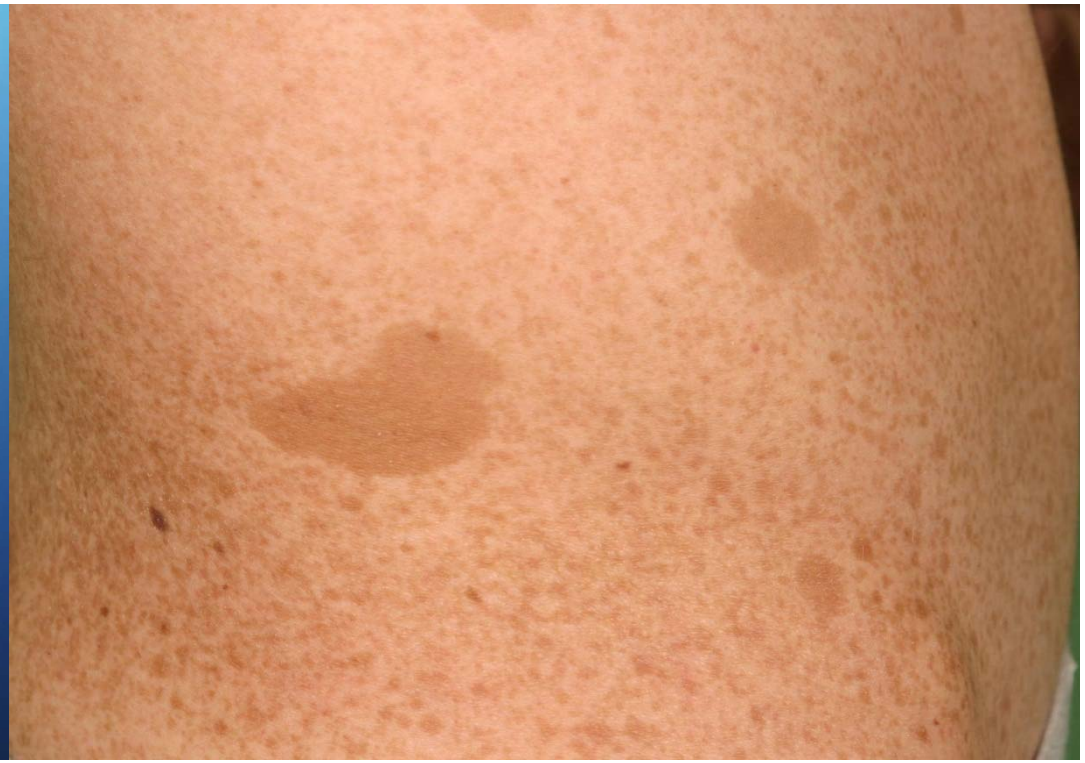
KCE REPORT 243Cs

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

SUMMARY

ONCOGENETIC TESTING, DIAGNOSIS AND FOLLOW-UP IN BIRT-HOGG-DUBÉ SYNDROME, FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA SYNDROME AND NEUROFIBROMATOSIS 1 AND 2



KCE REPORT 243Cs
GOOD CLINICAL PRACTICE

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ONCOGENETIC TESTING, DIAGNOSIS AND FOLLOW-UP IN BIRT-HOGG-DUBÉ SYNDROME, FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA SYNDROME AND NEUROFIBROMATOSIS 1 AND 2

JO ROBAYS, SABINE STORDEUR, FRANK HULSTAERT, JEAN-FRANÇOIS BAURAIN, LIEVE BROCHEZ, TEOFILA CAPLANUSI, KATHLEEN CLAES, ERIC LEGIUS, SYLVIE ROTTEY, DIRK SCHRIJVERS, DAPHNÉ T'KINT DE ROODENBEKE, URIELLE ULLMAN, TOM VAN MAERKEN, BRUCE POPPE

FOREWORD

This report is the fourth in a series of four practice guidelines on oncogenetic testing. After colon cancer, breast cancer and endocrine syndromes this guideline concerns a number of syndromes with a dermatological component, ranging from familial forms of malignant melanoma to multiple malformations as can be seen in some cases of neurofibromatosis. The genetic tests have in common that they have a major impact for the subject.

Publishing practice guidelines in a rapidly evolving field such as predictive medicine remains a challenge. First, the evidence for the predictive value and the clinical utility of many of these tests is still limited. Second, as it mainly concerns rare syndromes, the conduct of clinical research is difficult. Moreover, one runs the risk that by the time the practice guideline is published, other testing techniques and interventions are being proposed. Yet, it remains appropriate that at a given moment an independent body invests the time and means to summarize the current knowledge. Rapid evolutions typically go together with a broad variation in clinical practice. This makes it very complex for referring physicians to keep some oversight and this is even more the case for subjects concerned. In addition, such new fields of medicine may be claimed by multiple specialties, sometimes with a risk of polarisation. Finally, some of these tests are rather expensive, have a significant impact on the healthcare budget, and ask for a standardised evidence-based approach.

The subjects or patients concerned, often young people and their family, should however remain central to the discussion. With the appropriate counselling and use of such tests, individuals are better prepared to make informed decisions. We thank the many geneticists, dermatologists and oncologists who worked with us to produce this guideline.

Christian LÉONARD
Deputy general director

Raf MERTENS
General director

GLOSSARY

Family history	A family history of disease in an individual is the occurrence of the disease in a blood relative of that individual.
Gene	A gene is a molecular unit of heredity of a living organism.
Genetic counselling	A service delivered by a qualified health professional that provides a comprehensive evaluation of familial risk for inherited disorders using kindred analysis and other methods, patient education, discussion of the benefits and harms of genetic testing, interpretation of results after testing (consequences and nature of the disorder, probability of developing or transmitting it), and discussion of management options.
Genetic counsellor	A healthcare professional providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. If it is appropriate, they will discuss genetic testing, coordinate any testing, interpret test results, and review all additional testing, surveillance, surgical, or research options that are available to members of the family.
Genetic testing	Genetic testing is a type of medical test that identifies changes in chromosomes, genes, or proteins. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder.
Germline	The cells from which eggs or sperm (i.e., gametes) are derived.
Penetrance	A characteristic of a genotype; it refers to the likelihood that a clinical condition will occur when a particular genotype is present.
Relatives – First-degree relatives	These are the closest blood relatives (relatives by marriage do not count). These include father, mother, son, daughter, brother, sister.
Relatives – Second-degree relatives	These are blood related grandparents, grandchildren, uncle, aunt, nephews and nieces, half-brothers and half-sisters. They are on both the mother and father's side of the family.
Relatives – Third-degree relatives	These are blood related great grandparents, great grandchildren, great uncle, great aunt, first cousin, grand-nephew and grand-niece. They are on both the mother and father's side of the family.

SUMMARY

1. 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 which family members are at risk of developing specific forms of cancer when one member is diagnosed with a hereditary type of cancer. Criteria are needed for the identification and referral of patients to a centre of human genetics specialised in cancer genetics for counselling, possibly followed by germline mutation analysis.

This guideline is timely. Firstly because the new nomenclature, introduced on 1/1/2013, for genetic tests (article 33) and the agreement on genetic testing consultation led to distribute the RIZIV-INAMI budget between genetic counselling (€4.3 millions) and laboratory procedures (€37.8 millions). This new convention implies the development of genetic counselling activities by genetic centres. Secondly, there is a need to standardise the indications for oncogenetic testing based on the available evidence. Early identification of subjects at risk may lead to strategies such as enhanced surveillance, if supported by evidence.

The guideline is intended to be used by care providers involved in genetic counselling, testing and follow-up of patients with Birt-Hogg-Dubé syndrome, familial atypical multiple mole melanoma syndrome and neurofibromatosis 1&2. It also contains recommendations for persons that must decide when to refer for genetic counselling and testing such as general practitioners, paediatricians, dermatologists or surgeons, radiologists and pathologists.

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 is part of the short series of oncogenetic testing guidelines.

2. OBJECTIVES AND SCOPE OF THIS GUIDELINE

This guideline provides recommendations based on current scientific evidence for the identification and referral to genetic centres specialised in oncology of patients with the Birt-Hogg-Dubé syndrome, the familial atypical multiple mole melanoma syndrome and neurofibromatosis 1&2. These syndromes only have in common that dermatological manifestations are involved, but implications, risks and issues around testing and follow-up are very diverse. Patients are referred for counselling, possibly followed by germline mutation analysis. Clinicians are encouraged to interpret these recommendations in the context of the individual person/patient's situation, values and preferences.

All KCE guidelines are as much as possible based on clinical evidence. In case the clinical evidence is absent or very limited the recommendations are largely based on the opinion of experts in the field.

3. METHODS

3.1. Clinical research questions

The current guideline addresses the following clinical questions:

Among patients with suspicion of Birt-Hogg-Dubé syndrome or Familial atypical multiple mole melanoma syndrome or Neurofibromatosis 1 and Neurofibromatosis 2, either based on symptoms or family history:

- Who should undergo genetic testing?
- What type of follow-up should patients undergo, depending on test results and diagnosis?

3.2. Literature search

For each research question, a search for published guidelines was first performed to verify if high-quality, recent guidelines are available that address the clinical research questions. Clinical practice guidelines were identified using the National Comprehensive Cancer Network (NCCN) (http://www.nccn.org/), the National Guideline Clearinghouse (http://www.guideline.gov/), NICE guidelines (http://www.nice.org.uk) and the Guidelines International Network (www.g-i-n.net).

For each research question, a search for systematic reviews was conducted in MEDLINE, Embase and The Cochrane Library (Cochrane Database of Systematic Reviews, DARE and HTA database). If a recent high-quality systematic review was available, a search for primary studies published after the search date of the review was performed in MEDLINE and Embase. If no systematic review was available, a search for primary studies was performed in the same databases, without time restriction. Members of the guideline development group (GDG) were also consulted to identify additional relevant evidence that may have been missed by the search. The website 'Gene reviews' was consulted ad hoc for background information. It is however mainly based on expert opinion.

3.3. Quality appraisal

The retained guidelines were scored using the AGREE II instrument. 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.

3.4. 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.

3.5. Formulation of recommendations

A guideline development group was constituted consisting of the authors 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.

The report was validated by three external assessors, listed in the colophon. Their comments and questions were integrated into the report after discussion within the GDG.

Subsequently, the recommendations were circulated to stakeholders (associations of physicians and patient organisations) targeted by this guideline. Each association was asked to assign at least one key representative to review the draft guideline. All representatives and their association are listed in the colophon under the section stakeholders. They indicated for each recommendation within their field of expertise their agreement or disagreement and discussed them at a meeting. In case of disagreement with a specific recommendation they were expected to provide the scientific evidence supporting their point of view.

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

4. 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.

4.1. Birt-Hogg-Dubé syndrome

Birt-Hogg-Dubé syndrome (BHD) is an autosomal dominant condition. Skin fibrofolliculomas, pulmonary cysts, spontaneous pneumothorax, and renal cancer can occur. The BHD prevalence is estimated to be 1/200 000. To date, approximately 500 families have been reported worldwide.[1, 2 3]

Recommendations

- Referral to a specialist genetics clinic for counselling and testing should be considered based on personal and family history, whether the individual is affected or not.
- If possible, genetic testing for a family should usually start with the testing of an affected individual (mutation searching/screening) to try to identify a mutation in the relevant gene.

- Patients should be considered as a case of Birt-Hogg-Dubé syndrome if they fulfill one major or two minor criteria for diagnosis:

  Major criteria

  - At least five fibrofolliculomas or trichodiscomas, at least one histologically confirmed, of adult onset
  - Pathogenic FLCN germline mutation

  Minor criteria

  - Multiple lung cysts: bilateral basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax
  - Renal cancer in adults: early onset (<50 years) or multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology.
  - A first-degree relative with BHD

- The following patients should be referred for genetic testing and counseling:
  - Patients fulfilling the criteria for Birt-Hogg-Dubé syndrome mentioned above
  - Patients with multifocal or bilateral renal cancer

- Patients with renal cancer of mixed chromophobe and oncocytic histology
- Patients with renal cancer onset below 40 years of age with oncocytic histology
- Patients with unexplained cystic lung disease, and with lung cysts that are bilateral and basally located
- Patients who have familial cystic lung disease, familial pneumothorax or familial renal cancer,
- Patients with any combination of spontaneous pneumothorax and kidney cancer or with a family member presenting with this combination.
- Patients with a first-degree relative with BHD.

- Early detection of at-risk individuals affects medical management. However, in the absence of an increased risk of developing childhood malignancy, it is recommended to delay predictive genetic testing in at-risk individuals until they reach age 18 years and are able to make informed decisions regarding genetic testing.

For patients with confirmed BHD syndrome:

- Consider a yearly MRI of the kidney starting at age 20 to 25 years; if the MRI is not conclusive a CT scan may be required. Ultrasound is appropriate for the follow-up of lesions but is less sensitive than MRI and CT for screening purposes.
- Consider a low-dose high-resolution thoracic CT scan before surgery that requires general anaesthesia.
- Discourage smoking and scuba diving.

4.2. Familial atypical multiple mole melanoma syndrome

4.2.1. Introduction

Familial atypical multiple mole melanoma (FAMMM) syndrome is an autosomal dominant genodermatosis characterized by multiple melanocytic nevi, usually more than 50, and a family history of melanoma. In 60% of the cases it is associated with mutations in the CDKN2A gene. Some FAMMM kindreds show an increased risk for the development of pancreatic cancer and possibly other malignancies.

Globally, 5 to 10% of malignant melanomas would occur in familial clusters but variations in penetrance and expressivity of the genes involved, regional variations and the fact that only limited data are available make it difficult to have an accurate estimate of the prevalence of FAMMM.[4]

Recommendations

- Consider a patient as having FAMMM if all of the following criteria apply:
  - Malignant melanoma in one or more first- or second-degree relatives
  - High total body nevi count in the order of 50 or more, including some clinically atypical nevi

- Refer to a center for genetic counseling preferably an affected member of families with:
  - 2 first degree relatives with melanoma
  - 2 cases of melanoma (even if more distant relatives) if one or both have had multiple primary melanoma or the cases have the atypical mole syndrome (dysplastic nevi)
  - 3 or more cases of melanoma (one of these cases may be pancreatic cancer instead of melanoma)
  - a patient with 3 or more primary melanomas

- Testing should only be done after extensive counselling, including information on the limitations of genetic testing in FAMMM.

Follow-up of members of a FAMMM family

If a mutation in the family is found, carriers are considered at high risk and the following recommendations apply; non-carriers in such a family may nevertheless have an intermediate risk and should be managed as such.

If no mutation is found then all members of the family should be considered to be at intermediate risk.

The following recommendations guide the follow-up of high risk subjects and can also guide the follow-up of intermediate risk subjects, together with the clinical judgment that takes into account the personal history of melanoma, the number of nevi, the presence of atypical nevi, and the family history.

- Educate family members regarding the need for cutaneous photoprotection and the need to avoid sunburn, particularly in children;
- Educate family members regarding pigmented lesion characteristics that suggest the presence of melanoma;
- Perform a baseline, head-to-toe skin examination at age 12, and repeat every 6–12 months;
- Recommend to family members to perform monthly self-examination of the skin, seeking to identify new or changing pigmented lesions;
- Consider supplementing skin cancer surveillance with (standardized) clinical photographs to facilitate recognizing clinically important pigmented lesion changes, especially in patients with numerous clinically atypical nevi;
- Use dermoscopy (epiluminescence microscopy) and digital dermoscopy as an adjunct to evaluating pigmented lesions, particularly in high risk patients;
- Increase the frequency of skin examination during puberty and pregnancy, periods during which nevi may change rapidly;
- Excise all pigmented lesions that are clinically suggestive of melanoma as well as those that are changing in a clinically worrisome manner. Avoid wholesale, prophylactic removal of all nevi;
- In CDKN2A mutation carriers consider offering the option to screen for pancreatic cancer through endoscopic ultrasound in combination with MRI if there is a first or second degree relative with pancreatic cancer. Explain there is no proven benefit. This can start at the age of 50 or 10 years younger than the earliest family member with pancreatic cancer. As these screening tests are not currently considered standard of care, these patients should be included in clinical research screening programs if possible.

4.3. Neurofibromatosis type 1

Neurofibromatosis type 1 is a relatively common inherited disorder that affects about one in 2 500 to one in 3 000 people worldwide, irrespective of sex or ethnic origin. Individuals with neurofibromatosis type 1 are prone to develop benign and malignant tumors of the central nervous system and peripheral nervous system, in addition to malignant diseases affecting other parts of the body.

Tumours that are associated with the disorder include glomus tumor of the digits, glioma of the optic pathway, glioblastoma, malignant peripheral nerve sheath tumor, gastrointestinal stromal tumor, breast cancer, juvenile myelomonocytic leukemia (JMML), phaeochromocytoma, duodenal carcinoid tumor, and rhabdomyosarcoma.[5]

Recommendations

- Diagnostic criteria (National Insitute of Health, NIH criteria): two or more of the following criteria are required for diagnosis:
  - 6 or more *café au lait* macules (>0.5 cm in children or >1.5 cm in adults)
  - 2 or more cutaneous/subcutaneous neurofibromas or one plexiform neurofibroma
  - Axillary or inguinal freckling
  - Optic pathway glioma
  - 2 or more Lisch nodules (iris hamartomas seen on slit lamp examination)
  - Bony dysplasia (sphenoid wing dysplasia, bowing of long bone ± pseudarthrosis)
  - First degree relative with NF1
- Patients suspected with NF1 should be referred to a centre for genetic counselling and testing.
- Testing after counselling should be considered especially in case of:
  - Unclear presentation that is suggestive but not sufficient to make the diagnosis of the syndrome
  - Incomplete presentation at an early age
  - Reproductive decisions

- Patients presenting with multiple (6 or more) *café-au-lait* spots with or without axillary or inguinal freckling but no other NF1 related criteria should first be tested for mutations in the NF1 gene and if negative for SPRED1.

- Genetic counselling prior to conception is advised in all NF1 individuals of reproductive age.
- Preimplantation and prenatal diagnosis for neurofibromatosis can be offered.

- Children should be followed up every 6 to 12 months up to the age of 7 and annually until the age of 18. The following should be recorded :
  - Development and progress at school
  - Visual symptoms, visual acuity and fundoscopy until age 7 years (optic pathway glioma, glaucoma)
  - Head circumference (rapid increase might indicate tumour or hydrocephalus)
  - Height (abnormal pubertal development)
  - Weight (abnormal pubertal development)
  - Pubertal development (delayed/precocious puberty due to pituitary/hypothalamic lesion)
  - Blood pressure (consider renal artery stenosis, phaeochromocytoma)
  - Cardiovascular examination (congenital heart disease, especially pulmonary stenosis)
  - Evaluation of spine (scoliosis with or without underlying plexiform neurofibromas)
  - Evaluation of the skin (cutaneous, subcutaneous and plexiform neurofibromas)
  - Examination of other systems if specific symptoms are present
- After the age of 18 they should be seen every 2 to 3 years at a specialised multidisciplinary NF1 clinic.
- Blood pressure should be monitored regularly (at least annually).
- Annual breast cancer screening should be done from 40 years on.
- Patients should be instructed to consult if there is any rapid growth, pain, change in texture of a neurofibroma.
- Patients with a NF1 microdeletion or a high volume of neurofibromas should be seen annually in specialised care to monitor for malignancies.

4.4. Neurofibromatosis type 2

Neurofibromatosis type 2 is a multiple neoplasia syndrome that results from a mutation in the NF2 tumour suppressor gene. The genotype occurs in one in 25 000 live births and is inherited as an autosomal dominant trait. It has wide phenotypic variability.

The penetrance is nearly 100% by 60 years of age. Improvements in diagnosis and treatment have led to a rise in the diagnostic prevalence to one in 100 000 people.[6]

Recommendations

- Patients suspected with NF2 should be referred to a centre for genetic counselling and testing.
- Decision to test for NF2 should be based on clinical grounds. Manchester criteria (see below) can provide a guidance but clinical judgment is needed especially with early manifestations, as the sensitivity of the Manchester criteria is low.

Follow-up of NF2 patients should take place at a specialised multidisciplinary NF clinic:

- Ophthalmological examinations are recommended to begin at birth.
- Audiological examinations are suggested to start in early childhood.
- An annual full neurological examination is advised.
- Gadolinium-enhanced magnetic resonance imaging (MRI) of the head and full spine, starting around age 10–12 years, is recommended for all patients, as tumour growth may occur without symptoms.
  - It may be sufficient to perform MRIs every other year up to age 20 and every 3 years thereafter for asymptomatic at-risk individuals without tumours.
  - If tumours are present, MRIs should be conducted at least annually until the rates of tumour growth are established.
- Prenatal preimplantation diagnosis should be discussed with the patient.

Diagnostic criteria for NF2 were developed based on consensus, commonly referred to as the ‘Manchester criteria’ that are an expansion (additional criteria) of and include the NIH criteria:

- Bilateral vestibular schwannomas (VS) or
- Family history of NF2 plus
- Unilateral vestibular schwannoma (VS) or
- Any two of: meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities

Additional criteria:

- Unilateral VS plus any two of: meningioma, glioma, neurofibroma, schwannoma, and posterior subcapsular opacities

Or

- Multiple meningioma (two or more) plus unilateral VS or any two of: glioma, neurofibroma, schwannoma, and cataract

5. ADDITIONAL CONSIDERATIONS

5.1. Adequate information and support for patient and relatives

Genetic counselling, possibly followed by germline mutation analysis, has implications not only for the index person but also for his/her family. Hence, in addition to the medical aspects, patient preferences should be taken into account. Patients should be well and timely informed about all management options (surveillance and preventive treatment) and the advantages and disadvantages they offer.

Patients' representatives ask that a correct and understandable information be provided to individuals at increased genetic risk. Continued support in decision-making is important during the different phases of the process (referral, testing, steps after a positive or a negative test). It is important to clearly explain figures about the increased risk of (specific types of) cancer. Balanced and understandable information about the pros and cons of the various decisions has to be provided (e.g. about intensity of surveillance). There is a need for psychosocial support (by professionals and by fellow patients) when making choices, when informing children and family members about the genetic predisposition or with respect to fertility planning.

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5.2. Role of the genetic centres and the other professionals

A uniform policy followed by all Genetic Centres in Belgium is essential. It is important that general practitioners, oncologists, dermatologists and psychologists are well informed about genetic mutations.

5.3. Guideline update

This guideline should be updated when sufficient new clinical evidence is available. If, in the meantime, important new evidence would become available, this should be taken into consideration in the medical decision making.

RECOMMENDATIONS[a]

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.**
- **A working group composed of representatives of both Colleges has to be set up to further streamline the procedures and professional requirements for pre-test counselling and ordering of oncogenetic tests.**

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.

To the centres of human genetics and the training centres

- **The role of 'genetic counselor' should receive an important place in the counselling. In addition, an appropriate training should be provided (Master level).**

  The 'genetic counselor' should be integrated into a multidisciplinary team and should collaborate with a medical geneticist in the fields of genetics and predictive medicine (genetic counselling, assessment and management of risk, elaboration of family trees, contact and information for families, integration of social, psychological, cultural, legal and ethical dimensions,...).
  The training could be accessible to nurses, midwives, paramedics, bachelors in biomedicine, bachelors in medicine, pharmacists, psychologists (indicative and non-exhaustive list).

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

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COLOPHON

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Authors:	Jo Robays (KCE), Sabine Stordeur (KCE), Frank Hulstaert (KCE), Jean-François Baurain (Cliniques universitaires St-Luc), Lieve Brochez (Universiteit Gent), Teofila Caplanusi (UZ Brussel), Kathleen Claes (UZ Gent), Eric Legius (UZ Leuven), Sylvie Rottey (UZ Gent), Dirk Schrijvers (ZNA), Daphné t'Kint de Roodenbeke (Institut Jules Bordet), Urielle Ullman (Institut de Pathologie, Gosselies), Tom Van Maerken (UZ Gent), Bruce Poppe (UZ Gent)
Senior supervision and project coordination:	Sabine Stordeur (KCE)
Reviewers:	Chris De Laet (KCE), Marijke Eyssen (KCE), Raf Mertens (KCE)
Stakeholders:	Marc Abramowicz (Collège de Génétique Humaine), Sophie de Schepper (Koninklijke Belgische Vereniging voor Dermatologie en Venereologie), Valérie Dekeuleneer (Koninklijke Belgische Vereniging voor Dermatologie en Venereologie), Ward Rommel (Kom op tegen Kanker), Isabelle Tromme (Koninklijke Belgische Vereniging voor Dermatologie en Venereologie), Nele Van den Cruyce (Stichting tegen kanker), Geert Villeirs (Belgische Vereniging voor Radiologie)
External validators:	Fiona Lalloo (Manchester Centre for Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust, UK), Victor-Felix Mautner (School of Medicine and University Hospital Hamburg-Eppendorf, Germany), Pierre Wolkenstein (Pôle Cancérologie, CHU Henri Mondor, Paris, France)
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Layout:	Ine Verhulst

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