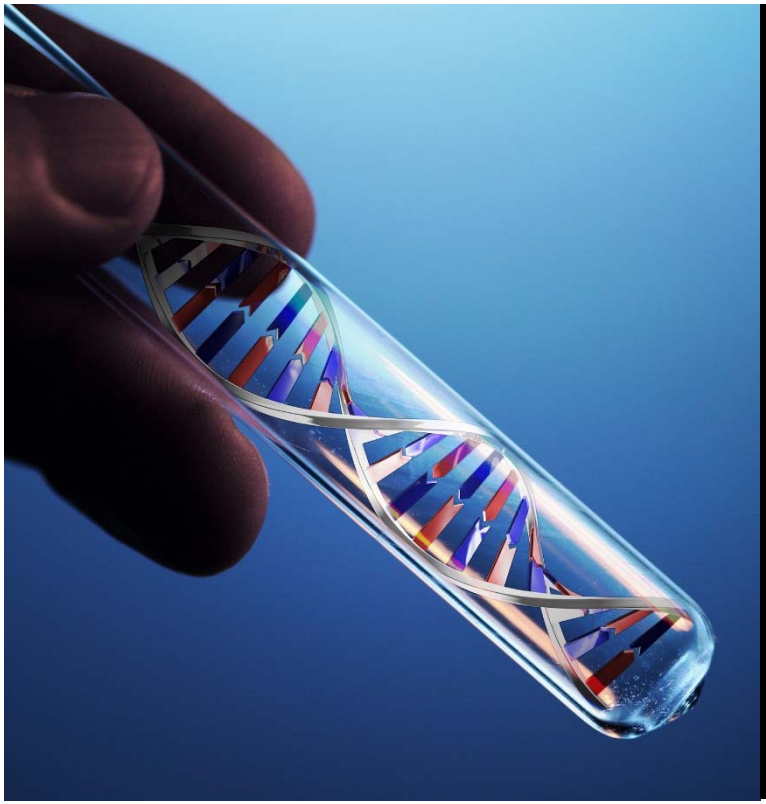
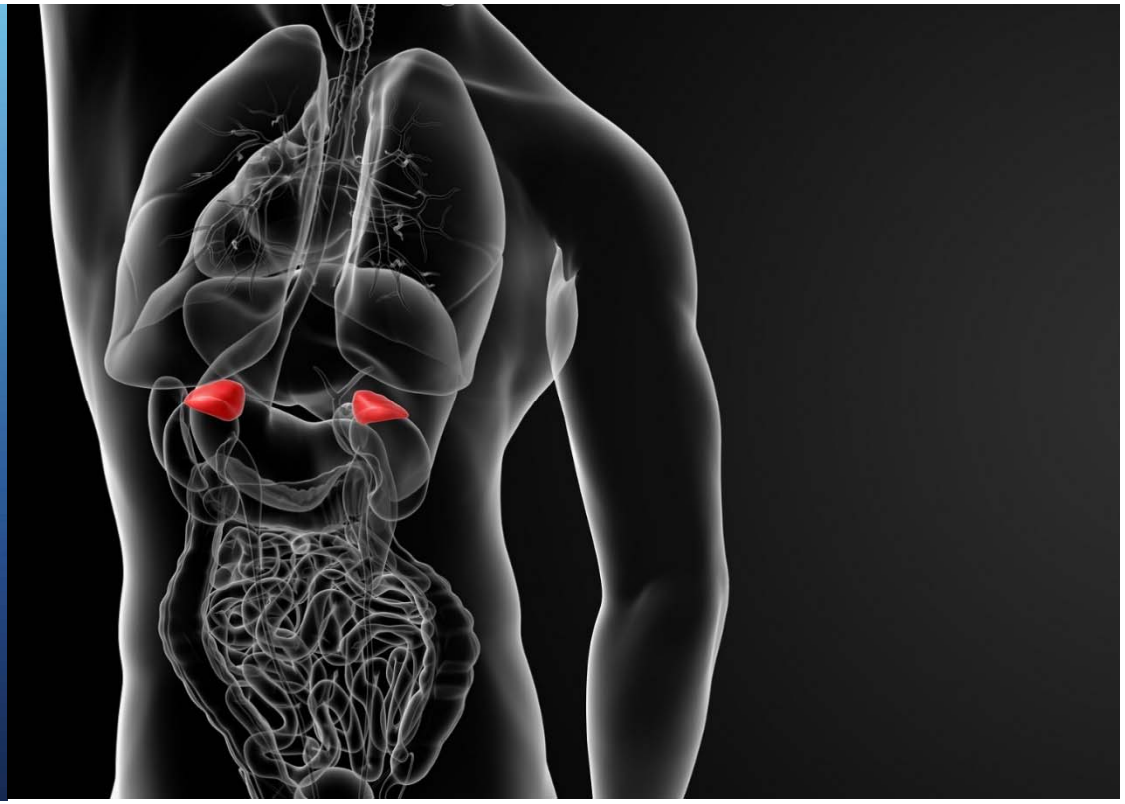
KCE REPORT 242Cs

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

ABSTRACT

ONCOGENETIC TESTING FOR PERSONS WITH HEREDITARY ENDOCRINE CANCER SYNDROMES





KCE REPORT 242Cs
GOOD CLINICAL PRACTICE

Federaal Kenniscentrum voor de Gezondheidszorg
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ABSTRACT

ONCOGENETIC TESTING FOR PERSONS WITH HEREDITARY ENDOCRINE CANCER SYNDROMES

JOAN VLAYEN, MARIE BEX, BERT BRAVENBOER, KATHLEEN CLAES, BRUNO LAPAUW, ALEXANDRE PERSU, KRIS POPPE, URIELLE ULLMAN, TOM VAN MAERKEN, LAURENT VROONEN, BRUCE POPPE

FOREWORD

If you can think of one medical field that is rapidly transforming, it is human genetics with its different applications, from predictive medicine through non-invasive prenatal tests to personalized treatment. Topics to which the KCE – not by coincidence – recently paid a lot of attention.

This report is the third in a series of four about oncogenetic tests: predictors of an increased risk for cancer caused by one or the other mutation in the genome. In other words familial diseases, albeit with different forms of inheritance and expression.

Just as the three other reports, this guideline focuses on the question whom to test and when. And of course, the test results also here have an impact on the fate of the concerned person … ànd of the family members. We already gave this a moment of thought in previous publications, but we still want to focus here on the broader relevance of this rather technical guideline.

Technically, the 'care product' being considered here is the detection of gene mutations. But in practice the care product should be much more than that. Care of high quality also implies the provision of understandable information, through which the person can take his or her part of the reponsability. And it even starts with yet another essential care 'intervention': carefully listening to the values and aspirations of the person, for example when it concerns the guidance for decisions about fertility and the desire to have children.

Listening is a care intervention: a beautiful challenge! How do we fit this in the technicity of these examinations, in the roles of the different care providers, in their training, in our reimbursement system and our health insurance? Some transformation will also be needed here!

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 probability 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.
Proband	The individual through whom a family with a genetic disorder is identified.
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, uncles, aunts, nephews and nieces, half-brothers and half-sisters, on mother's or father's side of the family.
Relatives – Third-degree relatives	These are blood related great grandparents, great grandchildren, great uncles, great aunts, first cousins, grand-nephews and grand-nieces, on mother's or father's side of the family.

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
95%CI	95% confidence interval
AACE	American Association of Clinical Endocrinologists
ATA	American Thyroid Association
CEBAM	Belgian Centre for Evidence-Based Medicine
DNA	Deoxyribonucleic acid
FMTC	Familial medullary thyroid carcinoma
GDG	Guideline development group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HNPGL	Head and neck paraganglioma
HTA	Health technology assessment
KCE	Belgian Health Care Knowledge Centre
MEN	Multiple Endocrine Neoplasia
MSAC	Medical Services Advisory Committee
MTC	Medullary thyroid carcinoma
NIHDI	National Institute for Health and Disability Insurance
NPV	Negative predictive value
OR	Odds ratio
PCR	Polymerase Chain Reaction
PGL	Paraganglioma
PHEO	Phaeochromocytoma
PICO	Population – Intervention – Comparator – Outcomes
PPV	Positive predictive value
RCT	Randomized controlled trial
RET	REarranged during Transfection proto-oncogene
RR	Relative risk
SDH	Succinate Dehydrogenase
STOET	Stichting opsporing erfelijke tumoren
VHL	von Hippel-Lindau

ABSTRACT

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, because the new billing codes (nomenclature) for genetic tests (article 33) and the agreement on genetic testing consultation led to redistribute the NIHDI budget between genetic counselling and laboratory procedures. This new agreement (“convention”) reinforces the role of genetic counselling by the genetic centres. Second, 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 or prophylactic interventions, if supported by evidence.

This clinical practice guideline is based on a joint effort of the Belgian Health Care Knowledge Centre (KCE), the College of Human Genetics and the College of Oncology. This guideline is the third report in a short series of oncogenetic testing guidelines.

2. OBJECTIVES AND SCOPE OF THIS GUIDELINE

This guideline provides evidence-based recommendations for the identification and referral to genetic centres, specialised in oncology, of patients with the following selection of endocrine tumours / syndromes:

- Multiple Endocrine Neoplasia type 1 (MEN1)
- Multiple Endocrine Neoplasia type 2 (MEN2)
- Von Hippel-Lindau (VHL) syndrome
- Phaeochromocytoma
- Paraganglioma.

Clinicians are encouraged to interpret these recommendations in the context of the individual person/patient situation, values and preferences.

All KCE guidelines are as much as possible based on clinical evidence and may not always be in line with the current criteria for NIHDI (RIZIV/INAMI) reimbursement of diagnostic and therapeutic interventions.

3. METHODS

3.1. Clinical research questions

The current guideline addresses the following clinical questions:

- What is the clinical effectiveness of genetic testing in patients presenting with MEN1 (MEN1 mutations), MEN2 (RET mutations), VHL (VHL mutations) or phaeochromocytoma / paraganglioma (SDH, VHL and RET mutations)?
- What is the accuracy of the use of clinical features for the triage for genetic testing of patients presenting with MEN1, MEN2, VHL or phaeochromocytoma / paraganglioma?
- What is the clinical effectiveness of genetic testing of relatives of MEN1, RET, VHL or SDH mutation carriers?

3.2. Literature search

A search for published guidelines was first performed to verify if high-quality, recent guidelines were available that address the clinical research questions. Guidelines were identified through the search for systematic reviews and primary studies (see below), and through a search of the websites of the following organisations: Stichting opsporing erfelijke tumoren (STOET, www.stoet.nl), American Thyroid Association (ATA, www.thyroid.org), American Association of Clinical Endocrinologists (AACE, www.aace.com), Endocrine Society (www.endocrine.org), and the European Thyroid Association (ETA, www.eurothyroid.com).

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 might have been missed by the search.

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. For diagnostic studies, the QUADAS 2 instrument 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 face-to-face meetings, 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 to the recommendations. However, the GRADE tools available on www.guidelinedevelopment.org were used to inform the GDG about the number of false positives and negatives associated with clinical features when used to predict the presence of a mutation. Furthermore, the general philosophy of the GRADE system for interventions (see KCE process book, http://processbook.kce.fgov.be/node/51) was also used for this report (more specifically for the grading of the recommendations).

The report was validated by three external assessors, listed in the colophon.

Subsequently, the recommendations were circulated to the GDG and the 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 associations are listed in the colophon under the section stakeholders. They indicated their agreement or disagreement for each recommendation within their field of expertise 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 external validators 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. Multiple Endocrine Neoplasia type 2 (MEN2)

Multiple Endocrine Neoplasia type 2 (MEN2) is a group of disorders associated with endocrine tumours (typically of the thyroid, parathyroids and adrenals). Nearly all patients develop a medullary thyroid carcinoma (MTC). In general, three major phenotypes are distinguished:

- MEN2A (60% of all MEN2 cases) combines MTC with phaeochromocytoma (10-50% of MEN2A cases) and/or primary hyperparathyroidism (5-20% of MEN2A cases).
- MEN2B (5% of all MEN2 cases) combines MTC with phaeochromocytoma (50% of MEN2B cases) and typical phenotypic features such as a Marfan-type dysmorphism, ganglioneuromatosis and/or skeletal abnormalities.
- Familial MTC (35% of all MEN2 cases), in which the other components of the disease are absent.

MEN2 is typically associated with mutations of the proto-oncogene RET. Epidemiological data are not available for Belgium, but the prevalence is estimated to be 2.5 per 100 000 in the general population.

Recommendations	Strength of Recommendation
• Pre- and post-test genetic counselling should be offered to all patients with a clinical diagnosis of MEN2 (see box) or a sporadic MTC.	Strong
• All patients with a clinical diagnosis of MEN2 *(see box)* or a sporadic MTC, and selected patients with a phaeochromocytoma *(see box)* should be offered germline RET testing.	Strong
• Once a germline RET mutation has been identified in a proband, RET mutation analysis should be offered to all first-degree relatives[#], preferably before the age of 5 years.	Strong

[#] *Or first-degree relatives of patients with clinical MEN2 who died before genetic testing was carried out.*

Criteria for clinical diagnosis of MEN2

- MEN2A: individual with (1) MTC and at least one family member with primary hyperparathyroidism and/or phaeochromocytoma, or (2) with at least two of the three major manifestations (MTC, phaeochromocytoma, primary hyperparathyroidism)
- MEN2B: individual with MTC, phaeochromocytoma and other characteristic features (i.e. mucosal ganglioneuromas, gastrointestinal ganglioneuromas, eye abnormalities including corneal nerve thickening, and/or skeletal abnormalities including marfanoid body habitus)
- Familial MTC: family with at least 4 members diagnosed with MTC (in the absence of pheochromocytoma or parathyroid adenoma/hyperplasia)

4.2. Multiple Endocrine Neoplasia type 1 (MEN1)

Multiple Endocrine Neoplasia type 1 (MEN1) is a polyglandular genetic syndrome characterized by tumours of the parathyroid glands, pancreatic islet cells and/or anterior pituitary gland. Parathyroid tumours with primary hyperparathyroidism is the most common presentation (95% of all MEN1 cases). In addition to these three 'major' locations, tumours can also occur in 'minor' locations, such as the adrenal cortex. MEN1 is usually inherited (as an autosomal dominant disorder), but *de novo* mutations of the menin gene associated with MEN1 are found in about 10% of patients. Epidemiological data are not available for Belgium, but the incidence has been estimated to be 0.25% from postmortem studies.

Recommendations	Strength of Recommendation
• Pre- and post-test genetic counselling should be offered to all patients with a clinical diagnosis or suspicion of MEN1 (*see box*).	Strong
• All patients with a clinical diagnosis of MEN1 *(see box)* should be offered MEN1 genetic testing.	Strong
• In patients with a clinical suspicion of MEN1 *(see box)* MEN1 genetic testing may be considered.	Weak
• MEN1 mutation analysis should be offered to all first-degree relatives of MEN1 mutation carriers.*	Strong

** Or first-degree relatives of patients with clinical MEN1 who died before genetic testing was carried out.*

Criteria for clinical diagnosis of MEN1

- At least two of the three major MEN1-associated tumours (parathyroid tumours, neuroendocrine tumours of pancreas/duodenum, anterior pituitary tumours).
- One of the three major MEN1-associated tumours in a first-degree relative of a case with a clinical diagnosis of MEN1.

Criteria for clinical suspicion of MEN1

- One of the three major MEN1-associated tumours in combination with one minor MEN1-associated tumour (adrenocortical tumours or neuroendocrine tumours of the stomach, lungs or thymus).
- Multiple MEN1-associated tumours in one organ.
- One MEN1-associated tumour at an age < 35 years and a family member with a different MEN1-associated tumour.

4.3. Von Hippel-Lindau (VHL) syndrome

The von Hippel-Lindau (VHL) syndrome is associated with a variety of benign and malignant tumours, in particular haemangioblastomas of the retina and central nervous system, endolymphatic sac tumours, phaeochromocytomas, renal cell carcinomas and cysts in various organs including the kidney, pancreas and liver. The VHL syndrome is inherited, and caused by germline mutations in the VHL tumour suppressor gene. Epidemiological data are not available for Belgium, but the disease prevalence is estimated to be around 1 in 90 000 people.

Recommendations	Strength of Recommendation
• Pre- and post-test genetic counselling should be offered to all patients with a clinical diagnosis or suspicion of VHL *(see box)*.	Strong
• All patients with a clinical diagnosis of VHL *(see box)* should be offered VHL genetic testing.	Strong
• In patients with a suspected phenotype of VHL *(see box)*, VHL genetic testing may be considered.	Weak
• Once a germline VHL mutation has been identified in a proband, VHL mutation analysis should be offered to all first-degree relatives as soon as possible*.	Strong

** Or first-degree relatives of patients with clinical VHL who died before genetic testing was carried out.*

Criteria for clinical diagnosis of VHL

An individual with no known family history of VHL disease presenting with two or more characteristic lesions:

- Two or more hemangioblastomas of the retina, spine, or brain or a single hemangioblastoma in association with a visceral manifestation (e.g., multiple kidney or pancreatic cysts)
- Renal cell carcinoma (typically of the clear cell subtype)
- Adrenal or extra-adrenal phaeochromocytoma
- Less commonly, endolymphatic sac tumour, papillary cystadenoma of the epididymis or broad ligament, or neuroendocrine tumour of the pancreas

An individual with a positive family history of VHL disease in whom one or more of the following disease manifestations is present:

- Retinal angioma
- Spinal or cerebellar hemangioblastoma
- Adrenal or extra-adrenal phaeochromocytoma
- Renal cell carcinoma (typically of the clear cell subtype)
- Multiple renal and pancreatic cysts

Criteria for clinical suspicion of VHL

- Isolated central nervous system hemangioblastoma
- Isolated endolymphatic sac tumour
- Isolated renal cell carcinoma (typically of the clear cell subtype) at an age < 40 years
- Multiple renal cell carcinomas (typically of the clear cell subtype)
- Renal cell carcinoma (typically of the clear cell subtype) and a first- or second-degree relative with a typical VHL tumour
- Phaeochromocytoma or paraganglioma (if no Succinate Dehydrogenase mutation)
- Isolated papillary cystadenoma of the epididymis
- Bilateral epididymal cysts
- Two or more pancreatic serous cystadenomas
- Two or more pancreatic neuroendocrine tumours
- Pancreatic serous cystadenoma or neuroendocrine tumour, and first- or second-degree relative with a typical VHL tumour
- Multiple pancreatic cysts and another typical VHL tumour

4.4. Paraganglioma and phaeochromocytoma

Phaeochromocytomas are tumours arising from adrenomedullary chromaffin cells that commonly produce catecholamines. Paragangliomas are tumours derived from extra-adrenal chromaffin cells of the sympathetic paravertebral ganglia of thorax, abdomen, and pelvis, or from parasympathetic ganglia located along the glossopharyngeal and vagal nerves in the neck and at the base of the skull. In addition to the three syndromes described above, phaeochromocytomas and paragangliomas can also occur sporadically, i.e. without syndromic features. Several susceptibility genes have been described, with SDH mutations occurring most frequently. In 2011, 16 phaeochromocytomas and 9 paragangliomas were registered at the Belgian Cancer Registry (personal communication), with a European Standardized Rate of 0.14 and 0.06 per 100 000 person years, respectively. However, these incidences are probably underestimated because of underregistration.

Recommendations	Strength of Recommendation
• Pre- and post-test genetic counselling should be offered to all patients with phaeochromocytoma / paraganglioma.	Strong
• In patients with phaeochromocytoma / paraganglioma and syndromic features, targeted genetic testing (*e.g. for MEN2 and VHL)* should be offered.	Strong
• All patients with phaeochromocytoma / paraganglioma that lack syndromic features should be offered genetic testing for SDHx genes (SDHD + SDHB + SDHC subtypes), VHL and RET (in this order).	Strong
• If tumour tissue is available, SDHB immunohistochemistry testing could be considered as a triage test before proceeding with genetic testing for SDHx genes.	Weak
• In patients with phaeochromocytoma / paraganglioma and clinical features suggestive of a mutation (i.e. age < 35 years, metastatic disease, recurrent disease, bilateral tumours and/or familial disease), who test negative for SDHx, VHL and RET, further genetic testing may be considered.	Weak
• Once a germline mutation has been identified in a proband, mutation analysis should be offered to all first-degree relatives irrespective of age.	Strong

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, psychosocial consequences and patient and family 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.

From contacts with patients' representatives it is clear that correct and understandable information should be provided to individuals at increased genetic risk (within the philosophy of the Belgian law on patients rights of 26 September 2002). 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 surveillance or prophylactic surgery). There is a need for psychosocial support (by professionals and by fellow patients if possible) when making choices, when informing children and family members about the genetic predisposition or with respect to fertility planning.

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 / endocrinologists / psychologists are well informed about where to refer patients with these rare syndromes and tumours. According to the patients' representatives, many people are currently not referred or do not receive the correct information.

5.3. Guideline update

In view of the rapidly evolving evidence due to the dynamic nature of this field, the clinical introduction of the routine analysis of a broad panel of germline DNA tests in at risk subjects will be monitored by the authors of this report. This guideline should be updated when sufficient new 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 Human Genetics and the College of Oncology

- **The implementation of this guideline should be facilitated by the College of Human Genetics and the College of Oncology, preferably 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 scientific 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.

COLOPHON

Title:	Oncogenetic testing for persons with hereditary endocrine cancer syndromes – Abstract
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Other reported interests:	Membership of a stakeholder group on which the results of this report could have an impact: Marie Bex (Belgian Endocrine Society; Belgian Thyroid Club), Bruce Poppe (Universiteit Gent, UZ Gent) Fees or other compensation for writing a publication or participating in its development: Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Marie Bex (participation ECE and ENDO congress (NOVARTIS-SANDOZ); Advisory Board IPSEN-NOVARTIS), Bruno Lapauw (several post-graduate courses including for GP's; support participation several congresses in the domain of endocrinology), Kris Poppe (Merck symposium 2011) Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Bruce Poppe (Universiteit Gent; UZ Gent) Participation in scientific or experimental research as an initiator, principal investigator or researcher: Marie Bex (somatostatine analogen in acromegalie and cushing, NOVARTIS), Kris Poppe (Takeda "L. Thyroxine" study)
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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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