direct mutation analysis. In other families either MSI or IHC-analysis might be used as first step. The results of pedigree analysis and MSI/IHC analysis should be discussed in a multidisciplinary setting (pathologist, clinical/molecular geneticist, gastroenterologist, surgeon etc)(Grade C).*

### Surveillance of the colorectum

Studies have shown that the adenoma-carcinoma sequence may also be applied in development of CRC in Lynch syndrome families. Since the 1980's colonoscopic surveillance has been recommended for these families. The following question is relevant.

**QUESTION:** *Does colonoscopic surveillance of the colorectum lead to early detection of colorectal cancer or adenoma and reduction of CRC-related-mortality?*

A literature search showed that nine studies have addressed at least the first part of the question.[32-40]The nature of these studies, the number of families involved and the categories of evidence produced are summarized in Table 6. All the studies showed that surveillance led to detection of CRC at an earlier stage compared to the stage in historical controls. The only prospective controlled trial showed that surveillance led to a 63% reduction of CRC.[37] Two studies assessed the effect of surveillance on CRC-associated-mortality. A Finnish study showed that colonoscopic surveillance significantly decreased the mortality associated with CRC.[37;41] A study from the Netherlands evaluated the relative mortality in a large series of families over a period of 45 years. In the Netherlands a national registry of Lynch syndrome families was established in 1985 to promote the identification of such families and to encourage participation in surveillance programs.[34] Mortality in these families has decreased significantly in the last 15 years.

**CONCLUSION:** *Periodic examination by colonoscopy leads to detection of colorectal cancer at an earlier stage, to a 63% reduction of the risk of CRC and to a significant reduction of the mortality associated with CRC (Category of evidence IIb).*

The protocols that have been used in studies of surveillance have varied with respect to the surveillance intervals. Some studies advised a 3-yearly colonoscopy and others colonoscopy every year.

**QUESTION:** *What is the optimal surveillance protocol for Lynch syndrome in terms of surveillance interval?*

A search of the literature did not reveal any studies that compared different surveillance intervals. The Finnish trial showed that 3-yearly colonoscopy significantly reduced colorectal cancer incidence and colorectal cancer-related- mortality.[37] Therefore, the only evidence available suggests that a 3-yearly interval may be adequate. However, several observational studies suggest that (interval) cancers can occur within a 3-year-interval after colonoscopy. In a Finnish study on surveillance of 56 families, the stage distribution of colorectal cancer was significantly more favourable in patients (n=35) with cancer detected by surveillance than in patients (n=115) with symptomatic presentation of colorectal cancer.[38] However, a total of 21 cancers were diagnosed after a previous "clean" colonoscopy and half of them were diagnosed within (or at) an interval of three years. These included two Dukes C cancers diagnosed 15 and 20 months after the previous examination. In a Dutch long-term follow-up study a number of interval cancers were also observed. Advanced cancers (Dukes C) were only observed at intervals of longer than two years, whereas all Dukes A and B tumours were detected within an interval of less than two years. These observations together with the finding that adenomas observed in HNPCC more often show high grade dysplasia and villosity suggest that the adenoma-carcinoma sequence is accelerated in Lynch syndrome.[31;42] Therefore, the most appropriate surveillance interval probably lies between one and two years. In highly selected cases,

for example, mutation carriers who have recurrent adenomas, a prophylactic subtotal colectomy may be discussed as option.

**CONCLUSION:** *A 3-yr-interval is proven to be (at least partly) effective (Category of evidence IIb); In view of the observation of advanced CRC detected 2-3 yr after colonoscopy, the optimal interval probably lies between 1 and 2 yrs (Category of evidence III, grade C)*

**QUESTION:** *At what age should surveillance be started and at which age might surveillance be discontinued?*

Many studies have shown that the risk of developing CRC before the age of 25 years is very low.[7-10] In a series of 246 CRC cases from Lynch syndrome families known at the Dutch HNPCC Registry, only two patients (0.8%) developed CRC before the age of 20 years and another two between ages 20- 25 years.[43] Based on these data, the group advises to start surveillance between age 20-25 yrs. In the literature, recommendations regarding the upper age limit of surveillance are very sparse. One study has reported that the risk of mutation carriers aged 70-75 years developing CRC in the next ten years is significant.[43] However, at the age of 80 years, they found that the risk of developing CRC in the next ten years relative to their expected life expectancy was low. Based on these findings, authors recommended continuing surveillance up to the age of 80 years in mutation carriers if they are in good health. However, the European Group advises that decisions on the upper age limit of surveillance should be made on an individual basis. For example, in a 75 year-old mutation carrier with severe cardiovascular disease, surveillance can be discontinued. On the other hand, in an 80-year-old mutation carrier who is still in good health, especially if there is a personal history of adenomas and colon cancer, it is reasonable to continue surveillance.

**CONCLUSION:** *Surveillance should start between age 20/25 yr. Decisions on the upper age limit of surveillance depends on the patient's general state of health and should be made on an individual basis (Category of evidence III, grade C)*

**QUESTION:** *Which surveillance protocol should be recommended in families with clustering of CRC without evidence of MSI in the tumours.*

In a significant proportion (approximately 30%) of families that meet the Amsterdam criteria, the results of the MSI and IHC-analysis of the colorectal tumour (s) are negative.[44] Clustering of colorectal cancer by chance or genetic defects other than those of mismatch repair may be responsible for the disease in such families and they do not have Lynch syndrome. These families are characterized by a more advanced age of onset of CRC than in Lynch families and the absence of endometrial cancer and multiple tumours. A recent study reported that the risk of developing CRC in such families is only increased by a factor of 2.3.[44] Another study compared the results of surveillance in families with clustering of CRC with and without MSI.[45] The results showed that the yield of adenomas was the same in both types of families. However, CRC was only identified in the families with MSI-tumours. In families without evidence for MMR-deficiency, a less intensive colonoscopic surveillance program (e.g. colonoscopy: 1x / 3-5 years, starting 5-10 years before the first diagnosis of CRC or >45 years) might be appropriate. In view of the absence of endometrial cancer in such families, surveillance of the endometrium is not indicated.

**CONCLUSION:** *In families with clustering of colorectal cancer but without evidence of MMR-deficiency (non-Lynch syndrome families), a less intensive surveillance protocol is recommended, i.e., colonoscopy at 3-5yr-intervals, starting 5-10 yrs before the first diagnosis of CRC or >45 yrs (Category of evidence III, grade C)*

#### Surveillance of the endometrium/ovary

Previous studies have shown that carriers of an MMR mutation have a high risk of developing endometrial cancer.[7] Although, it is known that the majority of (sporadic) endometrial cancers are detected at an early stage, about 10-15% of patients with such tumours will ultimately die from metastatic disease. In view of this significant mortality and the high risk of developing endometrial cancer in Lynch syndrome families, most authors advise surveillance of the endometrium.

**QUESTION:** *How effective is surveillance for endometrial cancer in families with the Lynch syndrome?*

British and Dutch investigators evaluated the outcome of surveillance of 269 women from families suspected of having Lynch syndrome.[46;47] The surveillance program consisted of ultrasound every 1-2 years. It did not lead to detection of pre-malignant lesions or endometrial cancer. However, two women presented with symptoms at 6 and 24 months after a normal ultrasound and were diagnosed with endometrial cancer. Both tumors were in an early stage (FIGO I). In another study from the

Netherlands, 41 women from Lynch families underwent surveillance by transvaginal ultrasound followed by aspiration biopsy in suspected cases. After a mean follow up of 5 years, premalignant lesions, i.e. complex atypia, were detected in three patients. There was one interval cancer diagnosed eight months after a normal ultrasound. This tumor was at an early stage. A recent study of 175 subjects from Finland reported the results of surveillance by transvaginal ultrasound (TVU) and aspiration biopsy.[48] Complex atypia was found in 5 patients, endometrial cancer was found in 11 and there were two interval cancers. Six of the eleven screen-detected cancers were only identified by aspiration biopsy and not by TVU. The outcome of the studies is summarized in Table 7. American investigators reported on a retrospective cohort of 315 women, all mutation carriers, 61 of whom had prophylactic surgery and were then followed up for approximately 10 years. No endometrial cancer or ovarian cancer developed in those women who had prophylactic surgery whereas 33% of women who did not have surgery developed endometrial cancer and 5.5% developed ovarian cancer.[49] In conclusion, two of the three available studies suggested that surveillance may lead to detection of pre-malignant lesions and one study also to detection of endometrial cancer at an early stage. More prospective studies are needed to establish the most appropriate screening protocol. Because of the higher risk of developing endometrial cancer in carriers of a *MSH6*-mutation, hysterectomy may be suggested to these women after menopause. This surgery may also be considered for carriers of mutations in the other MMR genes and for women who require surgery for a colorectal cancer. In view of the risk of ovarian cancer and the failure of early detection of such tumors by TVU and CA-125 estimation, bilateral salpingo-oophorectomy might be considered in mutation carriers after completion of family planning.

**CONCLUSION:** *The value of surveillance for endometrial cancer is unknown. Surveillance by gynaecological examination, TVU and aspiration biopsy starting from age 30-35 yrs may lead to detection of premalignant lesions and early cancers (Category of evidence III, grade C). Prophylactic hysterectomy and salpingo-oophorectomy may be an option for women with Lynch syndrome since it substantially reduces site-specific cancers (grade C).*

#### Surveillance for other related cancers

Other cancers associated with Lynch syndrome include cancer of the stomach, ureter, renal pelvis, small bowel, bile ducts and tumors of the brain. The lifetime risk of developing one of these cancers is relatively low (less than 10%) and may be associated with the underlying MMR defect. The risk of developing gastric cancer may be higher in some countries. The International Society of Gastrointestinal Hereditary Tumours (InSiGHT) recommends surveillance for cancer of the stomach, if the cancer clusters in the family (more than one case).[50] However, the European group is of the opinion that surveillance in Lynch syndrome families for gastric cancer may also be considered in countries with a high incidence of such tumours.

In the decision making process regarding which surveillance protocol should be recommended, a reasonable approach might be first to discuss all the various cancer risks with the patient, then discuss which screening protocols are established as effective based on published evidence, e.g. colon and possibly endometrium screening (see above). Finally, the physician and patient should weigh up the possible benefits versus costs and risks for screening for other cancers. In addition, it should be recommended to all at-risk family members that they should contact a physician early if they are worried about specific signs or symptoms.

The guidelines for surveillance of Lynch syndrome families recommended by the collaborative group of the European experts in hereditary gastrointestinal cancer are summarised in Table 8. This protocol is indicated not only in families with an identified MMR defect but also in families with clustering of CRC and other related cancers with evidence of mismatch repair deficiency for example by the presence of MSI or loss of expression in tumours (with the exception of families of patients with such features caused by hypermethylation of *MLH1*).

#### Surgical management of colorectal cancer

Several studies showed that Lynch syndrome patients have an increased risk of developing multiple (synchronous and metachronous) CRC's. Thus, before resection of a colon tumour it is important to visualize the complete colon because of the risk of a synchronous tumour.

**QUESTION:** *What is the best surgical treatment for a patient that is diagnosed with CRC associated with Lynch syndrome?*

A Dutch study reported that the risk of developing a second colon tumour after treatment of a primary colorectal cancer in Lynch syndrome was 16% after 10 years of follow-up.[40] In view of this

substantial risk, the question arises whether a subtotal colectomy instead of a segmental resection might be the preferred treatment in patients from Lynch syndrome families with a primary tumour. In a recent study, a decision analysis was performed to compare the life expectancy for patients undergoing subtotal colectomy or partial resection for a primary screen-detected colorectal cancer.[51] The results indicated that subtotal colectomy performed at a young age ( $\leq 47$  yrs) would lead to an increased life expectancy of up to 2.3 years. Unfortunately, the authors were not able to use quality of life (QOL) adjusted life expectancy because studies on QOL that specifically consider Lynch syndrome patients were not available in the literature. Although for sporadic CRC, QOL after segmental resection has been reported to be better than after subtotal colectomy, in Lynch syndrome families, QOL after segmental resection may be decreased by the need for colonoscopy (versus sigmoidoscopy after subtotal colectomy) and the fear of a second tumour.

Based on these findings plus the substantial risk of developing a second tumor, subtotal colectomy with ileorectal anastomosis can be considered if colon cancer is detected in a young patient participating in a surveillance program. A prospective study that also addresses QOL should evaluate which surgical option is the most appropriate in Lynch syndrome. Until the outcome of such studies is available, the Mallorca group recommends discussing the pros and cons of both options with a patient from a Lynch syndrome family who develops CRC.

**CONCLUSION:** *Regarding the treatment of CRC in patients from Lynch syndrome families, no controlled trials are available; one decision analysis study has reported an increase in life-expectancy with subtotal colectomy compared to partial resection; in view of this study and the high risk of a second CRC, the option of extensive resection should be discussed in young patients (e.g. <50 yrs)(Category of evidence III, grade C)*

#### Chemotherapy

Currently, at least three chemotherapeutic agents have been proven to be effective in the treatment of colorectal cancer, i.e., 5FU with or without leucovorin, oxaliplatin and irinotecan (CPT11).

Unfortunately, the effectiveness of these agents in patients with MSI-H or Lynch syndrome tumours is unknown. In vitro-studies suggested that MMR-deficient colon cancer cells might not respond to 5FU-based chemotherapy.[52] On the other hand, CRC cell lines defective of MMR exhibit increased sensitivity to CPT11 (irinotecan).[53]

**QUESTION:** *Is chemotherapy effective in patients with MSI-H tumors?*

The effect of chemotherapy in patients with MSI-H or HNPCC tumors has been reported in only a few studies (see Table 9).[54-58] Most studies showed that there was no benefit of 5FU treatment in such patients. One small study on Stage IV CRC-patients reported complete or partial responses to treatment with irinotecan in four out of 7 patients with MSI-H tumors compared to 7 out of 65 patients with MSI-L/MSS tumors.[58]

Because most studies are retrospective, all authors urge caution in implementing these findings in clinical practice until they are confirmed by prospective studies. Because it may be unethical to withhold chemotherapy in a clinical trial for potentially curable advanced-stage colon cancer, the best format of such studies is to compare effective drugs such as CPT11 or oxalaplalin with 5FU.

**CONCLUSION:** *Experimental and clinical studies suggest that MSI-H tumors are resistant to 5FU-based chemotherapy; however, prospective clinical trials are needed before definitive recommendations can be given (Category of evidence III)*

#### Discussion

The guidelines for the management of the Lynch syndrome provided in this manuscript are the result of intensive discussions among the participants of a two-day-workshop held in Mallorca in April 2006. Because most of the studies that form the basis for the recommendations were descriptive and/or retrospective of nature, many of these recommendations were based on expert opinion and we were fortunate to convene an extensive expert panel. During the workshop it became clear that there are still many aspects of Lynch syndrome where new knowledge needs to be gained through further research.

Regarding the identification of Lynch syndrome, the available criteria (revised Bethesda guidelines) appeared to be effective for the selection of families for analysis of tumour MMR status. However, even with the use of these guidelines, a significant proportion of mutation carriers may be missed. The sensitivity of the Bethesda criteria might be improved by investigating these missed cases. For example, since most missed mutation carriers are diagnosed with CRC between age 50 and 60 it may be appropriate to increase the age at diagnosis below which MSI-analysis is recommended. Another possibility might be to evaluate all CRCs, for example, by IHC. Because, there is increasing evidence

that MSI/IHC is an important prognostic factor and may predict the response to chemotherapy, these tests might in future be performed on a much larger scale, if not in all CRC cases.

Studies have shown that colorectal surveillance in Lynch syndrome leads to reduction of CRC and associated mortality. However, a substantial proportion (estimated at 5-10% per 10 years of follow-up) of patients develop (interval) cancers under surveillance. For this reason future research should address how new screening tools such as chromoendoscopy, high resolution colonoscopy with narrow banding or DNA-analysis of the feces might help in the early detection of colorectal tumors.[59]

Very little data is available on the effectiveness of surveillance for endometrial cancer. A prospective trial in which TVU is being compared with TVU and aspiration biopsy should be undertaken.

For patients with Lynch syndrome who present with CRC, the surgical choice lies between partial resection and more extensive surgery such as subtotal colectomy and ileorectal anastomosis. In view of the increased risk of developing a second tumor and also the evidence for improved life expectancy after extensive surgery, the best option appears to be a subtotal colectomy. However, because such an extensive surgical procedure might have significant impact on the quality of life, a randomised controlled trial should be performed which includes assessment of the quality of life and functional outcome after the two procedures.

The use of chemotherapy in Lynch syndrome CRC patients or patients with MSI-H tumors is controversial. Due to the effective surveillance programs few patients with metastatic disease are currently being identified. Therefore, future trials on the effect of various chemotherapeutic regimens in Lynch syndrome or in patients with MSI-high tumours should be conducted on a European level or even worldwide.

There is ample evidence that the expression of the Lynch syndrome is influenced by environmental factors. However, studies that indicate which environmental factors do play a significant role are rare. Since 1998, the effect of resistant starch and aspirin has been investigated in a large randomized placebo controlled trial with Lynch syndrome families from all over the world ([www.CAPPs.com](http://www.CAPPs.com)). The results will be published in 2007. A new trial (the POET (Prevention of Endometrial Tumours)-trial) is being developed to explore the possibility of chemoprevention using the progesterone releasing Mirena intrauterine device.

In conclusion, the guidelines described in this manuscript may be helpful to the appropriate management of Lynch syndrome families. In order to further improve the care of these families, there is an urgent need for prospective controlled studies.

The workshop in Mallorca identified several collaborative studies the group will focus on to clarify some of the controversial issues that exist in the clinical management of the Lynch syndrome.

"The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd to permit this article (if accepted) to be published in Journal of Medical Genetics and any other BMJ PGL products and sublicences such use and exploit all subsidiary rights, as set out in our licence (<http://JMG.bmjournals.com/misc/ifora/licenceform.shtml>)."

Table 1. Validity and grading of recommendations.

CATEGORY OF EVIDENCE		GRADING OF RECOMMENDATIONS
Meta-analysis of randomised controlled trial	Ia	A
Randomised controlled trial	Ib	
Well-designed controlled study without randomisation	IIa	B
Well designed quasi-experimental study	IIb	
Non-experimental descriptive study	III	
Expert opinion	IV	C

Table 2. Lifetime cancer risk reported in families with an identified MMR-mutation

Colorectal cancer (men)	28 – 75%
Colorectal cancer (women)	24 – 52%
Endometrial cancer	27 – 71%
Ovarian cancer	3 – 13%
Gastric cancer	2 – 13%
Urinary tract cancer	1 – 12%
Brain tumor	1 - 4%
Bile duct/gallbladder cancer	2%
Small bowel cancer	4 - 7%

Table 3. Amsterdam criteria II and revised Bethesda guidelines

**Amsterdam Criteria II**

There should be at least three relatives with colorectal cancer or with a Lynch syndrome - associated cancer: cancer of the endometrium, small bowel, ureter or renal pelvis.

- one relative should be a first degree relative of the other two;
- at least two successive generations should be affected,
- at least one tumour should be diagnosed before age 50,
- FAP should be excluded in the colorectal cancer case if any,
- tumours should be verified by histopathological examination.

Revised Bethesda guidelines

1. Colorectal cancer diagnosed in a patient <50 y of age.
2. Presence of synchronous, metachronous colorectal, or other Lynch syndrome-related tumours \*, regardless of age.
3. Colorectal cancer with MSI-H phenotype diagnosed in a patient < 60 y of age.
4. Patient with colorectal cancer and a first-degree relative with a Lynch syndrome-related tumor, with one of the cancers diagnosed under age 50 y.
5. Patient with colorectal cancer with two or more first-degree or second-degree relatives with a Lynch syndrome-related tumor, regardless of age.

\*Lynch syndrome related tumours include colorectal, endometrial, stomach, ovarian, pancreas, ureter, renal pelvis, biliary tract, and brain tumours, sebaceous gland adenomas and keratoacanthomas and carcinoma of the small bowel

Table 4. Outcome of MMR-gene mutation analysis in relation to clinical criteria and results of MSI- and IHC-analysis in population-based or consecutive series of unselected colorectal cancer

Author/yr	Primary test used		MMR-genes analysed	Total nr of CRC	Pathogenic mutations identified	Proportion of mutation carriers that meet the clinical criteria	
	IHC: antibodies	MSI: markers				Amsterdam II	(Revised) Bethesda guidelines
Aaltonen 1998	-	7	MLH1, MSH2	509	10 (1.9%)	7/10	10/10**
Debiak 2000	2	10	MLH1, MSH2	68*	6 (3.5 %)	1/6	?
Salovaara 2000	-	7	MLH1, MSH2	535	18 (3.3%)	12/18	17/18**
Cunningham 2001	3	6	MLH1, MSH2	257	5 (1.95%)	3/5	?
Hampel 2005	4	5	MLH1, MSH2, MSH6, PMS2	1,066	23 (2.1%)	3/23	18/23
Pinol 2005	2	1	MLH1, MSH2	1,222	11 (0.9%)	4/11	10/11
Total				4,627	111(2,4%)	30/73 (41%)	55/62 (89%)

\*The original number of consecutive CRCs was 168 including 143 sporadic cases and 25 suspected cases. A total of 43 of the sporadic cases and 25 suspected cases were analyzed.

\*\* communicated with authors

Table 5. Outcome of prospective molecular genetic analysis using both IHC- and MSI-analysis in selected and unselected cases of CRC.

Author/yr	Criteria for selection	Primary test used		MMR-genes analysed	CRC	Mutations Identified	Proportion of mutation carriers with an abnormal test	
		IHC: antibodies	MSI: markers				Abnormal IHC	MSI-H/L
Debniak 2000	consecutive cases	2	10	MLH1, MSH2	68*	6 (3.5 %)	5/6	5/6
Cunningham 2001	consecutive cases	3	6	MLH1, MSH2	257	5 (1.95%)	5/5	5/5
Scartozzi 2002	Bethesda criteria	2	12	MLH1, MSH2	37	4 (10.8%)	4/4	3/4
Engel 2005	Bethesda/Amsterdam	2	5	MLH1, MSH2	1,119	230 (20.5%)	216/230	230/230
Hampel 2005	Population-based	4	5	MLH1, MSH2, MSH6, PMS2	1,066	23 (2.1%)	21/23	21/23
Pinol 2005	Population-based	2	1	MLH1, MSH2	1,222	11 (0.9%)	11/11	10/11
Southey 2005	CRC<45 yrs	4	10	MLH1, MSH2, MSH6, PMS2	131	18 (13.7%)	18/18	17/18
Barnetson 2006	CRC<55 yrs	3	5	MLH1, MSH2, MSH6	870	38 (4.3%)	25/27	28/30
Niessen 2006	CRC<50 yrs or CRC plus cancer associated with CRC	3	5	MLH1, MSH2, MSH6	281	25 (8.9%)	23/25	25/25
Total						360	328/349 (94%)	344/352 (98%)

\*The original number of consecutive CRCs was 168 including 143 sporadic cases and 25 suspected cases. A total of 43 of the sporadic cases and 25 suspected cases were analyzed.

Table 6. Studies on surveillance of Lynch syndrome families

Author/year	Number of families	Type of study/category of evidence
Love 1984	4	Descriptive/III
Mecklin 1987	22	Descriptive/III
Vasen 1989	22	Descriptive/III
Vasen 1995	50	Descriptive/III
Järvinen 1995/2000	22	Non-randomised controlled trial/lib
Renkonen 2000	57	Descriptive/III
Arrigoni 2005	22	Descriptive/III
De Vos tot Nederveen Cappel 2002	114	Descriptive/III

Table 7. The outcome of surveillance for endometrial cancer in Lynch syndrome families

	UK/The Netherlands (Dove-Edwin et al 2002)	The Netherlands (Rijcken et al 2003)	Finland (Renkonen- Sinisalo et al 2006)
Number of subjects	269	41	175
Mutation carriers	not mentioned	27%	100%
Protocol	TV US*	TV US	TV US and aspiration biopsy
Patient years of follow-up	826	197	759
Number of scans	522	179	476
Surveillance interval	1-2 years	1 year	2-3 years
Premalignant lesions	-	3 complex atypia	5 complex atypia
Screen-detected cancer	-	-	12**
Interval cancer	2	1	2
Figo I	2	1	12
Figo II			1
Figo III			1

\*transvaginal ultrasound \*\*including one occult cancer detected at surgery

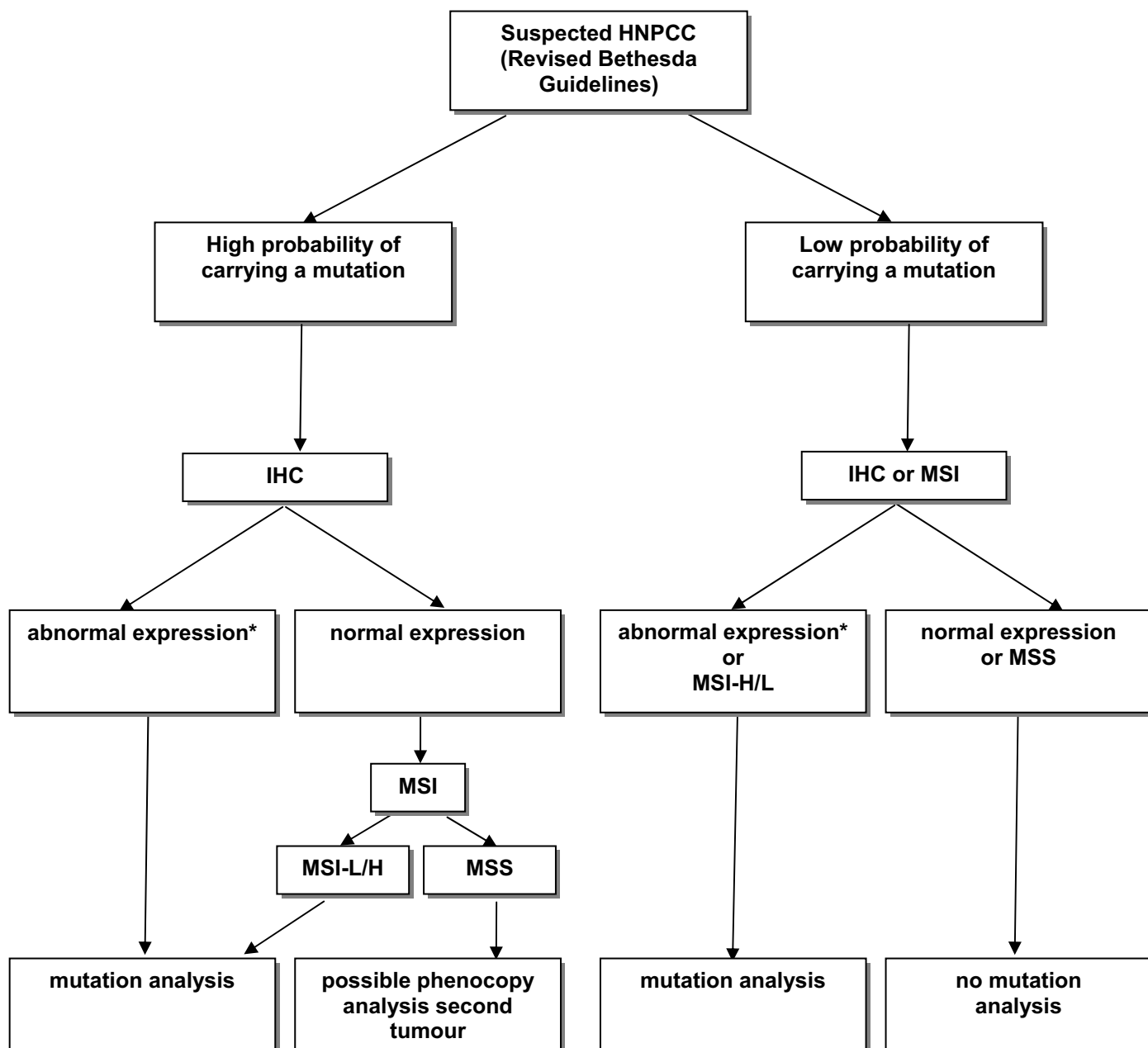
Table 8. Surveillance protocol in Lynch syndrome and familial clustering of CRC

Disorder	Lower age limit	Examination	Interval
Lynch syndrome	20-25 yrs	Colonoscopy	1-2 yrs
	30-35 yrs	Gynaecological examination, transvaginal ultrasound, aspiration biopsy	1-2 yrs
	30-35 yrs	Gastroduodenoscopy <sup>1</sup>	1-2 yrs
	30-35 yrs	Abdominal ultrasound, urinalysis and cytology urine <sup>2</sup>	1-2 yrs
Familial clustering of colorectal cancer without evidence of MSI <sup>3</sup>	45-50 yrs or 5-10 yrs before age diagnosis first CRC in family	Colonoscopy	3- 5 yrs

<sup>1</sup> if gastric cancer runs in the family or in countries with a high incidence of gastric cancer; <sup>2</sup> if urinary tract cancer runs in the family; <sup>3</sup>Amsterdam positive families

Table 9. Studies on the effectiveness of chemotherapy in patients with MSI-H tumors

Author/year	Type of study and selection criteria	Agents	Patients with MSI-H tumor	Effect chemotherapy
Liang 2002	Prospective, nonrandomised; Stage IV CRC	High-dose 5-FU/leucovorin	52	Better survival in patients with MSI-H tumors that received chemotherapy
Ribic 2003	Retrospective MSI-analysis of tumours from patients that participated in a multicenter RCT 20-25 yrs ago; CRC stage II/III	5FU/Leucovorin or levamisol	95	No survival differences
Carethers 2004	Retrospective, consecutive patients; CRC Stage II/III	5FU-based	36	No survival differences
De Vos 2004	Retrospective, CRC stage III-patients from HNPCC families	5FU/leucovorin or levamisol	92	No survival differences
Fallik 2005	Non-randomised controlled trial; CRC stage IV	Irinotecan (CPT11)	7	3 partial and 1 complete response



\* If MLH1 expression is lost DNA analysis of BRAF in tumour can be performed because the presence of BRAF-V600E mutation makes HNPCC very unlikely.[60]

Figure 1. Strategy for identification of CRC patients with a MMR-gene defect

#### Reference List

- [1] Lynch HT, Chapelle de la A. Hereditary colorectal cancer. *N Engl J Med* 2003; 348(10):919-932.

- [2] Al Tassan N, Chmiel NH, Maynard J, Fleming N, Livingston AL, Williams GT, Hodges AK, Davies DR, David SS, Sampson JR, Cheadle JP. Inherited variants of MYH associated with somatic G:C→T:A mutations in colorectal tumors. *Nat Genet* 2002; 30(2):227-232.
- [3] Vasen HF, Wijnen JT, Menko FH, Kleibeuker JH, Taal BG, Griffioen G, Nagengast FM, Meijers-Heijboer EH, Bertario L, Varesco L, Bisgaard ML, Mohr J, Fodde R, Khan PM. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. *Gastroenterology* 1996; 110(4):1020-1027.
- [4] Dunlop MG, Farrington SM, Carothers AD, Wyllie AH, Sharp L, Burn J, Liu B, Kinzler KW, Vogelstein B. Cancer risk associated with germline DNA mismatch repair gene mutations. *Hum Mol Genet* 1997; 6(1):105-110.
- [5] Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, de la CA, Peltomaki P, Mecklin JP, Jarvinen HJ. Cancer risk in mutation carriers of DNA-mismatch-repair genes. *Int J Cancer* 1999; 81(2):214-218.
- [6] Vasen HF, Stormorken A, Menko FH, Nagengast FM, Kleibeuker JH, Griffioen G, Taal BG, Moller P, Wijnen JT. MSH2 mutation carriers are at higher risk of cancer than MLH1 mutation carriers: a study of hereditary nonpolyposis colorectal cancer families. *J Clin Oncol* 2001; 19(20):4074-4080.
- [7] Hendriks YM, Wagner A, Morreau H, Menko F, Stormorken A, Quehenberger F, Sandkuijl L, Moller P, Genuardi M, Van Houwelingen H, Tops C, van Puijenbroek M, Verkuijlen P, Kenter G, Van Mil A, Meijers-Heijboer H, Tan GB, Breuning MH, Fodde R, Wijnen JT, Brocker-Vriends AH, Vasen H. Cancer risk in hereditary nonpolyposis colorectal cancer due to MSH6 mutations: impact on counseling and surveillance. *Gastroenterology* 2004; 127(1):17-25.
- [8] Quehenberger F, Vasen HF, van Houwelingen HC. Risk of colorectal and endometrial cancer for carriers of mutations of the hMLH1 and hMSH2 gene: correction for ascertainment. *J Med Genet* 2005; 42(6):491-496.
- [9] Hampel H, Stephens JA, Pukkala E, Sankila R, Aaltonen LA, Mecklin JP, de la CA. Cancer risk in hereditary nonpolyposis colorectal cancer syndrome: later age of onset. *Gastroenterology* 2005; 129(2):415-421.
- [10] Jenkins MA, Baglietto L, Dowty JG, Van Vliet CM, Smith L, Mead LJ, Macrae FA, St John DJ, Jass JR, Giles GG, Hopper JL, Southey MC. Cancer risks for mismatch repair gene mutation carriers: a population-based early onset case-family study. *Clin Gastroenterol Hepatol* 2006; 4(4):489-498.
- [11] Vasen HF, Mecklin JP, Khan PM, Lynch HT. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). *Dis Colon Rectum* 1991; 34(5):424-425.
- [12] Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology* 1999; 116(6):1453-1456.

- [13] Rodriguez-Bigas MA, Boland CR, Hamilton SR, Henson DE, Jass JR, Khan PM, Lynch H, Perucho M, Smyrk T, Sobin L, Srivastava S. A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: meeting highlights and Bethesda guidelines. *J Natl Cancer Inst* 1997; 89(23):1758-1762.
- [14] Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, Meltzer SJ, Rodriguez-Bigas MA, Fodde R, Ranzani GN, Srivastava S. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res* 1998; 58(22):5248-5257.
- [15] Umar A, Boland CR, Terdiman JP, Syngal S, de la CA, Ruschoff J, Fishel R, Lindor NM, Burgart LJ, Hamelin R, Hamilton SR, Hiatt RA, Jass J, Lindblom A, Lynch HT, Peltomaki P, Ramsey SD, Rodriguez-Bigas MA, Vasen HF, Hawk ET, Barrett JC, Freedman AN, Srivastava S. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 2004; 96(4):261-268.
- [16] Aaltonen LA, Salovaara R, Kristo P, Canzian F, Hemminki A, Peltomaki P, Chadwick RB, Kaariainen H, Eskelinen M, Jarvinen H, Mecklin JP, de la CA. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. *N Engl J Med* 1998; 338(21):1481-1487.
- [17] Debniak T, Kurzawski G, Gorski B, Kladny J, Domagala W, Lubinski J. Value of pedigree/clinical data, immunohistochemistry and microsatellite instability analyses in reducing the cost of determining hMLH1 and hMSH2 gene mutations in patients with colorectal cancer. *Eur J Cancer* 2000; 36(1):49-54.
- [18] Salovaara R, Loukola A, Kristo P, Kaariainen H, Ahtola H, Eskelinen M, Harkonen N, Julkunen R, Kangas E, Ojala S, Tulikoura J, Valkamo E, Jarvinen H, Mecklin JP, Aaltonen LA, de la CA. Population-based molecular detection of hereditary nonpolyposis colorectal cancer. *J Clin Oncol* 2000; 18(11):2193-2200.
- [19] Cunningham JM, Kim CY, Christensen ER, Tester DJ, Parc Y, Burgart LJ, Halling KC, McDonnell SK, Schaid DJ, Walsh VC, Kubly V, Nelson H, Michels VV, Thibodeau SN. The frequency of hereditary defective mismatch repair in a prospective series of unselected colorectal carcinomas. *Am J Hum Genet* 2001; 69(4):780-790.
- [20] Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, Nakagawa H, Sotamaa K, Prior TW, Westman J, Panescu J, Fix D, Lockman J, Comeras I, de la CA. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). *N Engl J Med* 2005; 352(18):1851-1860.
- [21] Pinol V, Castells A, Andreu M, Castellvi-Bel S, Alenda C, Llor X, Xicola RM, Rodriguez-Moranta F, Paya A, Jover R, Bessa X. Accuracy of revised Bethesda guidelines, microsatellite instability, and immunohistochemistry for the identification of patients with hereditary nonpolyposis colorectal cancer. *JAMA* 2005; 293(16):1986-1994.

- [22] Wijnen JT, Vasen HF, Khan PM, Zwinderman AH, van der KH, Mulder A, Tops C, Moller P, Fodde R. Clinical findings with implications for genetic testing in families with clustering of colorectal cancer. *N Engl J Med* 1998; 339(8):511-518.
- [23] Chen S, Wang W, Lee S, Nafa K, Lee J, Romans K, Watson P, Gruber SB, Euhus D, Kinzler KW, Jass J, Gallinger S, Lindor NM, Casey G, Ellis N, Giardiello FM, Offit K, Parmigiani G. Prediction of germline mutations and cancer risk in the Lynch syndrome. *JAMA* 2006; 296(12):1479-1487.
- [24] Barnetson RA, Tenesa A, Farrington SM, Nicholl ID, Cetnarskyj R, Porteous ME, Campbell H, Dunlop MG. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. *N Engl J Med* 2006; 354(26):2751-2763.
- [25] Scartozzi M, Bianchi F, Rosati S, Galizia E, Antolini A, Loretelli C, Piga A, Bearzi I, Cellerino R, Porfiri E. Mutations of hMLH1 and hMSH2 in patients with suspected hereditary nonpolyposis colorectal cancer: correlation with microsatellite instability and abnormalities of mismatch repair protein expression. *J Clin Oncol* 2002; 20(5):1203-1208.
- [26] Engel C, Forberg C, Holinski-Feder E, Pagenstecher C, Plaschke J, Kloor M, Poremba C, Pox CRJ, et al. Novel strategy for optimal sequential application of clinical criteria, immunohistochemistry and microsatellite analysis in the diagnosis of hereditary nonpolyposis colorectal cancer. *Int J.Cancer* . 2006.
- [27] Southey MC, Jenkins MA, Mead L, Whitty J, Trivett M, Tesoriero AA, Smith LD, Jennings K, Grubb G, Royce SG, Walsh MD, Barker MA, Young JP, Jass JR, St John DJ, Macrae FA, Giles GG, Hopper JL. Use of molecular tumor characteristics to prioritize mismatch repair gene testing in early-onset colorectal cancer. *J Clin Oncol* 2005; 23(27):6524-6532.
- [28] Niessen RC, Berends MJ, Wu Y, Sijmons RH, Hollema H, Ligtenberg MJ, de Walle HE, de Vries EG, Karrenbeld A, Buys CH, van der Zee AG, Hofstra RM, Kleibeuker JH. Identification of mismatch repair gene mutations in young colorectal cancer patients and patients with multiple HNPCC-associated tumours. *Gut* 2006.
- [29] de Jong AE, van Puijnenbroek M, Hendriks Y, Tops C, Wijnen J, Ausems MG, Meijers-Heijboer H, Wagner A, van Os TA, Brocker-Vriends AH, Vasen HF, Morreau H. Microsatellite instability, immunohistochemistry, and additional PMS2 staining in suspected hereditary nonpolyposis colorectal cancer. *Clin Cancer Res* 2004; 10(3):972-980.
- [30] de Leeuw WJ, Dierssen J, Vasen HF, Wijnen JT, Kenter GG, Meijers-Heijboer H, Brocker-Vriends A, Stormorken A, Moller P, Menko F, Cornelisse CJ, Morreau H. Prediction of a mismatch repair gene defect by microsatellite instability and immunohistochemical analysis in endometrial tumours from HNPCC patients. *J Pathol* 2000; 192(3):328-335.
- [31] de Jong AE, Morreau H, van Puijnenbroek M, Eilers PH, Wijnen J, Nagengast FM, Griffioen G, Cats A, Menko FH, Kleibeuker JH, Vasen HF. The role of mismatch

- repair gene defects in the development of adenomas in patients with HNPCC. *Gastroenterology* 2004; 126(1):42-48.
- [32] Love RR, Morrissey JF. Colonoscopy in asymptomatic individuals with a family history of colorectal cancer. *Arch Intern Med* 1984; 144(11):2209-2211.
- [33] Mecklin JP, Jarvinen HJ, Aukee S, Elomaa I, Karjalainen K. Screening for colorectal carcinoma in cancer family syndrome kindreds. *Scand J Gastroenterol* 1987; 22(4):449-453.
- [34] Vasen HF, Hartog Jager FC, Menko FH, Nagengast FM. Screening for hereditary non-polyposis colorectal cancer: a study of 22 kindreds in The Netherlands. *Am J Med* 1989; 86(3):278-281.
- [35] Vasen HF, Taal BG, Nagengast FM, Griffioen G, Menko FH, Kleibeuker JH, Offerhaus GJ, Meera KP. Hereditary nonpolyposis colorectal cancer: results of long-term surveillance in 50 families. *Eur J Cancer* 1995; 31A(7-8):1145-1148.
- [36] Jarvinen HJ, Mecklin JP, Sistonen P. Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology* 1995; 108(5):1405-1411.
- [37] Jarvinen HJ, Aarnio M, Mustonen H, Aktan-Collan K, Aaltonen LA, Peltomaki P, de la CA, Mecklin JP. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology* 2000; 118(5):829-834.
- [38] Renkonen-Sinisalo L, Aarnio M, Mecklin JP, Jarvinen HJ. Surveillance improves survival of colorectal cancer in patients with hereditary nonpolyposis colorectal cancer. *Cancer Detect Prev* 2000; 24(2):137-142.
- [39] Arrigoni A, Sprujevnik T, Alvisi V, Rossi A, Ricci G, Pennazio M, Spandre M, Cavallero M, Bertone A, Foco A, Rossini FP. Clinical identification and long-term surveillance of 22 hereditary non-polyposis colon cancer Italian families. *Eur J Gastroenterol Hepatol* 2005; 17(2):213-219.
- [40] de Vos tot Nederveen Cappel WH, Nagengast FM, Griffioen G, Menko FH, Taal BG, Kleibeuker JH, Vasen HF. Surveillance for hereditary nonpolyposis colorectal cancer: a long-term study on 114 families. *Dis Colon Rectum* 2002; 45(12):1588-1594.
- [41] de Jong AE, Hendriks YM, Kleibeuker JH, de Boer SY, Cats A, Griffioen G, Nagengast FM, Nelis FG, Rookus MA, Vasen HFA. Shift in mortality due to surveillance in the Lynch syndrome. *Gastroenterology* 2006; 130: 665-71.
- [42] Stormorken AT, Clark N, Grindedal E, Maehle L, Moller P. Prevention of colorectal cancer by colonoscopic surveillance in families with hereditary colorectal cancer. *Scand J Gastroenterol* 2007 (in press).
- [43] de Jong AE, Nagengast FM, Kleibeuker JH, van de Meeberg PC, van Wijk HJ, Cats A, Griffioen G, Vasen HF. What is the appropriate screening protocol in Lynch syndrome? *Fam Cancer* 2006.

- [44] Lindor NM, Rabe K, Petersen GM, Haile R, Casey G, Baron J, Gallinger S, Bapat B, Aronson M, Hopper J, Jass J, LeMarchand L, Grove J, Potter J, Newcomb P, Terdiman JP, Conrad P, Moslein G, Goldberg R, Ziogas A, Anton-Culver H, de Andrade M, Siegmund K, Thibodeau SN, Boardman LA, Seminara D. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. *JAMA* 2005; 293(16):1979-1985.
- [45] Dove-Edwin I, de Jong AE, Adams J, Mesher D, Lipton L, Sasieni P, Vasen HF, Thomas HJ. Prospective results of surveillance colonoscopy in dominant familial colorectal cancer with and without Lynch syndrome. *Gastroenterology* 2006; 130(7):1995-2000.
- [46] Dove-Edwin I, Boks D, Goff S, Kenter GG, Carpenter R, Vasen HF, Thomas HJ. The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary nonpolyposis colorectal carcinoma and familial colorectal carcinoma. *Cancer* 2002; 94(6):1708-1712.
- [47] Rijcken FE, Mourits MJ, Kleibeuker JH, Hollema H, van der Zee AG. Gynecologic screening in hereditary nonpolyposis colorectal cancer. *Gynecol Oncol* 2003; 91(1):74-80.
- [48] Renkonen-Sinisalo L, Butzow R, Leminen A, Lehtovirta P, Mecklin JP, Jarvinen HJ. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. *Int J Cancer* 2006.
- [49] Schmeler KM, Lynch HT, Chen LM, Munsell MF, Soliman PT, Clark MB, Daniels MS, White KG, Boyd-Rogers SG, Conrad PG, Yang KY, Rubin MM, Sun CC, Slomovitz BM, Gershenson DM, Lu KH. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. *N Engl J Med* 2006; 354(3):261-269.
- [50] Weber T. Clinical surveillance recommendation adopted for HNPCC. *Lancet* 348, 465. 2006.
- [51] de Vos tot Nederveen Cappel WH, Buskens E, van Duijvendijk P, Cats A, Menko FH, Griffioen G, Slors JF, Nagengast FM, Kleibeuker JH, Vasen HF. Decision analysis in the surgical treatment of colorectal cancer due to a mismatch repair gene defect. *Gut* 2003; 52(12):1752-1755.
- [52] Carethers JM, Chauhan DP, Fink D, Nebel S, Bresalier RS, Howell SB, Boland CR. Mismatch repair proficiency and in vitro response to 5-fluorouracil. *Gastroenterology* 1999; 117(1):123-131.
- [53] Jacob S, Aguado M, Fallik D, Praz F. The role of the DNA mismatch repair system in the cytotoxicity of the topoisomerase inhibitors camptothecin and etoposide to human colorectal cancer cells. *Cancer Res* 2001; 61(17):6555-6562.
- [54] Liang JT, Huang KC, Lai HS, Lee PH, Cheng YM, Hsu HC, Cheng AL, Hsu CH, Yeh KH, Wang SM, Tang C, Chang KJ. High-frequency microsatellite instability predicts better chemosensitivity to high-dose 5-fluorouracil plus leucovorin

- chemotherapy for stage IV sporadic colorectal cancer after palliative bowel resection. *Int J Cancer* 2002; 101(6):519-525.
- [55] Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM, Hamilton SR, Laurent-Puig P, Gryfe R, Shepherd LE, Tu D, Redston M, Gallinger S. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med* 2003; 349(3):247-257.
- [56] Carethers JM, Smith EJ, Behling CA, Nguyen L, Tajima A, Doctolero RT, Cabrera BL, Goel A, Arnold CA, Miyai K, Boland CR. Use of 5-fluorouracil and survival in patients with microsatellite-unstable colorectal cancer. *Gastroenterology* 2004; 126(2):394-401.
- [57] de Vos tot Nederveen Cappel WH, Meulenbeld HJ, Kleibeuker JH, Nagengast FM, Menko FH, Griffioen G, Cats A, Morreau H, Gelderblom H, Vasen HF. Survival after adjuvant 5-FU treatment for stage III colon cancer in hereditary nonpolyposis colorectal cancer. *Int J Cancer* 2004; 109(3):468-471.
- [58] Fallik D, Borrini F, Boige V, Viguier J, Jacob S, Miquel C, Sabourin JC, Ducreux M, Praz F. Microsatellite instability is a predictive factor of the tumor response to irinotecan in patients with advanced colorectal cancer. *Cancer Res* 2003; 63(18):5738-5744.
- [59] Hurlstone DP, Karajeh M, Cross SS, McAlindon ME, Brown S, Hunter MD, Sanders DS. The role of high-magnification-chromoscopic colonoscopy in hereditary nonpolyposis colorectal cancer screening: a prospective "back-to-back" endoscopic study. *Am J Gastroenterol* 2005; 100(10):2167-2173.
- [60] Domingo E, Niessen RC, Oliveira C, Alhopuro P, Moutinho C, Espin E, Armengol M, Sijmons RH, Kleibeuker JH, Seruca R, Aaltonen LA, Imai K, Yamamoto H, Schwartz S Jr, Hofstra RM. BRAF-V600E is not involved in the colorectal tumorigenesis of HNPCC in patients with functional MLH1 and MSH2 genes. *Oncogene* 2005; 24(24):3995-3998.