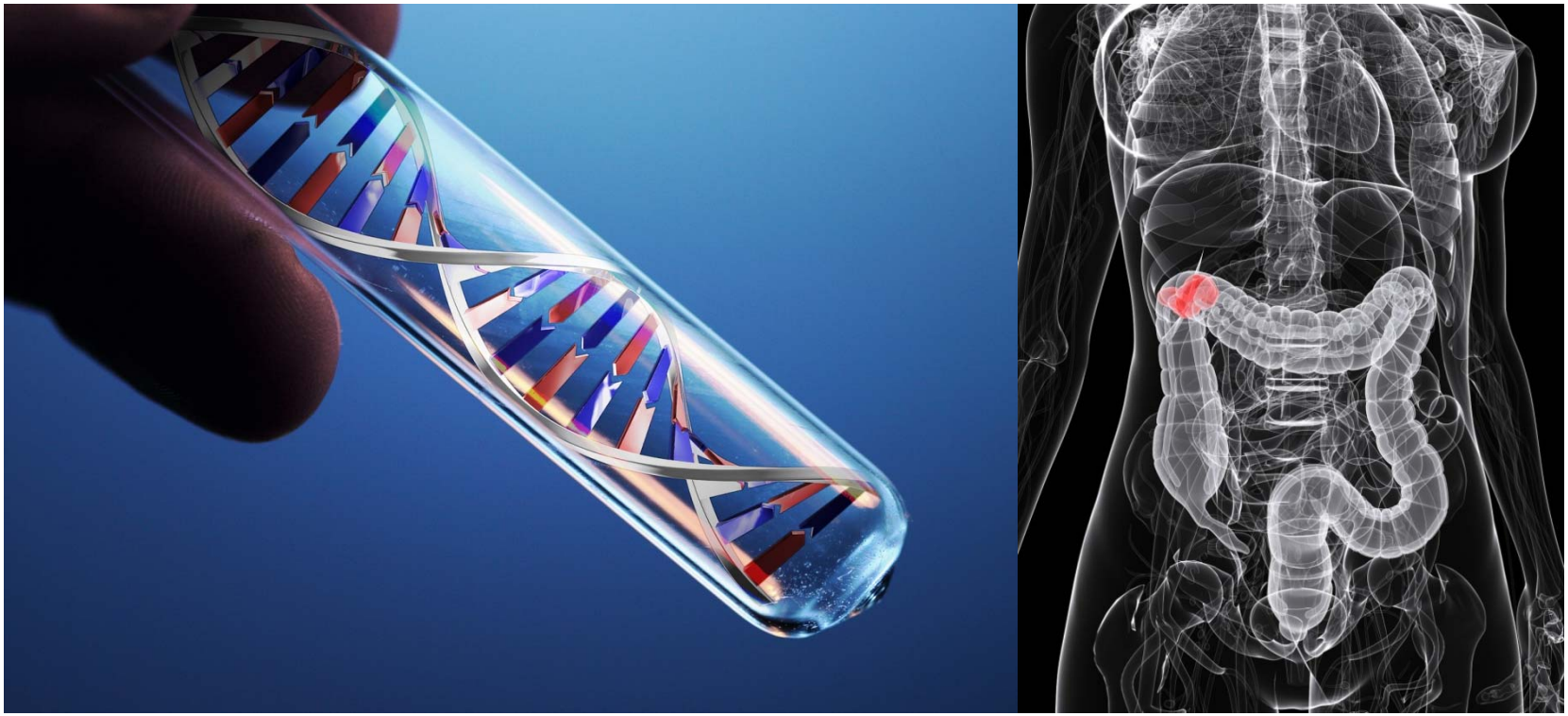
KCE REPORT 220

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Center

ONCOGENETIC TESTING FOR LYNCH SYNDROME AND FAMILIAL ADENOMATOUS POLYPOSIS



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KCE REPORT 220
GOOD CLINICAL PRACTICE

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ONCOGENETIC TESTING FOR LYNCH SYNDROME AND FAMILIAL ADENOMATOUS POLYPOSIS

JO ROBAYS, BRUCE POPPE

2014 www.kce.fgov.be

COLOPHON

Title:	Oncogenetic testing for Lynch syndrome and familial adenomatous polyposis
Authors:	Jo Robays (KCE), Bruce Poppe (Universitair Ziekenhuis Gent)
Project coordinator:	Sabine Stordeur (KCE)
Senior supervisor:	Frank Hulstaert (KCE)
Reviewers:	Germaine Hanquet (KCE), Raf Mertens (KCE)
External experts:	Marc De Man (gastroenterologist, OLV Ziekenhuis Aalst), Nicolas Janin (geneticist, Université catholique de Louvain), Patrick Pauwels (pathologist, UZ Antwerpen), Christine Sempoux (pathologist, Cliniques universitaires Saint-Luc), Isabelle Sinapi (medical oncologist, Grand hôpital de Charleroi), Marijke Spaepen (molecular biologist, geneticist, UZ Leuven), Sabine Tejpar (digestive oncologist, UZ Leuven), Urielle Ullmann (geneticist, Institut de Pathologie et de Génétique), Jenneke van den Ende (geneticist, UZ Antwerpen)
Stakeholders:	Marc Abramowicz (College of Human Genetics and Hôpital Erasme-ULB), Claude Cuvelier (Belgische Vereniging Pathologie and UZ Gent), Jacques De Greve (Belgische Vereniging voor Medische Oncologie and UZ Brussel), Marc Peeters (Belgische Vereniging voor Medische Oncologie and UZ Antwerpen), Eric Van Cutsem (Belgian Group of Digestive Oncology and president of the patient organisation Familial Adenomatous Polyposis Association (FAPA) and UZ Leuven)
External validators:	Eric Legius (UZ Leuven), Patrik Vankrunkelsven (Katholieke Universiteit Leuven and CEBAM), Hans Vasen (Stichting Opsporing Erfelijke Tumoren, Leiden, Nederland)
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Layout:	Ine Verhulst

Disclaimer:

- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
- **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.**
- **Finally, this report has been approved by common assent by the Executive Board.**
- **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AFAP	atenuated familial adenomatous polyposis
APC	adenomatous polyposis coli
CI	confidence interval
CRC	colorectal cancer
DFS	disease free survival
dMMR	defective DNA mismatch repair
FAP	familial adenomatous polyposis
FAPA	familial adenomatous polyposis association
5FU	5-fluorouracil
HNPCC	hereditary non-polyposis colorectal cancer
HR	hazard ratio
IHC	immunohistochemistry
pMMR	proficient MMR
PREMM1,2	Prediction of Mismatch Repair Gene Mutations in MLH1 and MSH2.
PREMM1,2,6	Prediction of Mismatch Repair Gene Mutations in MLH1, MSH2, and MSH6
MA	meta-analysis
MAP	adenomatous polyposis caused by bi-allelic mutations in the MUTYH gene
MMR	mismatch repair
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stable
OR	odds ratio
OS	overall survival
RFS	recurrence free survival
RR	relative risk
SIR	standardized incidence ratio
SMR	standardized mortality ratio
SR	systematic review

SCIENTIFIC REPORT

1 INTRODUCTION

This clinical practice guideline is based on the collaborative efforts of the Belgian Health Care Knowledge Centre (KCE), the College of Human Genetics and the College of Oncology. This guideline complements the recently published practice guideline for colorectal cancer and is a first report in a short series of oncogenetic testing guidelines.

1.1 Background

Oncogenetic tests are tests that assist in the diagnosis of specific cancers that have an important hereditary component. Such tests may also assist to identify family members at risk of developing specific forms of cancer. Criteria are needed for the identification and referral of subjects and patients to genetic centers for counselling, possibly followed by germline mutation analysis.

1.2 The need for a guideline

Criteria are needed for the identification and referral of patients to genetic centres for counselling, possibly followed by germline mutation analysis. It is important to provide such guidance to all clinicians active in the field of colon cancer care. In addition, the topic is timely as the budget and capacity for counselling and testing at genetic centres has been restricted.

1.3 Scope

This report concerns the oncogenetic testing aspects of colorectal cancer, more specifically Lynch syndrome and familial adenomatous polyposis (FAP). This report does not cover other interventions (e.g. prophylactic surgery) or treatment. Microsatellite instability is discussed both as a predictor of treatment effectiveness and as a predictor of Lynch syndrome.

1.4 Remit of the guideline

1.4.1 Overall objectives

This guideline provides recommendations based on current scientific evidence for the identification and referral of patients to genetic centres for counselling, possibly followed by germline mutation analysis. Clinicians are encouraged to interpret these recommendations in the context of the individual patient situation, values and preferences. The guidelines are based on clinical evidence and may not always be in line with the current criteria for RIZIV – INAMI reimbursement of diagnostic and therapeutic interventions. The RIZIV – INAMI may consider adaptation of reimbursement/funding criteria based on these guidelines.

1.4.2 Target users of the guideline

This guideline is intended to be used by all care providers involved in the management of colon cancer patients and all care providers involved in genetic counselling and testing. This guideline can also be of interest for patients and their families, and their general practitioner.

1.5 Statement of intent

Clinical guidelines are designed to improve the quality of health care and decrease the use of unnecessary or harmful interventions. This guideline has been developed by clinicians and researchers for use within the Belgian healthcare context. It provides advice regarding MSI testing and oncogenetic testing for Lynch syndrome and FAP.

The recommendations are not intended to indicate an exclusive course of action or to serve as a standard of care. Standards of care are determined on the basis of all the available clinical data for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Variations, which take into account individual circumstances, clinical judgement and patient choice, may also be appropriate. The information in this guideline is not a substitute for a proper diagnosis, treatment or the provision of advice by an appropriate health professional. It is advised, however, that significant deviations from the national guideline are fully documented in the patient's file at the time the relevant decision is taken.

1.6 Funding and declaration of interest

KCE is a federal institution funded for the largest part by RIZIV – INAMI, but also by the Federal Public Service of Health, Food chain Safety and Environment, and the Federal Public Service of Social Security. The development of clinical practice guidelines is part of the legal mission of the KCE. The development of guidelines is paid by KCE's budget. The sole mission of the KCE is providing scientifically valid information. KCE has no interest in companies (commercial or non-commercial i.e. hospitals and universities), associations (e.g. professional associations, unions), individuals or organisations (e.g. lobby groups) that could be positively or negatively affected (financially or in any other way) by the implementation of these guidelines. All clinicians involved in the Guideline Development Group (GDG), the stakeholders meeting or the validation completed a declaration of interest form. Information on potential conflicts of interest is published in the colophon of this report. All members of the KCE Expert Team make yearly declarations of interest and further details of these declarations are available upon request.

2 METHODOLOGY

2.1 Introduction

The KCE guideline is produced according to codified principles, based on scientific information regularly updated from the international literature. This guideline was developed using a standard methodology based on a systematic review of the evidence. Further details about KCE and the guideline development methodology are available at https://kce.fgov.be/content/kce-processes. First, clinical questions were developed. Second, a literature review was conducted (including a search for recent, high quality guidelines). Third, on the basis of the results of the literature review, recommendations were formulated. As the GRADE approach currently only applies for treatment interventions and not yet for diagnostic interventions, no grading of the recommendations was performed for this guideline.

2.2 The Guideline Development Group

This guideline was developed by a multidisciplinary groups of practising clinicians in collaboration with KCE experts. The GDG consists of the authors together with the external experts listed in the colophon under the section external experts. Guideline development and literature review expertise, support, and facilitation were provided by KCE.

The roles assigned to the GDG were:

- To provide feedback on the selection of studies and identify further relevant manuscripts which may have been missed;
- To provide feedback on the content of the guideline;
- To provide judgement about indirectness of evidence;
- To provide feedback on the draft recommendations;
- To address additional concerns to be reported under a section on 'other considerations'.

2.3 Clinical research questions

A draft selection of research questions was prepared by KCE end of June 2013 in consultation with Prof. B. Poppe, clinical geneticist at the University Hospital of Ghent. He had introduced the study proposal, supported by the Ministry of Health. Some questions overlapped with the ongoing development of the practice guidelines for colon cancer at KCE, in collaboration with the College of Oncology. Therefore, it was decided to prepare a separate report.

The following clinical questions are addressed in this guideline:

What is the role of MSI testing as a predictor of treatment effectiveness?

What is the role of MSI testing and immunohistochemistry testing in the screening for Lynch syndrome

Who should receive what follow-up in the context of screening for Lynch syndrome?

Who should be offered oncogenetic testing or receive follow-up in the context of screening for FAP?

2.4 Literature search and study selection

2.4.1 Study design

- Inclusion criteria for the study design:
  - Diagnostic studies: systematic reviews, guidelines, meta-analyses, RCTs, prospective studies;
- Articles in Dutch, English, French and German were included.
- Exclusion criteria for study design
  - Narrative review
  - Cadaver/animal studies
  - Case reports
  - Studies presented as conference abstract only. If no full-text was available, the study was not taken into account for the final recommendations.

- An iterative approach was followed:
  - First, the search focused on clinical guidelines of high quality;
  - Second, a search for recently published systematic reviews and meta-analyses published after the search date of the selected clinical guidelines was performed;
  - Third, the selected evidence synthesis was updated by a search for all relevant primary studies (RCTs and prospective studies) published after the search date of the selected systematic reviews and meta-analyses.

To be included, a systematic review had to:

- address at least one of the research questions;
- evaluate at least one of the selected (critical and important) outcomes;
- include RCTs;
- search MEDLINE and at least one other electronic database;
- include an assessment of risk of bias for each primary study listing at least the three following items: concealment of allocation, blinded outcome assessment and completeness of follow-up (preferably summarised in a table).

If more than one systematic review was identified for a particular research question, the focus was on the most complete systematic review.

To be included a primary study had to:

- be an RCT, an observational study or a diagnostic accuracy study;
- address at least one of the research questions;
- evaluate at least one of the selected (critical and important) outcomes.

The process used for the selection of relevant studies is detailed in Appendix 2.

2.4.2 Databases and date limits

The following databases were included in the literature search:

- The Cochrane Database of systematic reviews (http://www.cochrane.org)
- MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed)
- Embase (http://www.embase.com/)

For the guidelines the search engines were:

- G.I.N. guideline resource (http://www.g-i-n.net)
- National Guideline Clearinghouse http://www.guideline.gov/

Further information about ongoing research was obtained by contacting study authors and organisations. The EMA website was consulted to find all information about the authorization for medicines. Members of the GDG were also consulted to identify relevant evidence that might have been missed during the search process.

2.4.3 Search strategy

A combination of appropriate MeSH terms and free text words was used (Appendix 1). The PICOs and the search strategy corresponding to our research questions are documented in Appendix 1.

The number of articles by database is provided in Appendix 1.

Studies were screened on **title and abstract**. In case of doubt the content experts were consulted. First, the titles and abstracts of the identified studies were checked and irrelevant studies were eliminated. In a second step, the remaining papers were screened by reading their **full-text**. If no full-text was available, the study was excluded for the final recommendations. Reference lists of the selected studies were hand searched for additional relevant manuscripts.

The screening of the **guidelines** was performed on title and abstract based on the research questions. Only guidelines with a documented and adequate search strategy were retained.

2.5 Quality appraisal

2.5.1 Clinical practice guidelines

The AGREE II instrument was used to evaluate the methodological quality of the identified international guidelines (www.agreetrust.org).

2.5.2 Systematic reviews

Selected (systematic) reviews were critically appraised by a single KCE expert using the AMSTAR checklist[1] (http://amstar.ca/Amstar_Checklist.php). In case of doubt, a second KCE expert was consulted.

2.5.3 Primary articles

Critical appraisal of each study was performed by a single KCE expert. In case of doubt, a second KCE expert was consulted.

Study limitations in observational studies were evaluated using GRADE criteria: failure to develop and apply appropriate eligibility criteria (inclusion of control population); under- or overmatching in case-control studies; selection of exposed and unexposed in cohort studies from different populations; flawed measurement of both exposure and outcome; differences in measurement of exposure (e.g., recall bias in case-control studies); differential surveillance for outcome in exposed and unexposed in cohort studies; failure to adequately control confounding; failure of accurate measurement of all known prognostic factors; failure to match for prognostic factors and/or lack of adjustment in statistical analysis, and incomplete follow-up.

2.6 Data extraction

For each included CPG the following data were extracted: consulted databases and search terms, search date, publication year, in- and exclusion criteria, quality appraisal, availability of evidence tables, consistency between the evidence and its interpretation, and consistency between the interpretation of the evidence and the recommendations.

For each systematic review, the search date, publication year, included studies and main results were extracted. For RCTs and longitudinal studies, the following data were extracted: publication year, study population, study intervention, and outcomes.

Data extraction was performed and entered in evidence tables using standard KCE templates. Any disagreements were resolved by discussion or, if required, by a third party.

All evidence tables are reported in Appendix 2.

2.7 Grading evidence

Due to current methodological limitations of the GRADE system for diagnostic tests, GRADE was not applied to the recommendations on diagnosis.

2.8 Formulation of recommendations

The retrieved evidence, the evidence tables, and the first draft of recommendations for Lynch syndrome were discussed during a meeting on September 2, 2013 in the presence of the authors and a small group of GDG members: Patrick Pauwels, Marijke Spaepen; Sabine Tejpar and Jenneke van den Ende. A full draft report, including the evidence tables and draft recommendations, was circulated to the full guideline development group one week prior to the face-to-face meeting of November 20, 2013. The circulated draft recommendations (listed in Appendix 4) were discussed and changed if important new evidence supported this change. The following experts were present at the November 20 meeting: Marc De Man, Nicolas Janin, Patrick Pauwels, Christine Sempoux, Isabelle Sinapi, Marijke Spaepen, Sabine Tejpar, Urielle Ullmann, Jenneke van den Ende.

2.8.1 Stakeholder involvement - healthcare professionals

The recommendations prepared by the guideline development group were circulated to associations of physicians targeted by this guideline. Each association was asked to assign a key representative to review the draft guideline. All representatives and their association are listed in the colophon under the section stakeholders as are their declarations of interest. Other associations previously contacted in the context of the colon cancer guideline, were contacted but had an expert in the CDG or did not delegate a representative: Belgian Digestive Pathology Club, Belgian Section for Colorectal Surgery of the Royal Belgian Society of Surgery, Belgian Society of Surgical Oncology, Belgian Section for Colorectal Surgery of the Royal Belgian Society of Surgery, Vlaamse Vereniging voor Gastro-enterologie, Societé Royale Belge de Gastro-enterologie, Belgian Group for Endoscopic Surgery, Belgian Society of Gastrointestinal Endoscopy, Domus Medica, Société Scientifique de Médicine Générale.

The invited panellists at the stakeholder meeting (November 27, 2013) received in advance the scientific report covering all research questions and were asked to score each recommendation indicating their level of agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' 'somewhat disagree', '3' 'the recommendation is out of the domain of expertise', '4' 'somewhat agree', and '5' 'completely agree'. If panellists disagreed with the recommendation (score '1' or '2'), they were asked to provide an explanation supported by appropriate evidence. Scientific arguments reported by these experts were used to adapt the the clinical recommendations. Three (A, B, C) of the five experts provided scores. In Appendix 4, an overview is provided of the scores, the comments, as well as the recommendations before and after the stakeholder meeting.

2.8.2 Patient representatives - stakeholders

Associations of patient representatives (Familial Adenomatous Polyposis Association (FAPA) and the Fondation contre le cancer) were contacted to invite patient representatives to take part in stakeholder meeting (November 27, 2013). The patient representatives were asked to review the recommendations and add comments from a patients' perspective where needed. Prof Van Cutsem, president of FAPA, was present at the meeting. The representative of the patient organisation FAPA vzw, Myriam Renson, did not attend the stakeholder meeting but provided feedback in writing after the meeting. She mentioned that there is often a request for genetic testing at an age under 10-12 years, resulting sometimes in genetic testing for FAP at a younger age. This point was discussed during the validation meeting and it was decided after discussion not to change the recommendations with respect to the minimum age.

2.9 Final validation

In agreement with the standard KCE procedures, the report was validated by three external experts, whose names are listed in the colophon. The validation meeting was chaired by CEBAM and took place at December 20, 2013. In addition to a validation of the scientific content, the AGREE II checklist was used in the review. Minor modifications were made and all three validators approved the report.

3 MSI TESTING AS A PREDICTOR OF TREATMENT EFFECTIVENESS

This part is taken from the colon cancer practice guideline (KCE report 218).[2] Practice guidelines based on this chapter can be found in that report.

3.1 Introduction

DNA mismatch repair (MMR) corrects errors that spontaneously occur during DNA replication. Microsatellite instability (MSI) is the phenotypic evidence of a defective DNA mismatch repair (dMMR). The proteins involved in MMR form a complex that binds to the mismatch, identifies the correct strand of DNA, then subsequently excises the error and repairs the mismatch. Cells with abnormally functioning MMR tend to accumulate errors rather than correcting those errors. As a result, gene sequences are not preserved faithfully through DNA replication, and novel microsatellite DNA fragments are created. Microsatellite instability is detected by PCR based assays that reveal these novel microsatellites (repeated sequences of DNA).

MSI testing is both used as a predictor of treatment effectiveness and as a predictor of Lynch syndrome. Both parts are discussed in the document.

'Approximately 15% of the colorectal cancers (CRCs) have defective DNA mismatch repair (dMMR). Defective MMR has frequently been measured by either the presence of microsatellite instability (MSI) or by testing for loss of the protein products for genes involved in DNA mismatch repair, most commonly MLH1, MSH2, MSH6, and PMS2. CRCs with dMMR have distinctive features that include proximal colon predominance, poor differentiation and/or mucinous histology, intra- and peritumoral lymphocytic infiltration, and diploid DNA content'.[3]

Loss of expression of one or more of the mismatch repair (MMR) enzymes can be assessed by immunohistochemistry (IHC). IHC can therefore be a surrogate technique for the identification of MSI tumors. Tumors retaining MMR expression by IHC are referred to as proficient MMR (pMMR).

3.2 Predicting the effect of adjuvant therapy.

Des Guetz et al.[4] reviewed the role of microsatellite instability status in predicting the efficacy of adjuvant chemotherapy and performed a meta-analysis on seven studies representing 3 690 patients; mean age: 65.5 years; 810 stage II and 2 444 stage III (75%). MSI-high (MSI-H) was found in 454 patients (14% of the global population), and microsatellite stable (MSS) in 2 871. A total of 1 444 patients received 5-fluorouracil (5FU)-based chemotherapy, whereas 1 518 patients did not. For MSI-H patients, there was no statistically significant difference for recurrence free survival (RFS) whether or not they received chemotherapy (5 studies); hazard ratio (HR) RFS: 0.96 (95% confidence interval (CI): 0.62–1.49); HR OS (6 studies): 0.70 (95% CI: 0.44–1.09; p=0.12). They found a significant interaction between MSI status (MSI-H or MSS) and therapeutic status suggesting a lesser benefit for MSI-H than for MSS patients (HR interaction RFS: 0.77 (95% CI: 0.67–0.87)).

Sargent et al.[3] distinguished between stage II and III (Des Guetz et al. stated that they were not able to obtain data sufficiently detailed to do this) found that no benefit from 5FU based treatment was observed in a pooled data set (of which part of the data were included in Des Guetz et al.) including data for patients with either stage II (HR, 2.30; 95% CI, 0.85 to 6.24;P=0.09) or stage III (HR, 1.01; 95% CI, 0.41 to 2.51; P=0.98) disease with dMMR. No treatment benefit was present in patients with pMMR and stage II disease (HR, 0.84; 95% CI, 0.57-1.24; p=0.38). In patients with stage III disease and pMMR tumors, a benefit from treatment was observed (HR, 0.64; p=0.001). The interaction test between MMR status and treatment efficacy for DFS was significant (p= 0.04), which indicated that the effect of treatment differs by MMR status. All findings were consistent for the OS end point, with one exception. For the OS end point, there was a statistically significant decreased OS in patients with stage II disease and dMMR tumors who were treated compared with patients in the surgery-alone control (HR, 2.95; 95% CI, 1.02-8.54; p=0.04).

Hutchins et al. found no evidence for lesser sensitivity of 5FU based chemotherapy in dMMR patients, however, the confidence interval around the estimation is large 0.81 (0.29 to 2.22), and the study was not powered to confirm or exclude this.

A pooled analysis by Sinicrope et al. was excluded as is overlapped with Sargent et al., focussing (inconclusively, due to lack of power) on the difference beween germline versus sporadic CRC.

Bertagnolli et al. found that microsatellite instability predicts improved response to adjuvant therapy with irinotecan, fluorouracil, and leucovorin in stage III colon cancer but irinotecan is not a recommended treatment for this indication so we did not take this study into account.

Observational studies examined the relation between oxaloplatin based treatments (FOLFOX) and MSI instability but were inconclusive and not included in the review.

3.3 Metastatic colon cancer

Des Guetz et al.[5] pooled 6 studies representing 964 patients (mean age 63 years; 91 MSI-H; 873 microsatellite stable (MSS) tumours). A total of 287 patients received 5FU-based chemotherapy,whereas 678 patients received combinations of 5FU or capecitabine with oxaliplatin and/or irinotecan. They found no benefit of metastatic chemotherapy in terms of response rate for MSI-H patients compared with MSS patients. The global hazard ratio (HR) for respons rate was 0.82 (95% confidence interval, CI: 0.95; 0.65-1.03; p=0.09). Different treatments schedules containing 5FU were pooled, the appropriateness could be questioned but separate analysis would reach the same conclusion that there is no proof that MSI instability has the power to predict the effectiveness of 5FU containing regimens.

Two observational studies concerning FOLFOX and FOLFIRI were found in the update but were not incuded as they only assessed the prognostic value and not the predictive value of MSI instability.

3.4 Other considerations

An individual based meta-analysis based on the database of the Adjuvant Colon Cancer End Points (ACCENT) Group [a] is ongoing examining the role of MSI in predicting prognosis and effectiveness of 5FU. Results of this analysis may alter the conclusions.

Conclusions

- **MSI predicts treatment effectiveness of adjuvant treatment with 5FU alone in stage (I and) II colorectal cancer. However, the predictive value of MSI concerning combination therapies with oxaliplatin (FOLFOX) is uncertain.**
- **There is no proof that MSI instability predicts treatment effectiveness in metastatic colorectal cancer.**

[a] http://www.thecco.net/article/view/2219/3049

4 LYNCH SYNDROME

4.1 Role of MSI testing and immunohistochemistry in screening for Lynch syndrome

Lynch syndrome (HNPCC or hereditary nonpolyposis colorectal cancer) is an autosomal dominant genetic condition that has a high risk of colorectal cancer (CRC) as well as other cancers including endometrium, ovary, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain, and skin. The increased risk for these cancers is due to inherited mutations that impair DNA mismatch repair.

'Familial colorectal cancer accounts for 10-15% of all CRCs. In about 5% of all cases, CRC is associated with a highly penetrant dominant inherited syndrome. The most common inherited form of non-polyposis CRC is the Lynch syndrome which is responsible for about 2-4% of all cases. Surveillance of individuals at high risk for CRC prevents the development of advanced CRC.'[6]

'Common strategies to identify individuals at risk for Lynch syndrome include fulfillment of clinical criteria such as the Amsterdam criteria or the revised Bethesda guidelines, which were developed by a consensus of experts. The Amsterdam criteria were originally developed for research purposes to distinguish families suspected of having hereditary non-polyposis colorectal cancer and to determine the prevalence of MMR gene mutations. The Bethesda guidelines were developed as a broader screening tool to identify patients whose tumors should be tested for MSI and were revised in 2004 to include both personal and family history features, including extracolonic malignancies associated with Lynch syndrome, age at diagnosis and pathologic characteristics of the tumour. The revised Bethesda guidelines are thus probably the most commonly used criteria to select patients with CRC for further molecular analysis of their tumours (MSI/immunohistochemistry).[7] 'However, these criteria and guidelines have been criticised for being too complex and lacking in specificity and sensitivity.'[8]

We found 3 guidelines addressing this issue. Only the guideline of the Genomic Applications in Practice and Prevention (EGAPP) Working Group is based on a documented systematic review of the literature, conducted by AHRQ and published separately[9] and a targeted review specifically focussing on Lynch syndrome using a methodology specific for EGAPP.[10,11] This was used as a base for our recommendations. European experts (identifying themselves as the Mallorca group) published guidelines based on a consensus meeting among 35 specialists from 13 countries.[8] They state that a systematic literature search was performed using the Pubmed database and manual searches of relevant articles, but provide no further documentation on the methods used, such as criteria for exclusion or inclusion, articles found and selected. The National Society of Genetic Counselors (NSGC) and the Collaborative Group of the Americas on Inherited Colorectal Cancer (CGA-ICC) published a clinical practice testing guideline[12] but did not provide details on the way it was developed either. The last two guidelines were only used for comparison and tracking of references.

The EGAPP Working Group recommends offering genetic testing for Lynch syndrome to individuals with newly diagnosed colorectal cancer to reduce morbidity and mortality in relatives, either with MSI or IHC as entry point. They did however not recommend a specific genetic testing strategy due to lack of sufficient evidence. They estimated that sensitivity of MSI testing is about 89% for mutations in MLH1 and MSH2, with a lower sensitivity of about 77% for mutations in MSH6 (and PMS2) with a specificity of 90.2%, with an adequate level of evidence. They estimate that the sensitivity of IHC testing is 83%, regardless of the underlying MMR gene mutation and that specificity is more variable, with a central estimate of 88.8%.

The main problem with those estimations however is the fact that most studies are conducted in preselected high risk, as it is unfeasible to apply the gold standard, MMR testing, to all patients in a population-based cohort.

In order to obtain a clinical relevant estimation of the contribution of MSI and IHC testing among CRC patients, we selected publications where IHC and MSI were applied to a consecutive series of CRC patients, either with no age restriction or with a restriction < 70 years, published after 2008 (search date EGAPP guideline). Eight publications were assessed in full text, 3 were finally retained, reasons for the exclusion of the other 5 are listed in Appendix 1.1.

Canard et al. (2012)[13] prospectively included 1 040 patients between 2005 and 2009. Lynch syndrome screening modalities included the Bethesda criteria, immunochemistry (IHC) for MLH1, MSH2, and MSH6, and microsatellite instability (MSI) by using pentaplex markers. Promoter methylation was assessed in tumours with a loss of MLH1 expression. Gene sequencing was offered to patients with abnormal IHC or MSI status without promoter methylation. Sensitivity of IHC and MSI testing for detecting identified Lynch syndrome patients were, respectively, 92% (23 of 25) and 84% (21 of 25). After exclusion of patients not tested for an MMR mutation, the positive predictive value of IHC and MSI testing were 29.1% (23 of 79) and 27.3% (21 of 77), respectively. 12% of the patients with proven Lynch syndrome and 37.1% of the patients with possible Lynch syndrome did not fulfil the revised Bethesda criteria; moreover, a restriction of screening to patients younger than 50 years would have missed about half of patients with proven Lynch syndrome.

Moreira et al. (2012)[14] did a pooled-data analysis of 4 large cohorts of newly diagnosed CRC probands recruited between 1994 and 2010 (n=10 206) from the Colon Cancer Family Registry, the EPICOLON project, the Ohio State University, and the University of Helsinki examining personal, tumour-related, and family characteristics, as well as microsatellite instability, tumour MMR immunostaining, and germline MMR mutational status data. In the population-based cohorts (n=3 671 probands), the universal screening approach (sensitivity 100%; 95%CI: 99.3%-100%; specificity 93.0%; 95%CI: 92.0%-93.7%; diagnostic yield 2.2%; 95%CI: 1.7%-2.7%) was superior to the use of Bethesda guidelines (sensitivity 87.8%; 95%CI: 78.9%-93.2%; specificity 97.5%; 95%CI: 96.9%-98.0%; diagnostic yield 2.0%; 95%CI: 1.5%-2.4%;P<0.001), and a selective strategy based on tumour MMR testing of cases with CRC diagnosed at age 70 years or younger and in older patients fulfilling the Bethesda guidelines (sensitivity 95.1%; 95%CI: 89.8%-99.0%; specificity 95.5%; 95%CI: 94.7%-96.1%; diagnostic yield 2.1%; 95%CI: 1.6%-2.6%; p=0.001). This selective strategy missed 4.9% of Lynch syndrome cases but resulted in 34.8% fewer cases requiring tumour MMR testing and 28.6% fewer cases undergoing germline mutational analysis than the universal approach. They concluded that universal tumour MMR testing among CRC probands had a greater sensitivity for the identification of Lynch syndrome compared with multiple alternative strategies, although the increase in the diagnostic yield was modest.

Perez-Carbonell et al.[15] studied 2 093 patients with CRC from the EPICOLON I and II cohorts. Immunohistochemistry for MMR proteins and/or microsatellite instability (MSI) analysis was performed in tumour tissue. These data were also used in the pooled analysis of Moreira et al.(2012).[14]

Prediction models

'Three prediction models were introduced to quantify an individual's probability of carrying a MMR gene mutation most commonly associated with Lynch syndrome. These models include MMRPredict, MMRPro, and Prediction of Mismatch Repair Gene Mutations in MLH1 and MLH2 (PREMM1,2). The latter model has recently been extended to include prediction of MSH6 gene mutations and has been replaced by the PREMM1,2,6 model (Prediction of Mismatch Repair Gene Mutations in MLH1, MSH2, and MSH6)'.[7]

Kastrinos et al.[7] reviewed the evidence concerning the performance of these models but did not provide details on the search strategy. We performed a search strategy but identified the same studies in the review and one supplementary study concerning an outdated version of the PREMM model. Therefore we took over the conclusions and results of the Kastrinos review. Area under the curve for all 3 models in the study range from 0.76 to 0.93. Sensitivities and specificities vary depending the threshold used, but uncertainty is high given the fact that validations were based on relatively few confirmed mutation carriers. The authors conclude that more validation studies are needed before a specific model can be recommended for use in routine clinical practice.

MLH1 promotor methylation and BRAF mutations

MLH1 promoter methylation is correlated with tumour BRAF V600E mutation status, and BRAF V600E mutation and MLH1 promoter methylation tumour markers are negative predictors of germline MMR mutation status. We identified a systematic review specifically dealing with this issue by Parsons et al.[16] who identified CRC cohorts tested for MMR mutations, and tumour BRAF V600E mutation and/or MLH1 promoter methylation. They reported BRAF V600E results for 4 562 tumours from 35 studies, and MLH1 promoter methylation results for 2 975 tumours from 43 studies. In 550 MMR mutation carriers, the BRAF V600E mutation frequency was 1.40% (95%CI: 0.06%-3%). In MMR mutation-negative cases, the BRAF V600E mutation frequency was 5.00% (95%CI: 4%-7%) in 1 623 microsatellite stable (MSS) cases and 63.50% (95%CI: 47%-79%) in 332 cases demonstrating MLH1 methylation or MLH1 expression loss. Methylation of the 'C region' was a predictor of MMR mutation-negative status in MSI-H CRC cases (47% vs. 6% in MLH1 mutation carriers, $p<0.0001$). They conclude that tumour BRAF V600E mutation, and MLH1 promoter 'C region' methylation specifically, are strong predictors of negative MMR mutation status.

Other considerations

We found two cost-effectiveness analyses. Ladabaum et al. (2011)[17] compared different strategies based on clinical criteria, prediction algorithms, tumour testing, or up-front germline mutation testing, followed by tailored screening and risk-reducing surgery. Among tumour-testing strategies, immunohistochemisty followed by BRAF mutation testing was preferred, with an incremental cost-effectiveness ratio of $36 200 per life-year gained. - As the cost-effectiveness analysis was done in the US it is unclear to what degree their results are applicable to the Belgian context. Moreover, there is considerable structural and random uncertainty around the estimations. Main elements are cost structure, expected benefit of preventive intervention in identified Lynch syndrome relatives but also family structure and testing uptake among family members, as this determines not only the sensitivity of prediction algoritms using family history but also the potential benefit to relatives. Mvundura et al.[18] reached similar conclusions but was more limited in its scope.

Barrow et al[19] did a systematic review to appraise the published evidence for registration and screening in relation to colorectal cancer (CRC) incidence and mortality.They found that for FAP, 33 of 33 studies described a significant reduction of CRC incidence and mortality with registration and screening. For LS, nine of ten studies described a reduction of CRC incidence and mortality with registration and screening. Five studies (FAP, 2; LS, 3) provided evidence for complete prevention of CRC-related deaths during surveillance. Clinical and statistical heterogeneity prevented pooling of data for meta-analysis. They concluded that studies consistently report that registration and screening result in a reduction of CRC incidence and mortality in patients with FAP and LS.

Conclusions

Systematic testing of all CRC patients with MSI or IHC increases the number of Lynch syndrome patients identified with around 15 %.

There are no studies demonstrating the superiority of MSI compared to IHC.

MLH1 promoter methylation is correlated with tumour BRAF V600E mutation status, and BRAF V600E mutation and MLH1 promoter methylation tumour markers are negative predictors of germline MMR mutation status.

The value of prediction models needs further evaluation.

4.2 Follow-up of Lynch syndrome patients

The EGAPP guideline recommends colonoscopic surveillance in Lynch syndrome patients based on 2 cohort studies. They consider that the evidence for the follow up of gynecological cancers and prophylactic surgery is insufficient. Vaesen et al[8] take the same position and consider that it should be offered explaining the limitations and uncertainties.

From the search date of the EGAPP guideline on, we identified 3 cohort studies but no RCTs.

Vasen et al. (2010)[20] included 205 Lynch syndrome families with identified mutations in one of the mismatch repair genes (745 mutation carriers) together with data from non-Lynch syndrome families (46 families, 344 relatives). Patients were observed from January 1, 1995, until January 1, 2009. After a mean follow-up of 7.2 years, 33 patients developed CRC under surveillance. The cumulative risk of CRC was 6% after the 10-year follow-up period. The risk of CRC was higher in carriers older than 40 years and in carriers of MLH1 and MSH2 mutations. After a mean follow-up of 7.0 years, 6 cases of CRC were detected among non-Lynch syndrome families. No deaths were reported.

Engel et al.[21] in a prospective, multicentre cohort study, followed 1 126 individuals from 3 groups of hereditary non-polyposis colorectal cancer (HNPCC) families: those with a pathogenic germline mutation in a mismatch repair gene (MUT group), those without a mutation but with microsatellite instability (MSI group), and those who fulfilled the Amsterdam criteria without microsatellite instability (MSS group) with annual coloscopies. Ninety-nine CRC events were observed in 90 patients. Seventeen CRCs (17%) were detected through symptoms (8 before baseline colonoscopy, 8 at intervals >15 months to the preceding colonoscopy, and 1 interval cancer). Only 2 of 43 CRCs detected by follow-up colonoscopy were regionally advanced. Tumour stages were significantly lower among CRCs detected by follow-up colonoscopies compared with CRCs detected by symptoms (p=0.0.01).

Stuckless et al.[22] compared CRC incidence and survival in 54 male and 98 female MSH2 mutation carriers who underwent colonoscopic screening with 94 males and 76 females who were not screened. Controls were matched for age at entry into screening and also for gender. In males, median age to CRC was 58 years, whereas expected age was 47 years ($p<0.001$), and median survival was 66 years vs. 62 years ($p=0.034$). In screened females, median age to CRC was 79 years compared to 57 years in the non-screened group ($p<0.001$), and median survival was 80 years compared with expected survival of 63 years ($p=0.001$). Twenty percent of males and 7% of females developed an interval CRC within 2 years of previous colonoscopy.

Conclusions

Annual or biannual screening of Lynch syndrome patients allow to find more CRC at an earlier stage.

Recommendations
Family history should be evaluated using a validated prediction model (e.g. PREMM1,2,6) or the revised Bethesda criteria. Individuals considered at risk should be referred for genetic counseling. A first step may be the retrieval and immunohistochemical analysis of stored samples of family members after appropriate consent. This is possibly followed by germline mutation analysis of the referred individual.
Investigation of all colorectal cancers by immunohistochemistry (IHC) of the four mismatch repair (MMR) proteins or by microsatellite instability (MSI) testing is recommended. In case of a positive family history (e.g. based on PREMM1,2,6) or other risk factors, both IHC and MSI should be performed if either MSI of IHC performed alone remains inconclusive.
Immunohistochemistry and MSI tests should only be performed in laboratories that are ISO accredited for these tests.
If the only reason for germline mutation analysis is a positive IHC for MLH1, germline mutation analysis should be accompanied by MLH1 promotor methylation or BRAF mutation analysis.
Patients with a positive IHC or MSI result should be offered referral for genetic counseling, which may result in germline mutation analysis.
In families with a known causal mutation, predictive testing should be offered to all relatives from the age of 18 onwards and after genetic counseling.
In confirmed Lynch syndrome patients, yearly surveillance (including colonoscopy) is recommended. To maximally prevent the associated risk of endometrial and ovarian cancer, hysterectomy and bilateral oophorectomy is an option to be discussed with mutation carriers who have completed their families, especially after the age of 40 years. The option of surveillance for endometrial cancer should also be discussed with the patient; it should be mentioned that currently the benefit is unproven.
In families without identified causal mutation , the decision for surveillance should be based on the family or the personal history.
Participation of patients in the FAPA registry[b] is recommended and should be offered to patients concerned.

[b] Familial Adenomatous Polyposis Association, see Appendix 1

5 FAMILIAL ADENOMATOUS POLYPOSIS

5.1 Introduction

'Familial adenomatous polyposis (FAP) is a well-described inherited syndrome, which is responsible for 0.1% of all colorectal cancer (CRC) cases. The syndrome is characterised by the development of hundreds to thousands of adenomas in the colorectum. Almost all patients will develop CRC if they are not identified and treated at an early stage. The syndrome is inherited as an autosomal dominant trait and caused by mutations in the APC gene. Recently, a second gene has been identified that also gives rise to colonic adenomatous polyposis, although the phenotype is less severe than typical FAP. The gene is the MUTYH gene and the inheritance is autosomal recessive.'[23]

Three types are distinguished: familial adenomatous polyposis ('typical' FAP), atypical or attenuated familial adenomatous polyposis (AFAP), and adenomatous polyposis caused by bi-allelic mutations in the MUTYH gene (MAP). In 'typical' FAP, without surgical intervention, patients almost inevitably develop CRC by the mean age of 40–50 years. 'A milder form of FAP (AFAP) characterised by the presence of fewer adenomas and later onset of disease is observed in approximately 8% of cases. Adenomatous polyps also develop in the upper gastrointestinal tract, especially in the duodenum, and, if untreated, these polyps progress to malignancy in approximately 5% of cases. [23]

We found 2 guidelines addressing this issue. Only the guideline of the Association of Comprehensive Cancer Centres (ACCC)[24] is based on a documented systematic review of the literature, and was used as a base for our recommendations. European experts (identifying themselves as the Mallorca group) published guidelines based on a consensus meeting among 31 experts from nine European countries.[23] They state that a systematic literature search was performed using the Pubmed database and manual searches of relevant articles, but no further documentation on the methods used, such as criteria for exclusion or inclusion, articles found and selected was provided. The last guideline was only used for comparison and tracking of references.

We updated the ACCC guideline from their search date on. Details on the update can be found in Appendix 1.2.

The recommendations are based on a combination of expert opinion and observational studies, measuring the frequency of APC gene or pathogenic mutations in the MUTYH gene in FAP, AFAP and MAP and prognostic studies measuring the cumulative incidence of colorectal, duodenal and gastric cancer.

ACCC recommends to perform mutation analysis within a family first, if possible on a patient diagnosed with adenomatous polyposis (the index patient). Only if this is the case, and if a pathogenic mutation is detected in the index patient, will genetic diagnostics be conclusive in relation to remaining family members.

CCCA recommends DNA-based diagnosis in the following cases:

- It is preferable that first-degree family members of patients with classic adenomatous polyposis and a pathogenic APC mutation are referred for genetic diagnostics at the age of 10-12 years. If a clinical picture characteristic of AFAP is seen with multiple family members, this may take place at a later age (young adult age). If a pathogenic APC mutation is found in the index patient, genetic testing may provide a decisive answer for all family members in relation to risk of the disorder. Children of mutation carriers have a 50% chance of the genetic predisposition to (A)FAP.
- In the case of a person with MAP (biallelic MUTYH mutations), all brothers and sisters of this person should be referred for genetic evaluation given they have a 25% chance of a genetic predisposition. The a priori chance of MAP in a child of a patient with MAP is <1%, given the other parent has a small risk (± 2%) of being a carrier of a MUTYH mutation as well. To determine the risk for potential children of a patient with MAP, it is advised that MUTYH mutation testing is performed on the other parent. If the other parent is shown to be a mutation carrier, the children have 50% chance of biallelic MUTYH mutations.

- All patients under the age of 60 years with cumulative >10 adenomas, should be referred for genetic evaluation. Referral for genetic analysis should also be considered for younger persons with <10 adenomas and persons ≥60 years of age with more than 10 adenomas.

They recommend periodic endoscopic examination in the following patients:

1. Patients with the form of adenomatous polyposis FAP, AFAP, MAP or 'adenomatous polyposis of unknown origin'.
2. Persons with a pathogenic APC mutation.
3. Persons with biallelic pathogenic MUTYH mutations.
4. First-degree family members of patients with adenomatous polyposis where the disorder cannot be excluded by mutation analysis because a pathogenic mutation has not been found in the index patient.
5. First-degree family members of mutation carriers, who have not (yet) been tested themselves.

They recommend a different frequency and age of start of the surveillance through to colectomy per profile:

- Regular endoscopic surveillance in mutation carriers or risk carriers of classic FAP; twice yearly from the age of 10-12 using sigmoidoscopy.
- Regular endoscopic surveillance in mutation carriers or risk carriers of AFAP or MAP; twice yearly from the age of 18 using colonoscopy.

The recommended treatment for patients with adenomatous polyposis is colectomy; endoscopic or drug-based treatment prior to this operation is not indicated.

In the update following studies were found

Five observational studies and one individual based meta-analysis on the association between over the impact of monoallelic germline MUTYH mutations on colorectal carcinogenesis were identified.

Balaguer et al. (2007)[25] did a prospective, multicentre, case-control, population-based study. Genotyping for Y165C and G382D was performed and single-stranded conformation polymorphism analysis was performed in heterozygotes to screen for mutations in the entire gene. Biallelic and monoallelic MYH mutations were found in 8 (0.7%) and 19 (1.7%) of 1 116 CRC patients, respectively. None of the 934 control subjects carried biallelic mutations, whereas 22 (2.3%) of them were monoallelic carriers. Biallelic MYH mutation carriers had an unequivocal increased CRC risk in relation to non-mutation carriers (p=0.009, no OR as no events in control group). MYH mutations were not associated with an increased risk of developing CRC (OR: 0.72; 95%CI: 0.39–1.33; p=0.30). In the same publication they also did a meta-analysis including all previous case-control studies, monoallelic MYH carriers were not at increased risk for CRC (OR: 1.11; 95%CI: 0.90-1.37), although a significant association was found with the Y165C mutation in either homozygotes or heterozygotes (OR: 1.67; 95%CI: 1.17-2.40).

Kury et al. (2007)[26] screened 1 024 French sporadic colorectal cancer cases and 1 121 French healthy controls for Caucasian MUTYH-associated polyposis mutations, including already known mutations p.Gly382Asp and p.Tyr165Cys, and new mutation p.Val479Phe. They observed a non-statistically significant association between these MUTYH mutations at a heterozygous state and an increase in colorectal cancer risk (OR: 1.26, 95%CI: 0.70-2.27). They concluded that heterozygous MUTYH mutations do not play a major role in sporadic colorectal carcinogenesis although a modest effect on this process cannot be ruled out.

Cleary et al. (2008)[27] compared a total of 3 811 CRC cases and 2 802 controls collected from a multisite CRC registry who were screened for 9 germline MYH mutations; subjects with any mutation underwent screening of the entire MYH gene. Logistic regression was used to estimate age- and sex-adjusted odds ratios. They found twenty-seven cases and 1 control subject who carried homozygous or compound heterozygous MYH mutations (age- and sex-adjusted OR: 18.1; 95%CI: 2.5–132.7). Heterozygous MYH mutations were identified in 87 CRC cases and 43 controls; carriers were at increased risk of CRC (age- and sex-adjusted OR: 1.48; 95%CI: 1.02–2.16).

Jones et al. (2009)[28] performed a retrospective study of cancer incidence and causes of death among obligate MUTYH heterozygote individuals. MAP index cases were identified from polyposis registers in Germany, The Netherlands, and the United Kingdom. Cancer incidence, cancer mortality, and all-cause mortality data were collected from 347 parents of unrelated MAP index cases and the spouses of 3 index cases who were also found to be heterozygous for single MUTYH mutations. These data were compared with appropriate national sex-, age-, and period-specific population data to obtain standardized mortality ratios (SMR) and standardized incidence ratios (SIR). They found a 2-fold increase in the incidence of colorectal cancer among parents of MAP cases, compared with the general population (SIR: 2.12; 95%CI:: 1.30–3.28). Their colorectal cancer mortality was not increased significantly (SMR: 1.02; 95%CI: 0.41–2.10) nor was overall cancer risk (SIR: 0.92; 95%CI: 0.70–1.18), cancer mortality (SMR: 1.12; 95%CI: 0.83–1.48), or overall mortality (SMR: 0.94; 95%CI: 0.80–1.08).

Lubbe et al. (2009)[29] analyzed a population-based series of 9 268 patients with CRC and 5 064 controls for the Y179C and G396D MUTYH mutations. They related genotypes to phenotype and calculated genotype-specific CRC risks. They found that overall, biallelic mutation status conferred a 28-fold increase in CRC risk (95%CI: 17.66-44.06); this accounted for 0.3% of CRCs in the cohort. Genotype relative risks of CRC were strongly age dependent, but penetrance was incomplete at age 60 years. Monoallelic mutation was not associated with an increased CRC risk (OR: 1.07; 95%CI: 0.87-1.31).

Theodoratou et al. (2010)[30] did an individual-based meta-analysis of around 15 studies (some studies completely or partially overlapped, making giving an exact number difficult), including the above mentioned case control studies, including 20 565 cases and 15 524 controls.

MUTYH bi-allelic carriers demonstrated a 28-fold increase in risk (95%CI: 6.95–115). Significant bi-allelic effects were also observed for G396D and Y179C/G396D compound heterozygotes and a marginal mono-allelic effect for variant Y179C (OR:1.34; 95%CI: 1.00–1.80). A pooled metaanalysis of all published and unpublished datasets submitted showed bi-allelic effects for MUTYH, G396D and Y179C (OR:10.8, 95%CI: 5.02–23.2; OR:6.47, 95%CI: 2.33–18.0; OR: 3.35, 95%CI: 1.14–9.89) and marginal mono-allelic effect for variants MUTYH (OR:1.16, 95%CI: 1.00–1.34) and Y179C alone (OR:1.34, 95%CI: 1.01–1.77).

They confirm that biallelic mutation status is associated with a strongly increased CRC risk. The evidence on a link betwee monoallelic mutation is conflicting, some studies show a modest increase while others do not find an increased risk.

Conclusions

MUTYH bi-allelic carriers have strongly increased CRC risk. The evidence on a link between monoallelic mutation is conflicting, with studies showing a modest increase while others do not find an increased risk.

Recommendations
It is preferable that first-degree family members of patients with classic adenomatous polyposis and a pathogenic APC mutation are referred for genetic counseling at the age of 10-12 years. If a clinical picture characteristic of attenuated familial adenomatous polyposis (AFAP) is seen with multiple family members, this may take place at a later age (young adult age). If a pathogenic APC mutation is found in the index patient, genetic testing is recommended as it may provide a decisive answer for all family members in relation to risk of the disorder. Children of mutation carriers have a 50% chance of the genetic predisposition to (A)FAP.
In the case of a person with MAP (biallelic MUTYH mutations), all brothers and sisters of this person should be referred for genetic evaluation given they have a 25% chance of a genetic predisposition. The a priori chance of MAP in a child of a patient with MAP is <1%, given the other parent has a small risk (± 2%) of being a carrier of a MUTYH mutation as well. To determine the risk for potential children of a patient with MAP, it is advised that MUTYH mutation testing is performed on the other parent. If the other parent is shown to be a mutation carrier, the children have a 50% chance of biallelic MUTYH mutations.
All patients under the age of 60 years with >10 adenomas cumulatively, should be referred for genetic counseling. Exceptionally, referral for genetic analysis should also be considered for young persons with <10 adenomas (high grade dysplasia). In persons ≥60 years of age with more than 10 adenomas cumulatively genetic testing should be considered in case of positive family history of multiple adenomas.
Periodic endoscopic examination is recommended in the following patients: • Patients with FAP, AFAP, MAP or 'adenomatous polyposis of unknown origin.' • Persons with a pathogenic APC mutation • Persons with biallelic pathogenic MUTYH mutations • Risk carriers: first-degree family members of patients with adenomatous polyposis where the disorder cannot be confirmed by mutation analysis because a pathogenic mutation has not been found in the index patient • Risk carriers: first-degree family members of mutation carriers, who have not (yet) been tested themselves. Classic FAP: in mutation carriers or risk carriers of classic FAP; yearly surveillance using sigmoidoscopy is recommended from the age of 10-12 AFAP or MAP: in mutation carriers or risk carriers of AFAP or MAP, surveillance using colonoscopy is recommended once a year or every two years from the age of 18.
Participation of patients in the FAPA registry[c] is recommended and should be offered to patients concerned.
APC mutation carriers should be screened for extracolonic manifestations.

[c] Familial Adenomatous Polyposis Association, see Appendix 1

6 IMPLEMENTATION AND UPDATING OF THE GUIDELINE

6.1 Implementation

6.1.1 Multidisciplinary approach

In this report we focused on the effectiveness of specific diagnostic interventions. In clinical practice, a multidisciplinary approach by different health care professionals should be encouraged. This approach should not only cover the medical needs of the patient but also their psychosocial needs.

6.1.2 Patient-centered care

The choice of an intervention, e.g. germline mutation analysis, should not only consider medical aspects but also patient preferences. Patients should be well and timely informed about all options and the advantages and disadvantages they offer.

6.1.3 Barriers and facilitators for implementation of this guideline

During the stakeholders meeting, the potential barriers and facilitators related to the use of this guideline were discussed. Especially the need for pre-test and post-test counseling was discussed. Possible quality issues with immunohistochemistry tests were identified and solutions were discussed.

6.1.4 Actors of the implementation of this guideline

Clinical guidelines provide a tool for physicians to consult at different stages of the patient management pathway: screening, diagnosis, treatment and follow-up. They are developed according to codified principles, based on scientific information regularly updated from the international literature. KCE formulates recommendations addressed to specific audiences (clinicians, decision-makers, sickness funds, RIZIV – INAMI , professional organizations, hospital managers...). KCE is not involved in the decision making process itself, or in the execution of the decisions.

The implementation of this guideline will be facilitated by tools developed the College of Human Genetics and the College of Oncology. In addition, the content of this guideline is intended to be disseminated to caregiver groups by scientific and professional organisations using diverse channels such as websites and sessions of continuing education.

6.2 Monitoring the quality of care

This guideline should be considered as a starting point to develop quality improvement programs that target all caregivers concerned.

It can be used as a tool to support health policies to improve the quality of care, e.g. through the support of actions to increase caregivers' awareness and to improve their practice, or through the development (or revision) of sets of process and outcome quality indicators.

The obligatory yearly registrations to the RIZIV – INAMI of genetic testing activities (including numbers of cases identified) to the RIZIV – INAMI (Article 33) can be a useful source to monitor the activity and a possible impact of guideline implementation.

6.3 Guideline update

In view of the rapidly evolving evidence, especially with regard to genetic testing capabilities, the clinical introduction of the routine analysis of a broad panel of germline DNA in at risk subjects will be monitored by the authors and this guideline should be updated when sufficient clinical evidence is available justifying its routine use. If, in the meantime, important new evidence would become available, this should be taken into consideration.

APPENDICES

APPENDIX 1. SEARCH STRATEGIES

Appendix 1.1. MSI-Lynch

- G.I.N. guideline resource (http://www.g-i-n.net) 15 hits one identified
- National Guideline Clearinghouse http://www.guideline.gov/ 29 hits 3 identified

The Cochrane Database of systematic reviews (http://www.cochrane.org) 35 hits 0 results

Date	20 July 2013
Database	Medline through OVID
Search Strategy	1 lynch syndrome.mp. or exp Colorectal Neoplasms, Hereditary Nonpolyposis/ (3708) 2 (MLH1 or MSH2 or MSH3 or MSH6 or hMSH2 or hMSH1 or hPMS1 or hPMS2 or hMSH6 or hMLH3 or PMS1 or PMS2).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (5820) 3 HNPCC.mp. (2042) 4 (lynch$ adj3 syndrome).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1252) 5 ((lynch$ adj3 famil$) and (cancer$ or neoplasm$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (217) 6 hereditary non-polyposis Colorectal Cancer.mp. (877) 7 hereditary nonpolyposis Colorectal Cancer.mp. (1432) 8 (hereditary adj3 nonpolyposis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (4011) 9 (hereditary adj3 non-polyposis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1140) 10 (familial adj3 nonpolyposis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (15) 11 (familial adj3 non-polyposis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (20) 12 (colon or colorectal or lynch$ or HNPCC or hereditary).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (276022) 13 2 and 12 (3158) 14 1 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 13 (5863) 15 microsatellite instability.mp. or exp Microsatellite Instability/ (5546) 16 exp Genetic Testing/ or genetic test.mp. or exp

	Government Regulation/ or exp Genetic Predisposition to Disease/ (129253) 17 15 or 16 (134240) 18 14 and 17 (3021)

Date	**19 July 2013**
Database	Embase
Search Strategy	##18. 'microsatellite instability'/exp AND 'colorectal cancer'/exp AND ('genetic predisposition'/exp OR 'genetic screening'/exp OR 'gene mutation'/exp OR 'gene amplification'/exp OR 'molecular diagnosis'/exp OR 'nucleotide sequence'/exp) 1,602 19 Jul 2013 #17. 'hereditary nonpolyposis colorectal cancer'/exp AND ('genetic predisposition'/exp OR 'genetic screening'/exp OR 'gene mutation'/exp OR 'gene amplification'/exp OR 'molecular diagnosis'/exp OR 'nucleotide sequence'/exp) 1,022 19 Jul 2013 #16. 'genetic predisposition'/exp OR 'genetic screening'/exp OR 'gene mutation'/exp OR 'gene amplification'/exp OR 'molecular diagnosis'/exp OR 'nucleotide sequence'/exp 1,213,958 19 Jul 2013 #15. 'nucleotide sequence'/exp 412,959 19 Jul 2013 #14. 'molecular diagnosis'/exp 4,057 19 Jul 2013 #13. 'gene amplification'/exp 522,981 19 Jul 2013 #12. 'gene mutation'/exp 402,152 19 Jul 2013 #11. 'genetic screening'/exp 41,339 19 Jul 2013 #10. 'genetic predisposition'/exp 77,209 19 Jul 2013 #9. 'hereditary nonpolyposis colorectal cancer'/exp 4,107 19 Jul 2013 OR ('microsatellite instability'/exp AND 'colorectal cancer'/exp) #8. 'microsatellite instability'/exp AND 'colorectal cancer'/exp 2,512 19 Jul 2013 #7. 'colorectal cancer'/exp 72,385 19 Jul 2013 #4. 'microsatellite instability'/exp 6,831 19 Jul 2013 #2. 'hereditary nonpolyposis colorectal cancer'/exp 1,870 19 Jul 2013

Appendix 1.2. FAP

- G.I.N. guideline resource (http://www.g-i-n.net) 15 hits one identified
- National Guideline Clearinghouse http://www.guideline.gov/ 29 hits 2 identified

Date	Week 4 September 2013
Database	MEDLINE through OVID
Search Strategy	1 familial adenomatous polyposis.mp. or exp Adenomatous Polyposis Coli/ (6390) 2 limit 1 to yr="2007 -Current" (1632)
Database	Embase
Search Strategy	#2. 'familial adenomatous polyposis'/exp OR 'familial 1,789 25 Sept 2013 adenomatous polyposis' AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py) #1. 'familial adenomatous polyposis'/exp OR 'familial 5,650 25 Sept 2013 adenomatous polyposis'

Study	Reason for exclusion
Heald et al, 2013	Mix of strategies used over time, results of MSI and IPH testing not reported separately, no family history so Bethesda or othe criteria could not be evaluated.
Van Lier, 2013	results of MSI and IPH testing not reported separately, no family history so Bethesda or othe criteria could not be evaluated.
jerz et al 2013	MSI not consecutive, MSI or IPH, not in paralell
Schofield 2013	only 2/3 of MSI/IHP suspected BRAF negative patients was tested for germline mutation.
Musulen 2012	only abstract available

APPENDIX 2. EVIDENCE TABLES

Appendix 2.1. Systematic reviews on predictive value MSI status

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Des Guetz, 2009	• Design: SR and MA • Sources of funding: not mentioned • Search date: 2009 • Searched databases: Medline embase Cochrane ASCO annual proceedings • Included study designs: RCT • Number of included studies: 7	• Eligibility criteria: Patients for colorectal cancer stage II and III	• Intervention: receiving adjuvant treatment • Comparator: • No adjuvant treatment • Role of MSI in effectivness	HR RFS: 0.96 (95% confidence interval (CI): 0.62– 1.49); HR OS (6 studies): 0.70 (95% CI: 0.44–1.09; p = 0.12).	• They found a significant interaction between MSI status (MSI-H or MSS) and therapeutic status suggesting a lesser benefit for MSI-H than for MSS patients (HR interaction RFS: 0.77 (95% CI: 0.67–0.87)).	• No double selection.
Des Guetz, 2009,	• Design: SR and MA • Sources of funding: not mentioned • Search date: 2009 • Searched databases:	• Eligibility criteria: Patients for Metastatic colorectal cancer	• Intervention: 5FU based chemotherapy and combination therapy • Comparator: • No therapy	The global hazard ratio (HR) for RR was 0.82 (95% confidence interval, CI: 0.95; 0.65-1.03; p=0.09)	• Effect size secondary outcome	• No double assessment selection • Pooling of rather heterogeneous studies

	Medline embase Cochrane ASCO annual proceedings • Included study designs: RCT • Number of included studies: 6		• Role of MSI in effectivness			

Appendix 2.2. Cohort studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Canard, 2012	• Design: prospective cohort study • Sources of funding: not mentioned • 1,040 patients	• Eligibility criteria: Patients for colorectal cancer	• IHC for loss of MMR proteins • MSI • MMR sequencing on positive patients • Promoter methylationwas assessed in tumors with a loss of MLH1 expression	Sensitivity of IHC and MSI testing for detecting identifiedLS patients were, respectively, 92% (23 of 25) and 84% (21 of 25). After exclusion of patients not tested for an MMR mutation, the positive predictive value of IHC and MSI testing were 29.1% (23 of 79) and 27.3% (21 of 77),respectively.	• 12% of the patients with proven LS and 37.1% of the patients with possible LS did not fulfil the revised Bethesda criteria; moreover, a restriction of screening to patients younger than 50 years would havemissed about half of patients with proven LS.	• Prospective cohort with all patients tested for reference and screening test
Moreira, 2012	• Design: prospective cohort study • Sources of funding: not mentioned • 10 019	• Eligibility criteria: Patients for colorectal cancer	• IHC for loss of MMR proteins or MSI • MMR sequencing on positive patients	312 (3.1%) were MMR gene mutation carriers. In the population-based cohorts (n = 3671 probands), the universal screening approach (sensitivity, 100%; 95%	• 12% of the patients a selective strategy based on tumor MMR testing of cases with CRC diagnosed at age 70 years or younger and in older patients	• No comparison MSI or IHC possible, only sensitivity of Bethesda criteria compared to

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	patients underwent tumor MMR testing			CI, 99.3%-100%; specificity, 93.0%; 95% CI, 92.0%-93.7%; diagnostic yield, 2.2%; 95% CI, 1.7%-2.7%) was superior to the use of Bethesda guidelines (sensitivity, 87.8%; 95% CI, 78.9%-93.2%; specificity, 97.5%; 95% CI, 96.9%-98.0%; diagnostic yield, 2.0%; 95% CI, 1.5%-2.4%; P <.001),	fulfilling the Bethesda guidelines (sensitivity, 95.1%; 95% CI, 89.8%-99.0%; specificity, 95.5%; 95% CI, 94.7%-96.1%; diagnostic yield, 2.1%; 95% CI, 1.6%-2.6%; P < .001). This selective strategy missed 4.9% of Lynch syndrome cases but resulted in 34.8% fewer cases requiring tumor MMR testing and 28.6% fewer cases undergoing germline mutational analysis than the universal approach.	universal testing.
Perez-Carbonell, 2012	• Design: prospective cohort study • Sources of funding: not mentioned • 2093 patients	• Eligibility criteria: Patients for colorectal cancer	• IHC for loss of MMR proteins or MSI • MMR sequencing on positive patients	• Of the 14 (0.7%) patients who had a MMR gene mutation, 12 fulfilled at least one of the revised Bethesda criteria and two (14.3%) did not	• 80 patients (8.6%) showed loss of expression of some of the MMR proteins and/or MSI. Four hundred and eighty-six patients (23.2%) met some of the revised Bethesda criteria.	• No comparison MSI or IHC possible, only sensitivity of Bethesda criteria compared to universal testing.

Appendix 2.3. Observational studies MAP

Study ID	Method	Patient characteristics	Risk factor	Results	Critical appraisal
Balaguer et al., 2007 [25]	• Design: prospective, multicenter, matched case-control, • population-based study • Sources of funding: Supported by grants from the Fondo de Investigación, from the Instituto de Salud Carlos III from the Ministerio de Educación y Ciencia and from Merck, Co.,Germany) 1116 CRC patients, 934 control subjects	• Eligibility criteria: • Cases: Patients with colorectal cancer • Control: Age- and sex-matched control subjects with no personal history of cancer at the time of ascertainment were recruited from a large cohort of individuals attending the outpatient clinics of orthopedic surgery departments of participating institutions.	Genotyping for Y165C and G382D was performed by TaqMan technology. Single-stranded conformation polymorphism analysis was performed in heterozygotes to screen for mutations in the entire gene. All individuals were re-screened for any additionalpathogenic variant.	• Biallelic and monoallelic MYH mutations were found in 8 (0.7%) and 19 (1.7%) of 1116 CRC patients, respectively. None of the 934 control subjects carried biallelic mutations, whereas 22 (2.3%) of them were monoallelic carriers. • Biallelic MYH mutation carriers had an unequivocal increased CRC risk in relation to non-mutation carriers (P=0 .009). Quantification of this risk was not feasible becauseno control subject was homozygote for any MYH mutation • *monoallelic MYH mutations were not associated with an increased risk of developing* CRC (OR, 0.72;95% CI, 0.39 –1.33; P=0.30)	• Matched case control study, residual confounding and selection bias cannot be ruled out though
Kury et al.2007[26]	• Design: case-control, • cancer cases and 1121 French healthy controls	• Eligibility criteria: • Cases: Patients with colorectal cancer • Control: healthy persons of	• MUTYH-associated polyposis mutations, including already known mutations p.Gly382Asp and	• nonstatistically significant association between these MUTYH mutations at a heterozygous state and an increase in colorectal cancer risk (odds ratio [OR] 1.26, 95% confidence interval [CI] 0.70-2.27)	• case control study, residual confounding and selection bias cannot be ruled out though

Study ID	Method	Patient characteristics	Risk factor	Results	Critical appraisal
		French nationality	p.Tyr165Cys, and new mutation p.Val479Phe		
Cleary et al., 2008[27]	• Design: prospective, multicenter, matched case-control, • population-based study • Sources of funding: National Cancer Institute, National Institutes of Health under RFA #CA-95-011, the Ontario Registry for Studies of Familial Colorectal Cancer (U01 CA074783), and through cooperative agreements with members of the Colon Cancer Family Registry (CFRs) and P.I.s, and the National	• Eligibility criteria: • CRC cases aged 18–59 years identified through the Victoria Cancer Registry; • Control: controls were selected though electoral • Setting: Ontario, Canada; elbourne, Australia; and Seattle, WA, USA	• Cases and controls were screened for 12 known MYH mutations: G382D, Y165C, 1103delC, 891 + 3A ¨C, 466X,1395delGGA, Q377X, R260Q, Y90X, R227W 1186_7insGG, VS12-2A ¨G	Twenty-seven cases and 1 control subject carried homozygous or compound heterozygous MYH mutations (AOR, 18.1; 95% confidence interval, 2.5–132.7). CRC cases with homozygous/compound heterozygous mutations were younger at diagnosis (P = .01), had a higher proportion of right-sided (P = .01), synchronous cancers (P < .01), and personal history oadenomatous polyps (P = .003). Heterozygous MYH mutations were identified in 87 CRC cases and 43 controls; carriers were at increased risk of CRC (AOR, 1.48; 95% confidence interval, 1.02–2.16).	Matched case control study, Adjustment for study site and familial risk epidemiologic variables (CFR site, family history, nonsteroidal anti-inflammatory drug use, calcium supplementation, smoking status, inflammatory bowel disease, and red meat and vegetable intake) as potential confounder

Study ID	Method	Patient characteristics	Risk factor	Results	Critical appraisal
	Cancer Institute of Canada • 3811 CRC cases and 2802 controls				
Jones et al., 2009 [28]	• Design: Retrospective cohort study • Cancer Research Wales, the Wales Office of Research and Development through the Wales Gene Park, German Cancer Aid (Deutsche Krebshilfe e.V. Bonn, grant No. 106244) and the Dutch Digestive Diseases Foundation (grant No. MWO 0355) cancer • 347 parents of unrelated MAP index cases	• Eligibility criteria: • obligate *MUTYH* heterozygote parents of the MAP index cases and on 3 spouses of MAP patients who were also identified as heterozygote individuals because their offspring were affected by MAP	• *MUTYH* heterozygote parents of the MAP index cases	• There was a 2-fold increase in the incidence of colorectal cancer among parents of MAP cases, compared with the general population (SIR, 2.12; 95% confidence interval [CI]: 1.30–3.28). Their colorectal cancer mortality was not increased significantly (SMR, 1.02; 95% CI: 0.41–2.10) nor was overall cancer risk (SIR, 0.92; 95% CI: 0.70–1.18), cancer mortality (SMR, 1.12; 95% CI: 0.83–1.48), or overall mortality (SMR, 0.94; 95% CI: 0.80–1.08).	• Retrospecive cohort study, general population used as comparison group
Lubbe et al.,	• Design:, case-control,	• Eligibility criteria: • Cases: Patients	• Y179C and G396D MUTYH	• Overall, biallelic mutation status conferred a 28-fold increase in CRC risk (95% CI,17.66 to	• case control study, residual

Study ID	Method	Patient characteristics	Risk factor	Results	Critical appraisal
2009[29]	• Sources of funding: Cancer Research UK, CORE, the National Cancer Research Network and the European Union (CCPRB); by Grant No. QLG2-CT-2001-01861 from the Cancer Research UK, CORE, and the European Commission; by Cancer Research UK (PhD studentship, S.L.); by NCRN; and by NHS funding to the NIHR Biomedical Research Centre • 9 268 patients with CRC and 5 064 controls	with colorectal cancer • Control: subjects with no personal history of cancer at the time of ascertainment	mutations	44.06); this accounted for 0.3% of CRCs in the cohort. Genotype relative risks of CRC were strongly age dependent, but penetrance was incomplete at age 60 years. CRC that developed in the context of biallelic mutations were microsatellite stable. Biallelic mutation carriers were more likely to have proximal CRC (P = 4.0 x 10(-4)) and synchronous polyps (P = 5.7 x 10(-9)) than noncarriers. The performance characteristics of clinicopathologic criteria for the identification of biallelic mutations are poor. Monoallelic mutation was not associated with an increased CRC risk (odds ratio, 1.07; 95% CI, 0.87 to 1.31).	confounding and selection bias cannot be ruled out though
Theodoratou et al.2010 [30]	• Design: Indivdual based	• Eligibility criteria: • Cases: Patients	• bi-allelic and mono-allelic MUTYH	MUTYH bi-allelic carriers demonstrated a 28-fold increase in risk (95%confidence interval (CI):	• Includes all above described case

Study ID	Method	Patient characteristics	Risk factor	Results	Critical appraisal
	meta- analysis of case control studies Cancer Research UK,TK is funded by the Foundation Dr Henri Dubois-Ferriere Dinu Lipatti. The work in France was supported by a regional Hospital Clinical esearch Program, the Regional Council of Pays de laLoire, the Groupement des Entreprises Franc¸aises dans la LUtte contre le Cancer, the Association Anne de Bretagne Génétique and the Ligue Régionale Contre le Cancer. The work in Stockholm was supported by The Swedish Cancer Society, The Swedish Research council and The	with colorectal cancer • Control: subjects with no personal history of cancer at the time of ascertainment	variants • adjusted for age, sex and study	6.95–115). Significant bi-allelic effects were also observed for G396D and Y179C/G396D compound heterozygotes and a marginal mono-allelic effect for variant Y179C (odds ratio (OR)¼1.34; 95% CI: 1.00–1.80). A pooled metaanalysis of all published and unpublished datasets submitted showed bi-allelic effects for MUTYH, G396D and Y179C (OR¼10.8, 95% CI: 5.02–23.2; OR¼6.47, 95% CI: 2.33–18.0; OR¼3.35, 95% CI: 1.14–9.89) and marginal mono-allelic effect for variants MUTYH (OR¼1.16, 95% CI: 1.00–1.34) and Y179C alone (OR¼1.34, 95% CI: 1.01–1.77)	control studies

Study ID	Method	Patient characteristics	Risk factor	Results	Critical appraisal
	Stockholm Cancer Foundation. The work in Spain was supported by the Ministerio de Educación y Ciencia (SAF09-7319), Spanish Networks Instituto de Salud Carlos III grants (CIBERESP) 20 565 cases and 15 524 controls				

APPENDIX 3. FAPA (FAMILIAL ADENOMATOUS POLYPOSIS ASSOCIATION)

Taken from the website http://www.belgianfapa.be Dutch and French

Appendix 3.1. Dutch:

Appendix 3.1.1. Historiek

FAPA is een vzw die werd opgericht op 25 mei 1993. De stichtende leden vertegenwoordigen de 7 universiteiten van ons land en de verschillende medische disciplines die rechtstreeks met polypose te maken hebben. Ondertussen werken ook vele andere, niet-universitaire ziekenhuizen mee aan het nationale register.

Deze vereniging werd opgericht om artsen te helpen bij het informeren van hun polyposepatiënten en hun families over de risico's, de screeningsmogelijkheden en de behandelingen die mogelijk zijn. De informatie van het register dat zij beheert zal clinici, wetenschappers en epidemiologen toelaten FAP-families beter op te volgen, te begeleiden en te behandelen.

In 1996 werd een coördinerende verpleegkundige door FAPA aangeworven om zich met de dagelijkse werking van de vereniging bezig te houden. In 2008 werd de werking van de FAPA uitgebreid naar families met Lynch syndroom (HNPCC = erfelijke non-polyposis colorectale kanker). Momenteel staat een team van 3 gezondheidszorgmedewerkers in voor de dagelijkse werking van de vereniging.

Appendix 3.1.2. Doelstellingen

FAPA (Familial Adenomatous Polyposis Association) is een vzw met de volgende doelstellingen:

- FAPA heeft een register opgestart met als doel: alle families met FAP of Lynch syndroom (= HNPCC of erfelijke niet-polyposis dikkedarmkanker) erin op te nemen op een strikt anonieme wijze mee te werken aan klinisch, epidemiologisch en fundamenteel onderzoek zowel nationaal als internationaal
- FAPA informeert patiënten en hun familieleden met een risico op FAP of Lynch Syndroom over de aandoening
- FAPA staat dokters bij door families op te sporen en een regelmatige en blijvende opvolging van de patiënten op punt te stellen
- FAPA ondersteunt een zelfhulpgroep voor patiënten en hun familie

Appendix 3.2. French

Appendix 3.2.1. Historique

La FAPA est une asbl qui a été créée en 1993. Ses membres fondateurs représentent les 7 centres universitaires du pays et toutes les disciplines médicales directement concernées par la polypose adénomateuse familiale. Depuis sa création, l'association a élargi ses contacts à de nombreux centres hospitaliers non universitaires qui participent à l'élaboration du registre national.

Cette association a été créée spécifiquement pour aider les médecins à informer les patients porteurs de polypose et leur famille sur les risques, les possibilités de dépistage et le traitement à leur disposition. L'association gère un registre qui peut aider les cliniciens, les épidémiologistes et les scientifiques dans le suivi, l'accompagnement et le traitement des familles atteintes de FAP.

En 1996, une infirmière a été engagée par la FAPA pour s'occuper du fonctionnement quotidien de l'association. En 2008 la FAPA a élargi ses activités vers les familles atteintes du syndrome de Lynch (HNPCC = Cancer colorectal héréditaire sans polypose). Actuellement, une équipe paramédicale de 3 personnes assure le fonctionnement quotidien de l'association.

Appendix 3.2.2. Objectifs

La FAPA (Familial Adenomatous Polyposis Association) est une asbl dont les objectifs sont les suivants:

- La FAPA a créé un registre dont le but est: d'enregistrer, à titre anonyme, toutes les familles atteintes de FAP ou du syndrome de Lynch (= HNPCC ou cancer colorectal héréditaire sans polypose) de contribuer à la recherche scientifique, aussi bien sur le plan national qu'international
- La FAPA donne aux patients ainsi qu'à leur famille des informations concernant leur affection
- La FAPA apporte un support aux médecins pour dépister les familles concernées et pour élaborer un suivi régulier et de longue durée des patients
- La FAPA soutient le fonctionnement d'un groupe d'entraide pour les patients et leur famille

APPENDIX 4. CHANGES TO THE RECOMMENDATIONS MADE DURING THE PROJECT

Recommendations mailed to the guideline development group (external experts) and discussed at the meeting of 20 November 2013.

Recommendations Lynch
Investigation of all CRC (or individuals with CRC<70 years) by immunohistochemistry of the four MMR proteins or MSI is recommended.
These tests should be accompanied by methods that identify MLH1 promotor methylation.
Colonoscopic surveillance of confirmed Lynch syndrome patient with an interval between 1 and 2 years is recommended

Recommendations FAP
It is preferable that first-degree family members of patients with classic adenomatous polyposis and a pathogenic APC mutation are referred for genetic diagnostics at the age of 10-12 years. If a clinical picture characteristic of AFAP is seen with multiple family members, this may take place at a later age (young adult age). If a pathogenic APC mutation is found in the index patient, genetic testing may provide a decisive answer for all family members in relation to risk of the disorder. Children of mutation carriers have a 50% chance of the genetic predisposition to (A)FAP.
In the case of a person with MAP (biallelic MUTYH mutations), all brothers and sisters of this person should be referred for genetic evaluation given they have a 25% chance of a genetic predisposition. The a priori chance of MAP in a child of a patient with MAP is <1%, given the other parent has a small risk (± 2%) of being a carrier of a MUTYH mutation as well. To determine the risk for potential children of a patient with MAP, it is advised that MUTYH mutation testing is performed on the other parent. If the other parent is shown to be a mutation carrier, the children have 50% chance of biallelic MUTYH mutations.
All patients under the age of 60 years with cumulative >10 adenomas, should be referred for genetic evaluation. Referral for genetic analysis should also be considered for younger persons with <10 adenomas and persons ≥60 years of age with more than 10 adenomas.
Periodic endoscopic examination is recommended in the following patients: • Patients with the form of adenomatous polyposis FAP, AFAP, MAP or 'adenomatous polyposis of unknown origin.' • Persons with a pathogenic APC mutation • Persons with biallelic pathogenic MUTYH mutations • First-degree family members of patients with adenomatous polyposis where the disorder cannot be excluded by mutation analysis because a pathogenic mutation has not been found in the index patient • First-degree family members of mutation carriers, who have not (yet) been tested themselves.
Regular endoscopic surveillance is recommended in mutation carriers or risk carriers of classic FAP; twice yearly from the age of 10-12 using sigmoidoscopy.
Regular endoscopic surveillance is recommended in mutation carriers or risk carriers of AFAP or MAP; twice yearly from the age of 18 using colonoscopy.

Changes to the recommendations made at the stakeholders meeting, scores and comments

The left column gives the recommendations as formulated during the guideline development group meeting 20 November 2013.

Recommendations scored by stakeholders	Recommendations revised during stakeholder meeting	A	B	C	Comments (required if 1 or 2)
Lynch Syndrome					
	Patients considered at risk should be referred for genetic counseling, that may result in germline mutation analysis.				
Family history should be evaluated using a validated prediction model (e.g. PREMM) or the revised Bethesda criteria. High risk patients should be referred for genetic counseling, that may result in germline mutation analysis.	Family history should be evaluated using a validated prediction model (e.g. PREMM) or the revised Bethesda criteria.	5	4	4	Also patients without family history should be eligible for germline analysis
Investigation of all colorectal cancers by immunohistochemistry (IHC) of the four MMR proteins or by MSI is recommended. Especially in case of a positive family history (e.g. based on PREMM) both IHC and MSI should be performed if the first test is not conclusive.	Investigation of all colorectal cancers by immunohistochemistry (IHC) of the four MMR proteins or by MSI is recommended. Especially in case of a positive family history (e.g. based on PREMM) both IHC and MSI should be performed if the first test is not conclusive.	5	5	5	Patients should also be eligible for germline analysis with negative prior results
Immunohistochemistry and MSI tests should only be performed in laboratories that are ISO accredited for these tests.	Immunohistochemistry and MSI tests should only be performed in laboratories that are ISO accredited for these tests.	5	5	5	
In case germline mutation analysis is considered, these tests should be preceeded by MLH1 promotor methylation or BRAF mutation analysis. The decision to perform a germline mutation analysis should take into account these results as well as family history.	In case germline mutation analysis is considered solely after positive IHC for MLH1, germline mutation analysis should be accompanied by MLH1 promotor methylation or BRAF mutation analysis.	2	2	2	Test may be performed even if methyl or braf data missing // These analyses are specifically indicated if a MLH1 expression deficit (often in addition to a PMS2 deficit) is observed. Also, including this step will lengthen the turn around time for genetic testing: performing mutation analysis (especially with the perspective of NGS technology) might comprise a valuable option. // All patients should be eligible for germline testing.

Recommendations scored by stakeholders	Recommendations revised during stakeholder meeting	A	B	C	Comments (required if 1 or 2)
Patients with a positive immunohistochemistry or MSI result should be referred for genetic counseling, which may result in germline mutation analysis.	Patients with a positive immunohistochemistry or MSI result should be offered referral for genetic counseling, which may result in germline mutation analysis.	5	2	4	In some cases genetic counseling may be minimal, and/or should not delay analysis // Interval 1 year endometrial more than ovarian
In families in which the causal mutation is identified, predictive testing should be offered to all relatives from the age of 18 onwards and after genetic counseling.	In families in which the causal mutation is identified, predictive testing should be offered to all relatives from the age of 18 onwards and after genetic counseling.	5	5	5	
Surveillance of confirmed Lynch syndrome patients (including colonoscopy) with an interval between 1 and 2 years is recommended. Hysterectomy and bilateral oophorectomy largely prevents the development of endometrial and ovarian and is an option to be discussed with mutation carriers who have completed their families especially after the age of 40 years. Surveillance for endometrial cancer could be offered. The fact that benefit unproven however should be discussed.	Surveillance of confirmed Lynch syndrome patients (including colonoscopy) with a one year interval is recommended. Hysterectomy and bilateral oophorectomy largely prevents the development of endometrial and ovarian and is an option to be discussed with mutation carriers who have completed their families especially after the age of 40 years. The option of surveillance for endometrial cancer should be discussed with the patient. It should be mentioned that currently the benefit is unproven.	5	5	4	Surveillance for endometrial cancer should be offered. // Interval 1 year endometrial more than ovarian
In families with a strong family history but without molecular confirmation appropriate surveillance should be performed.	In families without molecular confirmation, surveillance should be based on family or personal history.	5	5	5	
Participation in the FAPA registry should be offered to the patients concerned.	Participation of patients in the FAPA registry is recommended and should be offered to patients concerned.	5	5	5	
It is preferable that first-degree family members of patients with classic adenomatous polyposis and a pathogenic APC mutation are referred for genetic counseling at the age of 10-12 years. If a clinical picture characteristic of AFAP is seen with multiple family members, this may take	It is preferable that first-degree family members of patients with classic adenomatous polyposis and a pathogenic APC mutation are referred for genetic counseling at the age of 10-12 years. Surveillance for hepatoblastoma is recommended between the age of 0 and 7. If a clinical picture characteristic of AFAP is seen	5	5	5	Mutation analysis can be offered at an earlier age, in view of the risk for hepatoblastoma in APC carriers.

Recommendations scored by stakeholders	Recommendations revised during stakeholder meeting	A	B	C	Comments (required if 1 or 2)
place at a later age (young adult age). If a pathogenic APC mutation is found in the index patient, genetic testing may provide a decisive answer for all family members in relation to risk of the disorder. Children of mutation carriers have a 50% chance of the genetic predisposition to (A)FAP.	with multiple family members, this may take place at a later age (young adult age). If a pathogenic APC mutation is found in the index patient, genetic testing may provide a decisive answer for all family members in relation to risk of the disorder. Children of mutation carriers have a 50% chance of the genetic predisposition to (A)FAP.				
In the case of a person with MAP (biallelic MUTYH mutations), all brothers and sisters of this person should be referred for genetic evaluation given they have a 25% chance of a genetic predisposition. The a priori chance of MAP in a child of a patient with MAP is <1%, given the other parent has a small risk (± 2%) of being a carrier of a MUTYH mutation as well. To determine the risk for potential children of a patient with MAP, it is advised that MUTYH mutation testing is performed on the other parent. If the other parent is shown to be a mutation carrier, the children have a 50% chance of biallelic MUTYH mutations.	In the case of a person with MAP (biallelic MUTYH mutations), all brothers and sisters of this person should be referred for genetic evaluation given they have a 25% chance of a genetic predisposition. The a priori chance of MAP in a child of a patient with MAP is <1%, given the other parent has a small risk (± 2%) of being a carrier of a MUTYH mutation as well. To determine the risk for potential children of a patient with MAP, it is advised that MUTYH mutation testing is performed on the other parent. If the other parent is shown to be a mutation carrier, the children have a 50% chance of biallelic MUTYH mutations. The clinical significance of the mutation should be taken into account.	5	4	5	
All patients under the age of 60 years with cumulative >10 adenomas, should be referred for genetic counseling. Referral for genetic analysis should also be considered for younger persons with <10 adenomas and persons ≥60 years of age with more than 10 adenomas.	All patients under the age of 60 years with cumulative >10 adenomas, should be referred for genetic counseling. Referral for genetic analysis should also be considered for younger persons with <10 adenomas. In persons ≥60 years of age with more than 10 adenomas genetic testing should be considered in case of positive family history of multiple adenomas.	5	4	2	Do not agree with age separation 60 years; relevance for family also!

Recommendations scored by stakeholders	Recommendations revised during stakeholder meeting	A	B	C	Comments (required if 1 or 2)
Periodic endoscopic examination is recommended in the following patients:	Periodic endoscopic examination is recommended in the following patients:	5		2	What about preventive surgery?
Patients with the form of adenomatous polyposis FAP, AFAP, MAP or 'adenomatous polyposis of unknown origin.'	Patients with the form of adenomatous polyposis FAP, AFAP, MAP or 'adenomatous polyposis of unknown origin.'		5		
Persons with a pathogenic APC mutation	Persons with a pathogenic APC mutation		5		
Persons with biallelic pathogenic MUTYH mutations	Persons with biallelic pathogenic MUTYH mutations		5		
First-degree family members of patients with adenomatous polyposis where the disorder cannot be confirmed by mutation analysis because a pathogenic mutation has not been found in the index patient	First-degree family members of patients with adenomatous polyposis where the disorder cannot be confirmed by mutation analysis because a pathogenic mutation has not been found in the index patient		5		
First-degree family members of mutation carriers, who have not (yet) been tested themselves.	First-degree family members of mutation carriers, who have not (yet) been tested themselves.		5		
Regular endoscopic surveillance is recommended in mutation carriers or risk carriers of classic FAP; yearly from the age of 10-12 using sigmoidoscopy.	Regular endoscopic surveillance is recommended in mutation carriers or risk carriers of classic FAP; yearly from the age of 10-12 using sigmoidoscopy.		4		
Regular endoscopic surveillance is recommended in mutation carriers or risk carriers of AFAP or MAP; yearly from the age of 18 using colonoscopy.	Regular endoscopic surveillance is recommended in mutation carriers or risk carriers of AFAP or MAP; once a year or every two years from the age of 18, using colonoscopy.		4		
Participation in the FAPA registry should be offered to patients concerned.	Participation of patients in the FAPA registry is recommended and should be offered to patients concerned.	5	5	5	
APC mutation carriers should be screened for extracolonic manifestations (gastroduodenal polyps, thyroid cancer...).	APC mutation carriers should be screened for extracolonic manifestations (gastroduodenal polyps, thyroid cancer,..).	5	5	5	

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