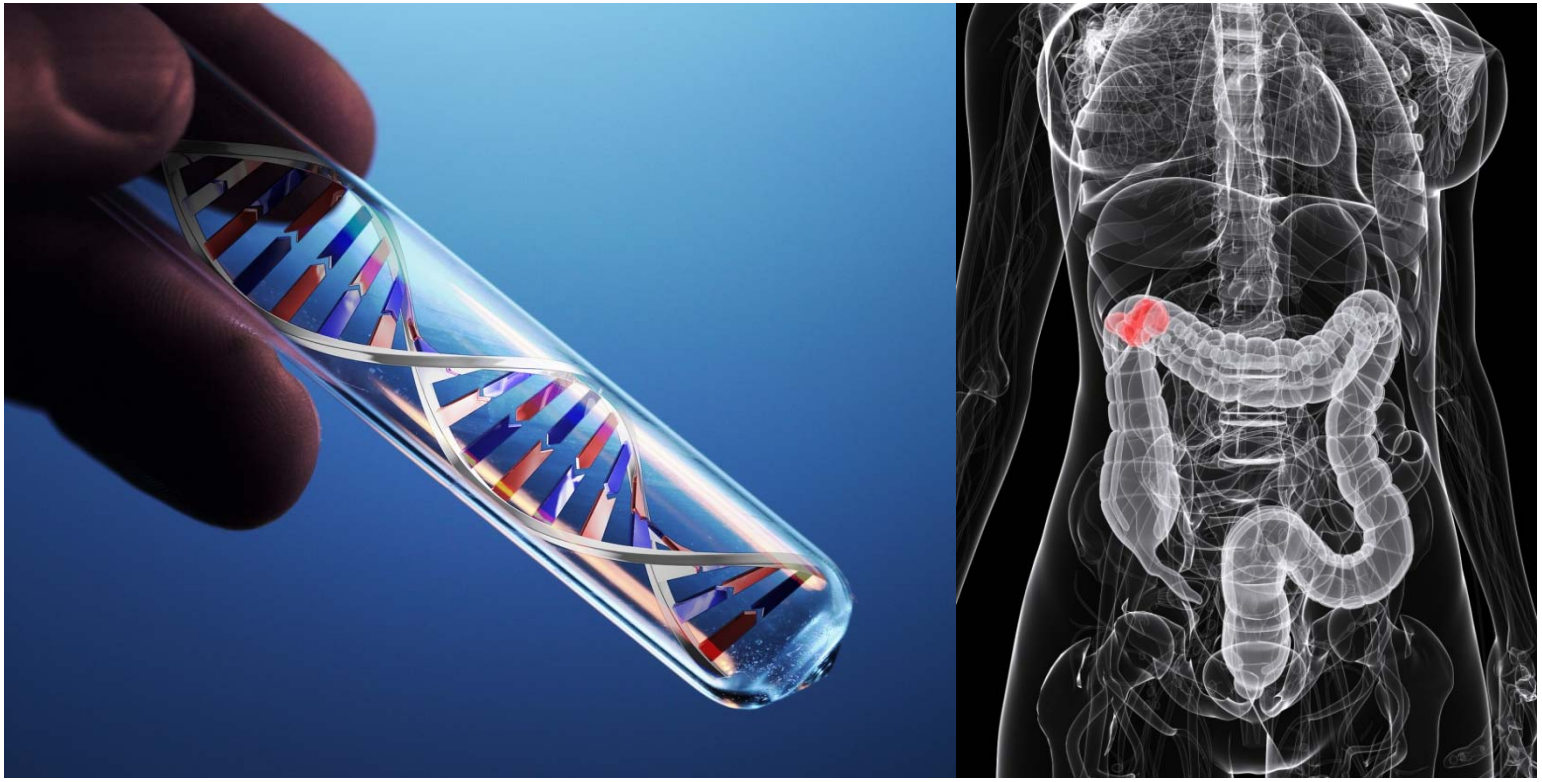
KCE REPORT 220Cs

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

ABSTRACT

ONCOGENETIC TESTING FOR LYNCH SYNDROME AND FAMILIAL ADENOMATOUS POLYPOSIS



Belgian Health Care Knowledge Centre

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GOOD CLINICAL PRACTICE

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ABSTRACT

ONCOGENETIC TESTING FOR LYNCH SYNDROME AND FAMILIAL ADENOMATOUS POLYPOSIS

JO ROBAYS, BRUCE POPPE

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COLOPHON

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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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FOREWORD

The ‘Human Genome Project’ started in 1990 with a budget of 3 billion dollar. The analysis of the human genome was completed in 2003, two years earlier than announced. Meanwhile sequencing techniques evolved rapidly. Illumina offers already a sequencer that can sequence a full genome for less than $ 1000. Also desktop genome sequencing is a reality. And we are not yet at the end of the evolution.

The evolution helps to make genetic information available for use in the routine clinical practice. This information can help predict the risk of future serious illnesses, not only for the patient but also for family members. This is for example the case for specific forms of colorectal cancer. After detection of the specific germline mutation, one can look for this mutation in family members, thus detecting an elevated risk for the specific type of colorectal cancer. The familiy members at risk can then be offered an appropriate periodic screening using colonoscopy or sigmoidoscopy, in order to detect and treat the cancer at an early stage.

Genetic tests are performed at centres for human genetics, after appropriate counseling. However, it is typically the oncologist who will see the patient with a newly diagnosed colon cancer. Therefore, it was crucial to bring together geneticists and oncologists for the development of this guideline.

These genetic tests exist for many years already and yet the know-how is not broadly spread. This report is a useful addition to the recently published practice guidelines for the diagnosis and treatment of colon cancer (KCE report 218). We thank the multidisciplinary group of external experts for their collaboration and scientific input.

While the possibilities of genetic diagnosis evolve rapidly, so does the risk for non appropriate use. This may lead to a further increase of the healthcare budget. Evidence based practice guidelines are therefore wanted. Talking about prediction: we predict more such oncogenetic guidelines are to follow.

Christian LÉONARD
Deputy general director

Raf MERTENS
General director

ABSTRACT

INTRODUCTION

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 of subjects at risk and their referral to genetic centres for counselling, possibly followed by germline mutation analysis.

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.

OBJECTIVES AND SCOPE OF THIS GUIDELINE

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

METHODS

Literature search

Independent searches were performed for Lynch syndrome and FAP. This is a general description of the strategy used and more details can be found in the report. Clinical practice guidelines were identified using OVID Medline, the National Guideline Clearinghouse (guideline.gov) and Guidelines International Network (www.g-i-n.net).

The retained guidelines were scored using the AGREE II instrument.

The update search for more recent peer-reviewed systematic reviews and primary studies included a search in OVID Medline, EMBASE, CENTRAL and the Cochrane Database of Systematic Reviews.

Quality appraisal

The quality of the systematic reviews was assessed using the AMSTAR checklist. For critical appraisal of randomized controlled trials, the Cochrane Collaboration's Risk of Bias Tool was used.

Data extraction and evidence summary

For each clinical question, the evidence base and recommendations were extracted from the selected guidelines and summarized in text form. The update consisted of new findings reported in additional systematic reviews or primary studies.

Formulation of recommendations

A guideline development group was constituted consisting of the authors and the external experts listed in the colophon. The evidence tables and draft recommendations were prepared by KCE and circulated to the guideline development group one week prior to the face-to-face meetings. Recommendations were changed if important new evidence supported this change. Based on the discussion at the first meeting a second draft of recommendations was prepared and once more circulated to the guideline development group for final approval. Due to current methodological limitations of the GRADE system for diagnostic tests, GRADE was not applied.

Subsequently, the draft recommendations were circulated to stakeholders (associations of physicians and patient organisations) 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. They acted as external reviewers of the draft guideline and rated all recommendations with a score ranging from 1 ('completely disagree') to 5 ('completely agree') and discussed them at a meeting.

Finally, the report was validated by three external validators, listed in the colophon. The validation meeting was chaired by CEBAM and took place December 20, 2013. In addition to a validation of the scientific content, the AGREE II checklist was also used in the validation process.

Declarations of interest of the external experts, stakeholders and validators are listed in the colophon.

CLINICAL RECOMMENDATIONS

The details of the evidence used to formulate the recommendations below are available in the scientific report and its appendices. The tables below follow the sequence of the chapters of the scientific report.

Lynch syndrome

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[a] is recommended and should be offered to patients concerned.

[a] Familial Adenomatous Polyposis Association

Familial adenomatous polyposis (FAP)

Recommendations
It is preferable that first-degree family members of patients with classic adenomatous polyposis and a pathogenic APC (adenomatous polyposis coli) 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 a 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[b] is recommended and should be offered to patients concerned.
APC mutation carriers should be screened for extracolonic manifestations.

[b] Familial Adenomatous Polyposis Association

ADDITIONAL CONSIDERATIONS

Genetic counselling, possibly followed by germline mutation analysis, has implications not only for the patient but also for the family of the patient. Hence, in addition to the medical aspects, patient preferences should be taken into account. Patients should be well and timely informed about all options and the advantages and disadvantages they offer.

During the stakeholders meeting, the need for pre-test and post-test counseling was stressed. It is clear that also oncologists have an important role to play in providing information to their patients and possibly the patient relatives.

Furthermore, successful implementation of these clinical recommendations also depends on the quality of the immunohistochemistry tests used to identify Lynch syndrome patients.

This guideline should be considered as a starting point to develop quality improvement programs that target all caregivers concerned. This includes actions to increase their awareness and improve the practice, and the development (or revision) of process and outcome quality indicators

Guideline update

There is a rapid evolution in the technical capabilities to perform multiple genetic tests. Therefore, the authors will monitor the clinical introduction of the routine analysis of a broad panel of germline DNA in at risk subjects. This guideline should be updated when sufficient clinical evidence has become available. In the meantime, important new evidence should be taken into consideration in the medical decision making.

RECOMMENDATIONS[c]

To the Technical Medical Council

- **Only clinically validated MSI and immunohistochemistry tests guiding Lynch syndrome identification should be used and reimbursed. They should be performed only in laboratories that participate to external quality assurance rounds and that are ISO accredited for these tests.**

To the College of Genetics and the College of Oncology

- **The implementation of this guideline should be facilitated by the College of Genetics and the College of Oncology, preferrably using a common set of (online) tools, e.g. on EBMPracticeNet**
- **The clinical introduction of the routine analysis of a broad panel of germline DNA in at risk subjects should be monitored. This guideline should be updated when sufficient clinical evidence has become available supporting this technology.**

To the associations of providers of care to these patients

- **This guideline should be disseminated through diverse channels such as websites or programmes of continuing education. The dissemination of this guideline can further be supported by transforming this material into attractive and user-friendly tools tailored to specific caregiver groups and patient associations.**

[c] The KCE has sole responsibility for the recommendations.