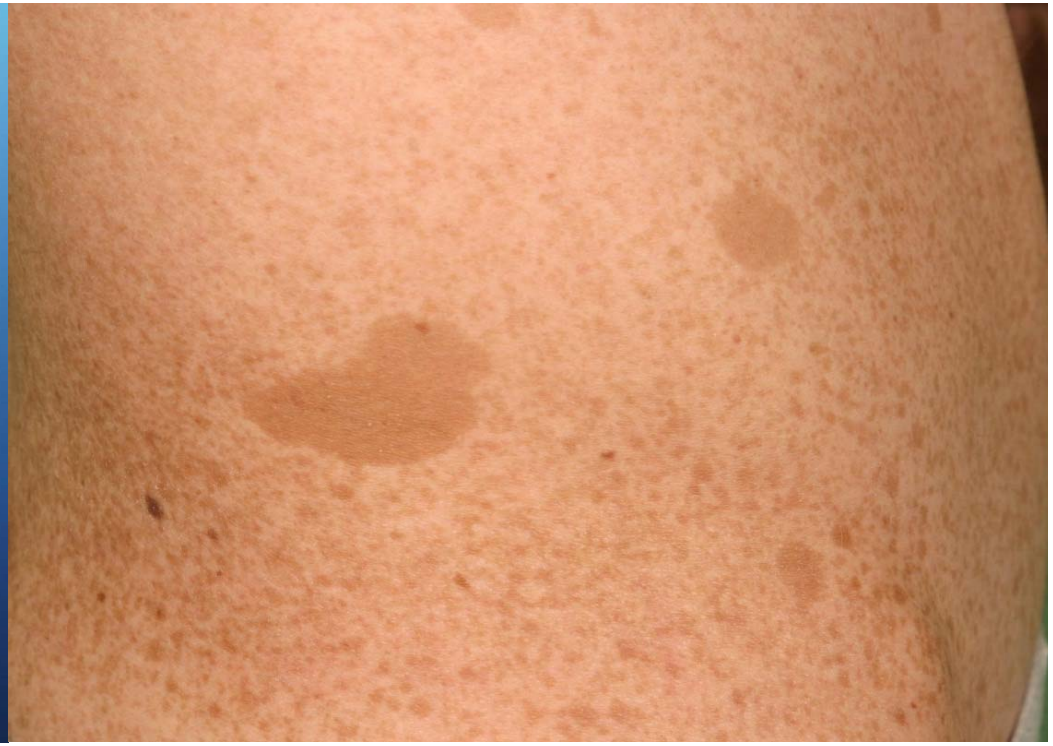
KCE REPORT 243

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

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



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KCE REPORT 243
GOOD CLINICAL PRACTICE

Federaal Kenniscentrum voor de Gezondheidszorg
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COLOPHON

Title:	Oncogenetic testing, diagnosis and follow-up in Birt-Hogg-Dubé syndrome, familial atypical multiple mole melanoma syndrome and neurofibromatosis 1 and 2
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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 (see http://kce.fgov.be/content/the-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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	This document is available on the website of the Belgian Health Care Knowledge Centre.

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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.

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ARF	Alternate Reading Frame
ASCO	American Society of Clinical Oncology
BHD	Birt-Hogg-Dubé syndrome
CDK4	Cyclin-dependent kinase 4
CDKN2A	Cyclin-dependent kinase inhibitor 2A
CT	Computed Tomography
DELM	Digital Epiluminescence Microscopy
ELM	Epiluminescence Microscopy
FAMM	Familial atypical multiple mole melanoma syndrome
FLCN	Folliculin
GDG	Guideline Development Group
genoMEL	Melanoma genetics consortium
HADS	Hospital Anxiety and Depression Scale
JMML	Juvenile myelomonocytic leukemia
MC1R	Melanocortin 1 receptor
MeSH	Medical Subject Headings
MRI	Magnetic Resonance Imaging
NF1	Neurofibromatosis 1
NF2	Neurofibromatosis 2
NIH	National Institutes of Health
NIHDI (RIZIV/INAMI)	National Institute for Health and Disability Insurance
NNFF	National Neurofibromatosis Foundation
PICO	Population Intervention Control Outcome
RCT	Randomised controlled trial
SPRED1	SProuty-Related, EVH1 Domain containing 1
SR/MA	Systematic reviews and meta-analyses
SSE	Skin Self Examination
VS	Vestibular Schwannomas

SCIENTIFIC REPORT

1 INTRODUCTION

1.1 Background

This guideline treats 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. A specific background will be given for each syndrome separately.

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. This guideline is timely 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 NIHDI budget between genetic counselling (€4,288 millions) and laboratory procedures (€37,795 millions)[a]. There is a need to standardise the use of these tests and base their use on available evidence. Early identification of persons at risk makes the initiation strategies possible that may reduce morbidity or be lifesaving, including enhanced surveillance and surgery. It may also help the patient in making decisions concerning preconception and antenatal screening and reproduction in general.

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 the fourth report in a short series of oncogenetic testing guidelines.

[a] In addition, a reimbursement is foreseen for tests performed abroad (if no Belgian specialised laboratory is able to perform the test) for diagnostic analysis of DNA samples from patients (and their relatives) suffering from rare cancers or rare diseases.

1.3 Scope

This guideline will cover following populations:

- Persons considered at risk based on clinical suspicion or family history.

This guideline will cover following issues:

- Who has to undergo genetic tests;
- Tests for which genes have clinical utility;
- What follow-up is recommended depending on test results and family history.

The guideline will not cover treatment of patients, including surgery.

1.4 Remit of the guideline

1.4.1 Overall objectives

This guideline provides recommendations based on current scientific evidence for the diagnosis and follow-up of patients with clinical suspicion of Birt-Hogg-Dubé syndrome, familial atypical multiple mole melanoma syndrome and neurofibromatosis 1&2. Clinicians are encouraged to interpret these recommendations in the context of the individual patient situation, values and preferences.

All KCE guidelines are 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. The NIHDI 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 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.

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 the care and management of patients with Birt-Hogg-Dubé syndrome, familial atypical multiple mole melanoma syndrome and neurofibromatosis 1&2.

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 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 INAMI/RIZIV, 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. Although 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) or the peer-review process 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 are available upon request.

2 METHODOLOGY

2.1 Introduction

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.

Several steps were followed to elaborate this guideline. Firstly, clinical questions were developed and the inclusion and exclusion criteria were defined in collaboration with members of the Guideline Development Group. Secondly, a literature review was conducted (including a search for recent, high quality guidelines). Thirdly, on the basis of the results of the literature review, recommendations were formulated.

2.2 The Guideline Development Group

This guideline was developed as a result of a collaboration between multidisciplinary groups of practising clinicians and KCE experts. The composition of the GDG is documented in the colophon. Guideline development and literature review expertise, support, and facilitation were provided by the KCE Expert Team.

The roles assigned to the GDG were:

- To define the clinical questions, in close collaboration with the KCE Expert Team and stakeholders;
- To identify critical and important outcomes;
- 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

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?

2.4 General approach

To verify if high-quality, recent guidelines are available that address the clinical research questions, a GCP project always starts with a search for guidelines. If such guidelines are available, the ADAPTE methodology is followed.

If no high-quality, recent guidelines in line with the defined PICOs are available, the general approach will begin with the search for systematic reviews.

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 were be performed in MEDLINE, Embase. If no systematic review is available a search for primary studies will be performed in those databases. Members of the guideline development group (GDG) will also be consulted to identify additional relevant evidence that may have been missed by the search.

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 reviews were only used for supplementary reference tracking;
  - 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 (SR/MA) 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 SR/MA.

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;
- search MEDLINE and at least one other electronic database;
- include an assessment of risk of bias for each primary study.

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, a cohort study on the effectiveness of follow up, an observational study giving information on either prognostic value of an oncogenitic test or the validity of a set of testing criteria;
- address at least one of the research questions;
- evaluate at least one of the selected (critical and important) outcomes.

2.4.2 Databases

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:

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

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. The PICOs, the search strategy and number of publications retrieved corresponding to our research questions are documented in □.

Studies were screened on **title and abstract**. 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.

2.5 Quality appraisal

2.5.1 Clinical practice guidelines

We looked at the methodological quality of the identified international guidelines focusing on the questions if there was a documented search strategy and we evaluated the congruence between evidence and recommendations.

2.5.2 Systematic reviews

Selected (systematic) reviews were critically appraised by a single KCE expert. The AMSTAR checklist[1] (http://amstar.ca/Amstar_Checklist.php) was used if it was a systematic review of interventions. 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. Details are described per syndrome.

2.6 Formulation of recommendations

Based on the retrieved evidence, the first draft of recommendations was prepared by a small working group (KCE experts). This first draft was, together with the evidence tables, circulated to the guideline development group 2 weeks prior to the face-to-face meetings (15/09/2014 and 18/11/2014). Recommendations were changed if important new evidence supported this change. Based on the discussion 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.

2.7 External scientific validation

As part of the standard KCE procedures, an external scientific validation of the report was conducted prior to its publication. The scientific content was assessed by 3 experts on 26th January 2015 (cf. names in the colophon).

2.8 External review

2.8.1 Healthcare professionals

The recommendations prepared by the guideline development group and after scientific validation by the external validators were circulated to Professional Associations (Table 1). Each association was asked to assign one or two key representatives to act as external reviewers of the draft guideline. All expert referees made declarations of interest.

Globally, 15 external experts were involved in the evaluation of the clinical recommendations and took part to the stakeholder meeting (10th February 2015). All invited panellists received the scientific report for all research questions and were asked to score each recommendation indicating their agreement (or not) with the recommendation or to mention the topic was out of their research field. If panellists disagreed with the recommendation, they were asked to provide an explanation supported by appropriate evidence. Scientific arguments reported by these experts were used to adapt the formulation of the clinical recommendations.

Table 1 – List of Professional Associations invited

- **College of Human Genetics**
- **Belgian Society of Human Genetics**
- **Belgian Society of Pathology**
- **Belgian Society of Medical Oncology***
- **Belgian Society of Radiology**
- **Royal Belgian Society of Dermatology and Venereology**
- **Société Scientifique de Médecine Générale***

** Representatives were assigned by these associations but did not join the meeting and did not send their evaluation form*

2.8.2 Patient representatives

No specific patients associations exist in Belgium to specifically represent patients with the syndromes covered by these guidelines. However, two main associations support cancer patients to face with their disease and to accompany them (information, social actions to improve their quality of life). Both associations (Fondation contre le Cancer-Stichting tegen Kanker and Kom op tegen Kanker) were contacted to invite representatives to take part in the stakeholder meeting (10th February 2015).

They were asked the following questions:

- Have important considerations from a patients' perspective been missed in the formulation of our recommendations?
- Do we need to add information that could assist patients in making clear choices when doctors discuss treatment options with them?

3 BIRT-HOGG-DUBÉ SYNDROME

3.1 Introduction

Birt-Hogg-Dubé syndrome (BHD) is an autosomal dominant condition characterized clinically by skin fibrofolliculomas, pulmonary cysts, spontaneous pneumothorax, and renal cancer.[2] In 2001, a BHD-associated gene locus was localized to chromosome 17p11 and truncating germline mutations were identified in the FLCN (BHD) gene, coding for a protein of unknown function called folliculin (FLCN).[3, 4]

Its prevalence is estimated to be 1/200 000, based on a systematic search of the literature done by Orphanet, a consortium specialized in orphan drugs and rare diseases, but there may be underreporting.[5] To date, approximately 500 families have been reported worldwide according to the European Birt-Hogg-Dubé Consortium (http://www.europeanbhdconsortium.eu).

3.2 Search results

Details of our search can be found in Appendix 1.1.

We found 3 guidelines from which 2 were consensus based and did not have a formal search strategy.[6, 7] In a third guideline, the BHD consortium put forward criteria for the diagnosis of BHD and criteria for testing. These recommendations are based on a literature search and expert opinion.[2] An overall search strategy was provided but we could not find details on the search strategy they used nor on the relation between evidence and recommendations.

We did not find studies that corresponded to our criteria, as we only found case reports and descriptions of data from registries of limited size with clinical descriptions and inventories of different mutations found on BHD patients, who were included from various sources and using variable inclusion criteria, clinical implications of these are therefore unclear.

In what follows diagnostic criteria and testing criteria are proposed. Diagnostic criteria are the criteria that are used to decide if a patient has BHD syndrome. Test results for FLCN are included in those criteria. Testing criteria on the contrary are criteria to decide what patients need to be referred for testing and counseling. The diagnostic criteria for BHD are part of those criteria.

3.2.1 Diagnostic criteria for Birt-Hogg-Dubé syndrome

The European Birt-Hogg-Dubé Consortium proposed criteria for BHD, largely based on expert opinion.

Patients should 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: 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

3.2.2 Criteria for referral to a genetic center and FLCN testing

According the BHD consortium, all patients fulfilling the above mentioned diagnostic criteria should undergo genetic testing. However, BHD should also be considered in patients who do not fulfill the diagnostic criteria but still might have an underlying FLCN mutation.

- Patients with early-onset renal cancer (<50 years), in particular with multifocal or bilateral disease (or both) with chromophobe or oncocytic histology.
- Patients with unexplained cystic lung disease, pneumothorax, or both, especially if the lung cysts are bilateral and basally located.
- Patients who have familial cystic lung disease, pneumothorax, familial renal cancer, or any combination of spontaneous pneumothorax and kidney cancer in an individual or family.

These recommendations however are largely based on expert opinion. There is not sufficient information from cohort studies nor validation studies to give a credible estimate of sensitivity, specificity or predictive value of these criteria.

3.2.3 Management and follow-up

The consortium recommends preventive measures largely aimed at early recognition and treatment of renal cancer. The optimum program for surveillance has not yet been established.

They recommend to consider a yearly MRI scan of the kidney starting at age 20 years. They also recommend to consider an assessment of lung involvement by thoracic CT scan before surgery that requires general anesthesia.

These recommendations however are largely based on expert opinion. There is not sufficient information from cohort studies on the clinical benefit of surveillance.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	*Patients with confirmed diagnosis may benefit from early diagnosis of renal cancer, however this remains unproven.* *The GDG considered that it was necessary to provide a statement on testing in underage patients. This was done based on the recommendations provided by American Society of Clinical Oncology (ASCO) and cited in gene reviews.[8] 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 genetic testing in at-risk individuals until they reach age 18 years and are able to make informed decisions regarding genetic testing.* *The GDG found it necessary to put forward a recommendation to discourage scuba diving that is based on expert opinion, given the increased risk of pneumothorax among patients affected by BHD.*
Quality of evidence	*We only found case reports and descriptions of data from registries of limited size with clinical descriptions and inventories of different mutations found on BHD patients, who were included from various sources and using variable inclusion criteria, clinical implications are therefore unclear. We did not find studies on follow-up. Therefore, recommendations are largely consensus-based. KCE recommendations are based on the recommendations of the BHD consortium. The recommendations were slightly modified by the GDG at points where the GDG considered that the recommendations were not sufficiently clear, based on their expert opinion.*

	The GDG added ultrasound as a valid screening tool for renal cancer. They also found it necessary to specify that CT should be a high resolution CT. *The consortium calls for further research, because the disease is rare and it will be difficult to collect evidence from studies with sufficient statistical power.*
Costs (resource allocation)	*Both BHD syndrome and conditions that cause BHD testing criteria to be fulfilled are rare, therefore it is likely that the impact of the recommendations on resource use is limited.* *The year of onset of renal cancer was lowered from 50 to 40 by the GDG, due to considerations on resource use.*
Patients values and preferences	*Due to the impact of such diagnosis on patients and their relatives, psychosocial support (how to deal with distress, how to deal with social issues ex. insurance, return to work etc.) should be offered to every patient during the entire process (before diagnosis, during testing and follow-up).*

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 appropriate 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

- Following patients should be referred for genetic testing and counseling:
  - Patients fulfilling the criteria for Birt-Hogg-Dubé syndrome mentioned above
  - Multifocal or bilateral renal cancer
  - Renal cancer of mixed chromophobe and oncocytic histology
  - Renal cancer onset below 40 with oncocytic histology

- Patients with unexplained cystic lung disease, and if the lung cysts are bilateral and basally located
- Patients who have familial cystic lung disease, familial pneumothorax, familial renal cancer, or any combination of spontaneous pneumothorax and kidney cancer in an individual or family
- 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 compared with MRI and CT for screening purposes.
- Consider a low dose thoracic high resolution CT scan before surgery that requires general anaesthesia.
- Discourage smoking and scuba diving.

4 FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA SYNDROME

4.1 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. It is associated with mutations in the CDKN2A gene and shows reduced penetrance and variable expressivity. Some FAMMM kindreds show an increased risk for the development of pancreatic cancer and possibly other malignancies.'[9] 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.[10]

We found 2 guidelines that were consensus-based and did not have a formal search strategy.[6, 7]

We did a search for primary studies and found a number of observational studies that corresponded to the criteria mentioned in 2.4.1 (details of our search can be found in 0).

4.2 FAMMM criteria

Melanoma Genetics Consortium, GenoMEL (www.genomel.org), an international research consortium publicly funded, published (on their website) consensus based criteria for families who require specialist counselling about risk:

- Families with 2 first degree relatives with melanoma
- Families with 2 cases (even if more distant relatives) if one or more have had multiple primaries or the cases have the atypical mole syndrome (dysplastic nevi) as self-examination is then rather more difficult
- Families with 3 or more cases of melanoma

This recommendation is based on prevalence studies of mutations in melanoma families.

4.2.1 Prevalence of mutations in melanoma families and in the general population

GenoMEL, comprising major familial melanoma research groups from North America, Europe, Asia and Australia included 466 families (2 137 patients) with at least three melanoma patients from 17 centers. They found that overall, 41% (n = 190) of families had mutations; most involved p16 (n = 178). Mutations in CDK4 (n = 5) and ARF (n = 7) occurred at similar frequencies (2-3%). They found large differences in mutations across geographic locations.[11] The proportion of families with CDKN2A mutations was highest in Europe (57%) where the baseline incidence of melanoma is relatively low, and lowest in Australia (20%), where the melanoma incidence is high. These differences are attributed to the fact that in regions of high melanoma incidence, such as Australia, there may be familial clustering of melanomas purely based on low-risk genes or statistical chance. This dilutes the apparent CDKN2A mutation rate.

Berwick et al.[12] showed that prevalence in first incident cases in the general population is much lower, around 1.2%.

4.2.2 Risk of melanoma (penetrance) among CDKN2A mutation carriers in high risk families and families with population risk.

Bishop et al.[13] analysed 80 high risk (more than 3 melanoma cases) families containing 402 melanoma patients, 320 of whom were tested for mutations and 291 were mutation carriers. Overall, CDKN2A mutation penetrance was estimated to be 0.30 (95% confidence interval (CI) = 0.12 to 0.62) by age 50 years and 0.67 (95% CI = 0.31 to 0.96) by age 80 years. By age 50 years CDKN2A mutation penetrance reached 0.13 in Europe, 0.50 in the United States, and 0.32 in Australia; by age 80 years it was 0.58 in Europe, 0.76 in the United States, and 0.91 in Australia.

However, these estimates are only valid for multiple-case families. Orlow et al.[14] showed in a population based study (n = 3 550) that the risk of melanoma in CDKN2A mutation carriers was approximately 14% (95% CI = 8% to 22%) by age 50 years, 24% (95% CI = 15% to 34%) by age 70 years, and 28% (95% CI = 18% to 40%) by age 80 years.

4.2.3 Risk of other cancers

An association of FAMMM with pancreatic cancers was shown in a number of studies. Goldstein et al.[15] reported on a study done by the 17 GenoMEL groups (see above), on 385 families with ≥3 patients with melanoma. They found an association of pancreatic cancer with CDKN2A mutations in Europe and North America, but not in Australia.

Desnoo et al.[16] showed an increased risk of pancreatic cancer, cancer of the lip, mouth and pharynx, respiratory tumors, non-melanoma skin tumors, soft-tissue tumours, and tumours of the eye/brain associated with CDKN2A founder mutation (p16-Leiden)-positive melanoma families.

4.2.4 Interpretation of genetic tests within families affected by FAMMM

FAMMM is associated with mutations in CDKN2A and CDK4. It is less clear however what the optimal interpretation and clinical implications of the test are within affected families. In the absence of these mutations the familial clustering is either caused by unknown susceptibility genes or the presence of a combination of low penetrance genes and/or other risk factors. It is unclear what the relative risk is of a member of a multiple case family where a susceptibility gene has been identified or where no susceptibility gene is identified. Moreover, within a family where a susceptibility gene is identified, the risk for individuals who happen to be tested negative, may remain higher than in the general population.

4.3 Diagnostic work-up and follow-up of FAMMM

There is only very limited evidence on the follow-up of FAMMM. No approach was ever tested in an RCT. Only a limited number of cohort studies were published.

Vasen et al.[17] screened nine families with the dysplastic nevus syndrome in the Leiden area (The Netherlands). A total of 50 primary melanomas were diagnosed in 38 persons. Nineteen of these melanomas had been diagnosed before the start of the screening programme (category I), 11 were detected at the initial examination of the families (category II), and 20 were found during the course of follow-up (category III). To assess the effect of screening, we compared these categories with respect to the developmental stage of the melanomas. One of the 19 melanomas in category I, two of the 11 in category II and seven of the 20 in category III were melanoma in situ. The average thickness of the invasive melanomas in categories I, II and III was 1.75, 0.80 and 0.54 mm respectively. Sixteen of the 19 melanomas in category I (84%) were Clark III or IV, whereas 15 of the 20 melanomas in category III (75%) were Clark I or II. Effect on survival or morbidity remains to be proven.

Hansson et al.[18] reported on a program initiated in 1987 by the Swedish Melanoma Study Group where 2 080 individuals belonging to 280 melanoma families were followed for 14 years between 1987 and 2001 at 12 participating centers. Among 1 912 skin lesions excised during follow-up, 41 melanomas were removed in 32 individuals. Of these, 15 (37%) were in situ melanomas and 26 (63%) invasive melanomas. The median tumor thickness of invasive melanomas was 0.5 mm. Ulceration was absent in 24 of 26 invasive melanomas (92%) and 12 (46%) lacked vertical growth phase. Compared with melanomas in the general Swedish population, the melanomas identified in these kindreds during follow-up had better prognostic characteristics. However, this may be due to lead time or overdiagnosis. Any effect on survival or morbidity remains to be proven.

Hansson et al.[18] documented a surveillance program using epiluminescence microscopy (ELM) and digital epiluminescence microscopy (DELM). High-risk patients (n=212) were categorized by the number and phenotype of their naevi and their personal and family history of melanoma. Then patients were screened by the unaided eye, conventional photography, ELM and, in selected cases of atypia, DELM. Median follow-up was 18 months, and 2 939 pigmented lesions were followed by DELM. Examination on the first visit identified 17 cutaneous melanomas. During the following observation period, another 17 melanomas were identified. Fifteen of these follow-up melanomas were exclusively identified based upon DELM. Clinical implications of these findings and to what degree DELM influences prognosis are unclear though.

Skin Self Examination (SSE) has been advocated, but compliance could be a problem. Mesters et al.[19] reported on 71 members of 18 FAMMM families where only 70% performed SSE at least once every 2-3 months. Adequate performers were more likely to have a partner, had a more positive attitude toward SSE, perceived SSE as less difficult to perform and had a stronger intention to perform SSE compared to poor performers. Logistic regression indicated attitude as the only reliable predictor of SSE performance.

No studies were performed on the effectiveness of screening for pancreatic cancer.

4.4 Patient perception of counselling and testing - impact on behavior and distress levels

Desnoo et al.[20] found low levels of distress compared to the general population as measured by the Hospital Anxiety and Depression Scale (HADS) following counselling in both persons who took up the test and who did not among family members with a pre-test risk of being p16-Leiden mutation carriers of 50% or higher (melanoma patients and first degree relatives of melanoma or pancreas cancer patients).

These low levels of anxiety were confirmed in a prospective follow up study by Aspinwall et al.[21] among 60 high-risk patients in Utah (USA).

Rieman et al.[22] looked at the reasons to decline testing and found that a part of persons offered testing, categorized by the authors as 'emotionally motivated respondents' were hesitant to inform their family about an unfavorable test result and had unrealistic perceptions of what caused melanoma.

Bergenmar et al.[23] interviewed 11 consecutive members of families with CDKN2A mutation attending a pigmented lesion clinic at four occasions: before genetic testing, at disclosure of genetic test result and six months and one year after disclosure. The following areas were measured: anxiety and depression, risk perception, and sun-related habits. Disclosure of the test result did not seem to change family members' perception of their risk of developing melanoma. Few members reported anxiety of clinical significance and no one was depressed. Genetic testing of the members of melanoma families with CDKN2A mutations attending a pigmented lesion clinic did not appear to induce behavioral changes related to sun habits or emotional problems.

Aspinwall et al.[24] found that CDKN2A/p16 test reporting enhances compliance with early detection measures among CDKN2A/p16+ participants without diminishing the compliance of CDKN2A/p16- participants in high-risk patients in Utah (USA). This effect was confirmed after 2 years follow up.[25, 26]

Bränström et al.[27] gathered self-report data using online and paper-based surveys available in four languages among 312 individuals (62% from Europe, 18% from Australia, 13% from the USA and 7% from Israel). They found that participants were influenced by their phenotype and test results in risk estimations. Participants in the study expressed positive views on genetic research and towards genetic testing, but the study reported also that a non-informative (negative) test result might be associated with an (erroneous) perception of reduced risk and fewer preventive behaviours.

Glanz et al.[28] randomly assigned seventy-three adults with a family history of melanoma to be offered individualized CDKN2A and MC1R genotyping results in the context of a genetic counselling session, or the standard practice of not being offered counselling or disclosure of genotyping results. Participants in the intervention group reported an increase in the frequency of skin self-examinations compared with a slight decrease in the control group ($p = 0.002$). Participants in the intervention group reported a smaller decrease in frequency of wearing a shirt with long sleeves than did participants in the control group ($p = 0.047$). No effect of the intervention was noted for other outcomes. They concluded that feedback of CDKN2A and MC1R genotype among families without known pathogenic CDKN2A mutations does not seem to decrease sun protection behaviours. Because the study included only 3 individuals with deleterious mutations in the intervention group, these results provide relatively little insight into the effect of mutation testing on behaviors of individuals who test positive. However, they provide important evidence that genetic testing and counseling do not lead to false reassurance and reductions in sun protection behaviors among individuals who test negative.

Conclusions

- In multi-case (>2) families in Europe, 57% had CDKN2A mutations, but regional variability is high. In Belgium this frequency may be lower.
- Risk of melanoma in CDKN2A positive members coming from multi-case families varies by region. By age 50 years CDKN2A mutation penetrance reached 0.13 in Europe, 0.50 in the United States, and 0.32 in Australia; by age 80 years it was 0.58 in Europe.
- Risk of melanoma in CDKN2A positive persons coming from the general population is lower.
- Members of FAMMM families have an increased risk of pancreatic cancer in Europe.

- Compared with melanomas in the general population, the melanomas identified in follow up programs have better prognostic characteristics. However, this may be due to lead time or over-diagnosis. Any effect on survival or morbidity remains to be proven.
- There is no proof that screening for pancreatic cancer has a beneficial effect.
- Evidence on the impact of offering counselling and testing, including counselling on sun protection, self-examination and compliance to screening is conflicting, with some studies showing indications of false reassurance and others an increased level of protective behaviour.
- Counselling and testing is associated with low levels of distress.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	*Benefit of genetic testing is controversial. As only 40 to 60% of FAMMM families test positive, a negative diagnosis in a family does not alter the need for enhanced surveillance and sun protection. A negative test in a family with a known mutation means a lower risk compared to a mutation positive family member but the risk may remain higher than the population risk and a negative test could give false reassurance. Therefore the Melanoma Genetics Consortium does not recommend systematic testing, but this position is controversial.*
Quality of evidence	*There is convincing proof from observational studies that there is an association between CDKN2A mutations and risk of melanoma, but prevalence of the mutations and risk of melanoma among carriers vary between regions and source of the mutation. When a mutation is found in a non FAMMM family member the risk is lower, indicating that other factors play a role explaining melanoma risk. Observational evidence shows that enhanced surveillance and follow up results in melanomas with better prognosis, but the role of lead time and over-diagnosis remains unclear. The effect on mortality or morbidity is unproven. Recommendations are therefore essentially based on expert opinion.* *Recommendations for follow up of patients are based on the consensus statement of the Melanoma Genetics Consortium*
Patients values and preferences	*The literature summarised above shows that some patients may be hesitant to inform family member of the test results but overall perception of testing and counselling is favourable.* *Due to the impact of such diagnosis on patients and their relatives, psychosocial support (how to deal with distress, how to deal with social issues ex. insurance, return to work etc.) should be offered to every patient during the entire process (before diagnosis, during testing and follow-up).*

Recommendations

- Consider a patient as FAMMM if all of the following criteria apply:
  - Malignant melanoma in one or more first- or second-degree relatives
  - High total body nevi count (often >50) including some of which are clinically atypical

- Refer to a center for genetic counseling (preferably an affected member):
  - Families with 2 first degree relatives with melanoma
  - Families with 2 cases (even if more distant relatives) if one or more have had multiple primaries or the cases have the atypical mole syndrome (dysplastic nevi) as self-examination is then rather more difficult
  - Families with 3 or more cases of melanoma in the family (one of these cases may be pancreatic cancer)
  - Families with a patient with 3 or more primary melanoma

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

Follow-up of members of a FAMMM family

If you find a mutation in the family, carriers are considered at high risk and the following recommendations apply. Non-carriers in a known risk family may have an intermediate increased risk and should be managed as such.

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

The following recommendations can 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;
- 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 pancreas cancer. As these tests are not currently considered standard of care, these patients should be included in clinical research screening programs if possible.

5 NEUROFIBROMATOSIS 1

5.1 Introduction

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. Tumors 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.[29]

We found 2 guidelines that were consensus based and did not have a formal search strategy.[6, 7] These guidelines based themselves on the consensus guideline of the UK Neurofibromatosis Association.[30] Members of the United Kingdom Neurofibromatosis Association Clinical Advisory Board collaborated to produce a consensus statement on the current guidelines for diagnosis and management of NF1.[31]

We did a search for primary studies, details of our search can be found in Appendix 1.3.

5.2 Diagnostic criteria

The Consensus Development Conference proposed the name neurofibromatosis 1 and formulated the current diagnostic criteria, commonly indicated as the 'National Institutes of Health (NIH) Diagnostic Criteria for neurofibromatosis 1'.[32]

Two or more of the below 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 groin 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

Early diagnosis is hampered by the fact that clinical signs appear at different times. Ferner et al. reviewed the clinical symptoms and the age of onset.[33] Common features as skin-fold freckling (85%) and Lisch nodules (>95%) appear after 3 years and cutaneous neurofibromas (>99%) appear after 7 years and usually in the late teens.

Debella et al.[34] studied 1 893 NF1 patients under 21 years old from the National Neurofibromatosis Foundation International Database to determine the age at which the features included in the NIH Diagnostic Criteria appear. Approximately 46% of sporadic NF1 cases fail to meet the NIH Diagnostic Criteria by 1 year of age. Nearly all (97%; 95% confidence interval: 94-98) NF1 patients meet the criteria for diagnosis by the age of 8 years, and all do so by the age of 20 years. The usual order of appearance of the clinical features listed as NIH criteria is *café-au-lait* macules, axillary freckling, Lisch nodules, and neurofibromas. Symptomatic optic glioma is usually diagnosed by 3 years old, and characteristic osseous lesions are usually apparent within the first year of life.

'Legius syndrome presents as a mild neurofibromatosis type 1 (NF1) phenotype. Multiple *café-au-lait* spots and macrocephaly are present with or without axillary or inguinal freckling. Other typical NF1-associated features (Lisch nodules, bone abnormalities, neurofibromas, optic pathway gliomas, and malignant peripheral nerve sheath tumors) are systematically absent.'[35] Messiaen et al.[36] reported a pathogenic NF1 mutation was identified in 43% of sporadic cases (*café-au-lait* spots only with or without freckling and no other diagnostic criteria) and only in 1.3% a pathogenic SPRED1 mutation was found. In the cohort of familial cases with the same phenotypic criteria, 73% carried a NF1 mutation and 19% a SPRED1 mutation.

5.3 Genetic testing

Role of genetic testing in the diagnosis of NF1 is not assessed in formal validation studies, information comes mainly from reports of testing of series of patients fulfilling NF1 criteria to a variable degree.

Messiaen et al.[37] studied 67 unrelated NF1 patients fulfilling the NIH diagnostic criteria, 29 familial and 38 sporadic cases, using a cascade of complementary techniques. They identified the germline mutation in 64 of 67 patients and 32 of the mutations were novel.

Griffiths et al.[38] studied 169 unrelated individuals suspected of having neurofibromatosis type I (NF1) over a 2 year period. Possible disease causing mutations were identified in 109 (64%) cases. These comprised 88 different sequence alterations, of which 57 were novel. Out of the 169 cases referred, there were 102 patients with reliable clinical data, of whom 78 satisfied the NIH diagnostic criteria for NF1. Within this cohort of NF1 patients, NF1 mutations were identified in 61 individuals (78%).

Valero et al.[39] validated their genetic protocol for molecular diagnosis of NF1 it in a cohort of 56 unrelated NF1 patients. All of the cases presented at least two diagnostic criteria for NF1. They identified a germline mutation in 53 cases (95%), none of the three negative patients displayed a SPRED1-like phenotype.

Sabbagh et al.[40] did a comprehensive mutation analysis of 565 unrelated patients from the NF-France Network. A NF1 mutation was identified in 546 of the 565 patients, this corresponds to a mutation detection rate of 97%.

5.4 Diagnostic work-up and follow-up

The optimal follow up of NF1 patients is based on expert opinion. The United Kingdom Neurofibromatosis Association Clinical Advisory Board[31] made a consensus statement recommending regular annual visits and to record the following:

- 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 and/or underlying plexiform neurofibromas)
- Evaluation of the skin (cutaneous, subcutaneous and plexiform neurofibromas)
- System examination if specific symptoms

They recommend visual assessment in young children because they do not complain of visual impairment. They also consider, given the high frequency of learning and behavioral problems in NF1 children, that monitoring is essential. Baseline brain and spine MRI, and routine imaging of the chest and abdomen to identify asymptomatic tumors, do not influence management and international guidelines discourage its use.

Conclusions

- NF1 mutations are found in 78 to 97% of cases fulfilling the consensus NF criteria.
- Early diagnosis is hampered by the fact that clinical signs appear at different times.
- There is a consensus that follow-up should be regular and focus on visual and cognitive impairment.
- There is no proof that routine screening with imaging is helpful.
- Part of the attenuated forms are caused by mutations in SPRED1 and may be undistinguishable from NF1 on clinical grounds.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	*Direct benefit of genetic testing for patients with a clear diagnosis is not clear, but can help with reproductive decisions. Testing is especially useful in cases of doubt, e.g. to distinguish NF1 and SPRED1 in attenuated forms.*
Quality of evidence	*We only have limited observational evidence on the presence of mutations among NF1 patients and prognostic evidence. Evidence is often difficult to interpret because testing is done on a subset of patients responding to certain criteria and not population based. Recommendations on follow up are essentially expert opinion based.*
Patients values and preferences	*Due to the impact of such diagnosis on patients and their relatives, psychosocial support (how to deal with distress, how to deal with social issues ex. insurance, return to work etc.) should be offered to every patient during the entire process (before diagnosis, during testing and follow-up).*

Recommendations

- Diagnostic criteria: two or more of the below 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 groin 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 testing and counselling.
- 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 according to the NIH) *café-au-lait* spots with or without axillary or inguinal freckling but no other NF1 related NIH criteria should be tested for NF1 first and if negative for SPRED1.

- Genetic counselling prior to conception is advised in all NF1 individuals.

- Children should be followed up every 6 to 12 months up to the age of 7 and annually until the age of 18. After the age of 18 they should be seen every 2 to 3 years, The following should be recorded annually:
  - 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 ± underlying plexiform neurofibromas)
  - Evaluation of the skin (cutaneous, subcutaneous and plexiform neurofibromas)
  - System examination if specific symptoms
- 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.
- Preimplantation and prenatal diagnosis for neurofibromatosis can be offered.

6 NEUROFIBROMATOSIS 2

'Neurofibromatosis type 2 is a multiple neoplasia syndrome that results from a mutation in the NF2 tumour suppressor gene on chromosome 22q12. The disorder occurs in one in 25 000 live births and is inherited as an autosomal dominant trait. It has wide phenotypic variability and nearly 100% penetrance by 60 years of age. Improvements in diagnosis and treatment have led to a rise in the diagnostic prevalence from one in 210 000 in 1992, to one in 100 000 people in 2005.'[41]

6.1 Diagnostic criteria

We found 2 guidelines that were consensus based and did not have a formal search strategy.[6, 7] These guidelines based themselves on the consensus guideline of the UK Neurofibromatosis Association.[30]

We did a search for systematic reviews and primary studies, details can be found in Appendix 1.4

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

1. Unilateral vestibular schwannoma (VS) or

2. 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

We found 2 validation studies on the diagnostic criteria in patients with no family history and without bilateral schwannomas (considered to be pathognomonic). Both validation studies are based on the United Kingdom NF2 registry. We did not apply the QUADAS checklist for diagnostic tests as these are not classic validation studies for diagnostic test. We will discuss the possible biases of the studies instead.

Baser et al.[42] evaluated the Manchester criteria, the NIH criteria and the criteria of the national Neurofibromatosis Foundation (that are very similar to the Manchester criteria) on 163 of 403 people in the United Kingdom NF2 registry (41%) who presented without bilateral vestibular schwannomas. The authors applied the sets of criteria to each person at initial assessment and at the most recent clinical evaluation (mean length of follow-up 13 years). In people with "definite NF2" and a negative family history of NF2, the 1987 US NIH and 1991 NIH criteria each identify 78% of people at the most recent clinical evaluation but 0% at initial assessment. The National Neurofibromatosis Foundation (NNFF) criteria and the Manchester criteria each identify higher proportions at both time points (NNFF criteria, 91% and 10%; Manchester criteria, 93% and 14%), but the proportions at initial assessment are still low.

Main limitation of this study is the fact that recruitment in the registry is based on clinical suspicion and therefore entry into the database is not independent from the criteria, part or even most of the patients are tested precisely because they respond to a certain degree to some of the criteria that were evaluated.

Baser et al.[43] calculated the sensitivity and specificity of the Manchester criteria, the NIH criteria and the criteria of the national Neurofibromatosis Foundation based on 67 patients with definite NF2 and 142 who definitely do not have NF2 at the age of onset of the first characteristic sign of NF2. They found a sensitivity of 70% for the Manchester criteria, and lower sensitivities for the other sets of criteria. All sets had 100% specificity. Apart from the limitations related to the use of a registry, similar to the limitations mentioned for the first study, a case control design was used, with clearly defined cases and clearly defined controls. This design is known to lead to overestimation of both the sensitivity and specificity. They developed a scoring system (that they called themselves 'Baser criteria') that has sensitivity of 79 % (a 9 to 15 increase compared to existing sets of criteria) without loss of specificity (still 100 %) at age of onset of first symptom.

It weights symptoms before the age of 30 more, to address the problem of low sensitivity at age of onset. Development and validation were done in a case control design, independent validation is needed. Details of the scoring is given in Appendix 2.

Hagel et al.[44] suggested that the term “glioma” in the current diagnostic criteria for NF2 should be specified as “spinal ependymoma”.

6.2 Follow-up

The UK Neurofibromatosis Association has published consensus guidelines for the management of NF2. On the basis of expert opinion, they made following recommendations:

- Children of affected patients should be considered to be at 50% risk of NF2. Ophthalmology 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) monitoring 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 tumors. If tumors are present, MRIs should be conducted at least annually until the rates of tumour growth are established.

We did not find studies on follow-up of patients.

Conclusions

- Manchester criteria seem highly specific but only moderately sensitive among patients without family history or bilateral schwannomas. Sensitivity is low at age of onset, as most criteria only become apparent over time.
- A more sensitive scoring systems was developed but needs more independent validation.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	*Given the poor sensitivity of clinical diagnostic criteria and the debilitating nature of the disease, testing has a clear added value*
Quality of evidence	*Two validation studies show that the Manchester criteria have good specificity but moderate to poor sensitivity, especially at onset of the symptoms. The studies suffer from several forms of bias.* *No studies assessing different follow up methods were found, recommendations are consensus based.*
Patients values and preferences	*Due to the impact of such diagnosis on patients and their relatives, psychosocial support (how to deal with distress, how to deal with social issues ex. insurance, return to work etc.) should be offered to every patient during the entire process (before diagnosis, during testing and follow-up).*

Recommendations

- Patients suspected with NF2 should be referred to a centre for genetic testing and counselling.
- Decision to test for NF2 should be based on clinical suspicion. Manchester criteria 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) monitoring 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.

7 ADDITIONAL CONSIDERATIONS

7.1 Adequate information and support for patients 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.

7.2 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 / psychologists are well informed about genetic mutations.

7.3 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 in at risk subjects will be monitored by the authors. This guideline should be updated when sufficient 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.

APPENDICES

APPENDIX 1. DETAILED SEARCH STRATEGIES

Appendix 1.1. Birt-Hogg-Dubé syndrome

Appendix 1.1.1. PICO

Project number		
Project name	**Oncogenetic_testing_dermatology**	
Search question(s)	**Birt-Hogg-Dubé**	
Structured search question(s) (PICO, SPICE, ECLIPSE, ..)		***and related keywords***
P (patient)	Suspected Birt-Hogg-Dubé	
I (Intervention)	Genetic testing	
C (comparison)	No testing	
O (outcome)	any	
S (settings)	**any**	

Appendix 1.1.2. Search strategies

Date	**2014-07-30**		
Database	**Medline (OVID)**		
Search Strategy	#	***Query***	*Results*
	1	exp genetic counseling/	**11952**
	2	exp Genetic testing/	**26876**
	3	exp DNA mutational analysis/	**47423**
	4	exp Heterozygote Detection/	**8115**
	5	exp Microarray Analysis/	**75859**
	6	(genet* adj3 (test* or screened or screening or detect* or assess* or profil* or counsel?ing)).tw.	**45982**
	7	((proteom* or genom* or gene? or sequence?) adj3 (screening or profil* or sequencing or screening or screened)).tw.	**74243**
	8	(expression adj3 profil*).tw.	**50610**
	9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	**263958**
	10	Birt-Hogg-Dube Syndrome/	**108**
	11	(birt adj5 hogg adj5 dube).tw.	**346**
	12	fibrofolliculoma?.tw.	**147**
	13	trichodiscoma?.tw.	**73**
	14	acrochordon?.tw.	**104**
	15	12 and 13 and 14	**25**
	16	hornstein.tw.	**13**
	17	kickenberg.tw.	**0**
	18	"bhd syndrome".tw.	**72**
	19	10 or 11 or 15 or 16 or 17 or 18	**375**
	20	9 and 19	**52**
Note			

Date	**2014-07-30**		
Database	**Embase (Embase.com)**		
Search Strategy (attention, for PubMed, check « Details »)	#	***Query***	*Results*
	#1	'genetic screening'/exp	**46,028**
	#2	'genetic counseling'/exp	**21,431**
	#3	'nucleotide sequence'/exp	**423,978**
	#4	'heterozygote detection'/exp	**5,882**
	#5	'microarray analysis'/exp	**39,450**
	#6	(genet* NEAR/3 (test* OR screened OR screening OR detect* OR assess* OR profil* OR counseling OR counselling)):ab,ti	**58,604**
	#7	((proteom* OR genom* OR gene OR genes OR sequence OR sequences) NEAR/3 (screening OR profil* OR sequencing OR screening OR screened)):ab,ti	**90,794**
	#8	(expression NEAR/3 profil*):ab,ti	**65,069**
	#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	**633,109**
	#10	'birt hogg dube syndrome'/exp	**635**
	#11	(birt NEAR/5 hogg):ab,ti	**553**
	#12	fibrofolliculoma:ab,ti OR fibrofolliculomas:ab,ti	**246**
	#13	trichodiscoma:ab,ti OR trichodiscomas:ab,ti	**104**
	#14	acrochordon:ab,ti OR acrochordons:ab,ti	**135**
	#15	#12 AND #13 AND #14	**38**
	#16	hornstein:ab,ti	**23**
	#17	kickenberg:ab,ti	**0**
	#18	'bhd syndrome':ab,ti	**137**
	#19	#10 OR #11 OR #15 OR #16 OR #17 OR #18	**787**
	#20	#9 AND #19	**125**
Note			

Date	**2014-07-30**		
Database	**Cochrane**		
Search Strategy (attention, for PubMed, check « Details »)	#	***Query***	*Results*
	#1	MeSH descriptor: [Birt-Hogg-Dube Syndrome] explode all trees	**0**
	#2	birt:ab,ti	**1**
	#3	hogg:ab,ti	**7**
	#4	dube:ab,ti	**2**
	#5	#2 and #3 and #4	**1**
	#6	fibrofolliculoma*:ab,ti	**0**
	#7	trichodiscoma*:ab,ti	**0**
	#8	acrochordon*:ab,ti	**0**
	#9	hornstein:ab,ti	**1**
	#10	kickenberg:ab,ti	**0**
	#11	"bhd syndrome":ab,ti	**0**
	#12	#1 or #5 or #9	**2**
Note			

Appendix 1.2. FAMMM

Appendix 1.2.1. PICO

Project number		
Project name	**Oncogenetic_testing_**	
Search question(s)	**FAMM**	
Structured search question(s) (PICO, SPICE, ECLIPSE, ..)		***and related keywords***
P (patient)	Suspected FAMMM	
I (Intervention)	Genetic testing	
C (comparison)	No testing	
O (outcome)	any	
S (settings)	**any**	

Appendix 1.2.2. Search strategies

Date	**2014-07-17**		
Database	**Medline (OVID)**		
Search Strategy	*#*	***Query***	*Results*
	1	fammm.tw.	**61**
	2	Dysplastic Nevus Syndrome/	**990**
	3	(familial adj3 melanoma?).ti,ab.	**471**
	4	("B-K mole" adj3 (syndrome or melanoma)).ab,ti.	**19**
	5	1 or 2 or 3 or 4	**1447**
	6	exp Genetic testing/	**26846**
	7	exp genetic counseling/	**11945**
	8	exp DNA mutational analysis/	**47377**
	9	exp Heterozygote Detection/	**8114**
	10	exp Microarray Analysis/	**75780**
	11	6 or 7 or 8 or 9 or 10	**159284**

	12	(genet* adj3 (test* or screened or screening or detect* or assess* or profil* or counsel?ing)).tw.	**45842**
	13	((proteom* or genom* or gene? or sequence?) adj3 (screening or profil* or sequencing or screening or screened)).tw.	**73883**
	14	(expression adj3 profil*).tw.	**50366**
	15	12 or 13 or 14	**139820**
	16	11 or 15	**263221**
	17	5 and 16	**115**
	18	limit 17 to systematic reviews	**2**
Note	**Results imported in endnote in 3 parts with automatic duplicates removal.** **Part 1: Systematic reviews (line 18) 2 results, no duplicates** **Part 2: genetic testing (line 17) 115 results, 4 duplicates removed** **Part 3: fammm all (line 5) 1447 results, 132 duplicates removed**		

Date	**2014-07-18**		
Database	**Embase (Embase.com)**		
Search Strategy (attention, for PubMed, check « Details »)	#	***Query***	*Results*
	#1	'familial atypical multiple mole melanoma syndrome'/exp	**102**
	#2	'dysplastic nevus'/exp	**1,854**
	#3	familial:ab,ti OR multiple:ab,ti OR syndrome:ab,ti	**1,858,111**
	#4	#2 AND #3	**516**
	#5	#1 OR #4	**609**
	#6	fammm:ab,ti	**76**
	#7	(familial NEAR/3 melanoma*):ab,ti	**566**
	#8	('b-k mole' NEAR/3 (syndrome OR melanoma*)):ab,ti	**27**
	#9	#5 OR #6 OR #7 OR #8 AND [embase]/lim	**1,028**
	#10	#5 OR #6 OR #7 OR #8 AND [medline]/lim AND [embase]/lim	**765**
	#11	#9 NOT #10	**263**

	#12	'genetic screening'/exp	**45,842**
	#13	'genetic counseling'/exp	**21,372**
	#14	'nucleotide sequence'/exp	**423,100**
	#15	'heterozygote detection'/exp	**5,879**
	#16	'microarray analysis'/exp	**39,287**
	#17	#12 OR #13 OR #14 OR #15 OR #16	**517,244**
	#18	(genet* NEAR/3 (test* OR screened OR screening OR detect* OR assess* OR profil* OR counsel?ing)):ab,ti	**50,570**
	#19	((proteom* OR genom* OR gene OR genes OR sequence OR sequences) NEAR/3 (screening OR profil* OR sequencing OR screening OR screened)):ab,ti	**90,472**
	#20	(expression NEAR/3 profil*):ab,ti	**64,854**
	#21	#18 OR #19 OR #20	**166,431**
	#22	#17 OR #21	**629,356**
	#23	#11 AND #22	**37**
Note	**Results imported in endnote in 2 parts with automatic duplicates removal.** **Part 1: fammm genetic testing (line 23) no duplicates discarded** **Part 2: fammm all (line 11) 263 results, 37 duplicates removed**		

Date	**2014-07-18**		
Database	**Cochrane**		
Search Strategy (attention, for PubMed, check « Details »)	#	***Query***	*Results*
	#1	fammm:ti,ab,kw	**0**
	#2	MeSH descriptor: [Dysplastic Nevus Syndrome] explode all trees	**6**
	#3	(familial near/3 melanoma*):ti,ab	**1**
	#4	("B-K mole" near/3 (syndrome or melanoma)):ti,ab	**0**
	#5	#1 or #2 or #3 or #4	**7**
Note	**7 results found in central, 1 title was relevant, after importation in Endnote, 5 duplicates were discarded including relevant one.**		

Appendix 1.3. Neurofibromatosis 1

Appendix 1.3.1. PICO

Project number		
Project name	**Oncogenetic_testing_**	
Search question(s)	**Neurofibromatosis 1**	
Structured search question(s) (PICO, SPICE, ECLIPSE, ..)		***and related keywords***
P (patient)	Suspected Neurofibromatosis 1	
I (Intervention)	Genetic testing	
C (comparison)	No testing	
O (outcome)	any	
S (settings)	**any**	

Appendix 1.3.2. Search strategies

Date	**2014-07-28**		
Database	**Medline (OVID)**		
Search Strategy	#	***Query***	*Results*
	1	Neurofibromatosis 1/	**7584**
	2	(neurofibromatos* adj3 ("1" or i)).tw.	**4876**
	3	recklinghausen*.tw.	**2963**
	4	(recklinghausen* adj3 disease).tw.	**1995**
	5	(watson adj2 syndrome).tw.	**21**
	6	nf1.tw.	**3589**
	7	"molluscum fibrosum".tw.	**15**
	8	("cafe au lait" adj3 spot?).tw.	**748**
	9	2 or 3 or 4 or 5 or 6 or 7 or 8	**9001**
	10	1 or 9	**11722**
	11	exp Genetic testing/	**26876**
	12	exp genetic counseling/	**11952**

	13	exp DNA mutational analysis/	**47423**
	14	exp Heterozygote Detection/	**8115**
	15	exp Microarray Analysis/	**75859**
	16	11 or 12 or 13 or 14 or 15	**159440**
	17	(genet* adj3 (test* or screened or screening or detect* or assess* or profil* or counsel?ing)).tw.	**45962**
	18	((proteom* or genom* or gene? or sequence?) adj3 (screening or profil* or sequencing or screening or screened)).tw.	**74174**
	19	(expression adj3 profil*).tw.	**50561**
	20	17 or 18 or 19	**140326**
	21	16 or 20	**263850**
	22	Genes, Neurofibromatosis 1/	**746**
	23	(test* or screened or screening or detect* or assess* or profil* or counsel?ing).tw.	**5303412**
	24	22 and 23	**276**
	25	10 and 21	**719**
	26	24 or 25	**880**
	27	limit 26 to systematic reviews	**7**
	28	neurofibromatoses/	**1545**
	29	neurofibroma?.tw.	**4348**
	30	28 OR 29	**5695**
	31	21 AND 30	**175**
	32	31 NOT 26	**37**
Note	**7 results for systematic reviews** **880 results for all publications** **Line 32: Additional references using a more general MeSH but not specific to Neurofibromatosis type I. References were imported into a separate folder in EndNote file.**		

Date	**2014-07-28**		
Database	**Embase (Embase.com)**		
Search Strategy (attention, for PubMed, check « Details »)	*#*	***Query***	*Results*
	#1	'neurofibromatosis'/exp	**16,058**
	#2	(neurofibromatos* NEAR/3 (1 OR i OR peripheral)):ab,ti	**5,950**
	#3	recklinghausen*:ab,ti	**3,568**
	#4	(recklinghausen* NEAR/3 disease):ab,ti	**2,388**
	#5	(watson NEAR/3 syndrome):ab,ti	**31**
	#6	nf1:ab,ti	**4,465**
	#7	'molluscum fibrosum':ab,ti	**8**
	#8	('cafe au lait' NEAR/3 (spot OR spots)):ab,ti	**1,068**
	#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	**19,065**
	#10	'genetic screening'/exp	**46,016**
	#11	'genetic counseling'/exp	**21,430**
	#12	'nucleotide sequence'/exp	**423,886**
	#13	'heterozygote detection'/exp	**5,881**
	#14	'microarray analysis'/exp	**39,433**
	#15	#10 OR #11 OR #12 OR #13 OR #14	**518,344**
	#16	(genet* NEAR/3 (test* OR screened OR screening OR detect* OR assess* OR profil* OR counseling or counselling)):ab,ti	**58,587**
	#17	((proteom* OR genom* OR gene OR genes OR sequence OR sequences) NEAR/3 (screening OR profil* OR sequencing OR screening OR screened)):ab,ti	**90,765**
	#18	(expression NEAR/3 profil*):ab,ti	**65,051**
	#19	#16 OR #17 OR #18	**174,610**
	#20	#15 OR #19	**632,950**
	#21	#9 AND #20	**1,512**
	#22	#21 AND [medline]/lim	**1,116**
	#23	#21 NOT #22	**396**

	#24	#23 AND ([editorial]/lim OR [letter]/lim OR [note]/lim)	**12**
	#25	#23 NOT #24	**384**
	#26	#25 AND [animals]/lim NOT (#25 AND [humans]/lim)	**8**
	#27	#25 NOT #26	**376**
	#28	[cochrane review]/lim OR 'systematic review'/de OR 'meta analyse' OR [meta analysis]/lim OR [systematic review]/lim OR 'meta analyses' OR 'meta analysis'/de	**142,474**
	#29	#27 AND #28	**1**
Note			

Date	**2014-07-28**		
Database	**Cochrane**		
Search Strategy	*#*	***Query***	*Results*
	#1	MeSH descriptor: [Neurofibromatosis 1] explode all trees	**14**
	#2	(neurofibromatos* near/3 ("1" or i or peripheral)):ti,ab	**20**
	#3	recklinghausen*:ti,ab	**0**
	#4	(recklinghausen* near/3 disease):ti,ab	**0**
	#5	(watson near/2 syndrome):ti,ab	**0**
	#6	nf1:ti,ab	**18**
	#7	"molluscum fibrosum":ti,ab	**0**
	#8	("cafe au lait" near/3 (spot or spots)):ab,ti	**1**
	#9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8	**25**
	#10	MeSH descriptor: [Genetic Testing] explode all trees	**487**
	#11	MeSH descriptor: [Genetic Counseling] explode all trees	**142**
	#12	MeSH descriptor: [DNA Mutational Analysis] explode all trees	**231**
	#13	MeSH descriptor: [Heterozygote Detection] explode all trees	**65**
	#14	MeSH descriptor: [Microarray Analysis] explode all trees	**268**
	#15	#10 or #11 or #12 or #13 or #14	**1040**

	#16	(genet* near/3 (test* or screened or screening or detect* or assess* or profil* or counselling or counseling)):ti,ab	**639**
	#17	((proteom* or genom* or gene or genes or sequence or sequences) near/3 (screening or profil* or sequencing or screening or screened)):ab,ti	**8584**
	#18	(expression near/3 profil*):ti,ab	**305**
	#19	#16 or #17 or #18	**9262**
	#20	#15 or #19	**9883**
	#21	MeSH descriptor: [Genes, Neurofibromatosis 1] explode all trees	**0**
	#22	#9 and #20	**0**
Note			

Appendix 1.4. Neurofibromatosis 2

Appendix 1.4.1. PICO

Project number		
Project name	**Oncogenetic_testing_**	
Search question(s)	**Neurofibromatosis 2**	
Structured search question(s) (PICO, SPICE, ECLIPSE, ..)		***and related keywords***
P (patient)	Suspected Neurofibromatosis 2	
I (Intervention)	Genetic testing	
C (comparison)	No testing	
O (outcome)	any	
S (settings)	**any**	

Appendix 1.4.2. Search strategies

Date	**2014-07-28**		
Database	**Medline (OVID)**		
Search Strategy	#	***Query***	*Results*
	1	Neurofibromatosis 2/	**1083**
	2	nf2.tw.	**1359**
	3	nf2s.tw.	**3**
	4	(neurofibromatos* adj ("2" or ii or central)).tw.	**491**
	5	((neuroma? or schwannoma? or neurinoma?) adj5 acoustic adj5 (bilateral or familial)).tw	**214**
	6	2 or 3 or 4 or 5	**1712**
	7	1 or 6	**2107**
	8	Genes, Neurofibromatosis 2/	**420**
	9	(test* or screened or screening or detect* or assess* or profil* or counsel?ing).tw.	**5303412**
	10	8 and 9	**167**
	11	exp Genetic testing/	**26876**
	12	exp genetic counseling/	**11952**
	13	exp DNA mutational analysis/	**47423**
	14	exp Heterozygote Detection/	**8115**
	15	exp Microarray Analysis/	**75859**
	16	11 or 12 or 13 or 14 or 15	**159440**
	17	(genet* adj3 (test* or screened or screening or detect* or assess* or profil* or counsel?ing)).tw	**45962**
	18	((proteom* or genom* or gene? or sequence?) adj3 (screening or profil* or sequencing or screening or screened)).tw.	**74174**
	19	(expression adj3 profil*).tw.	**50561**
	20	17 or 18 or 19	**140326**
	21	16 or 20	**263850**
	22	7 and 21	**263**

	23	10 or 22	**357**
	24	limit 23 to systematic reviews	**9**
Note			

Date	**2014-07-28**		
Database	**Embase (Embase.com)**		
Search Strategy (attention, for PubMed, check « Details »)	#	***Query***	*Results*
	#1	'neurofibromatosis'/exp	**16,058**
	#2	nf2:ab,ti	**1,636**
	#3	nf2s:ab,ti	**3**
	#4	(neurofibromatos* NEAR/2 (2 OR ii OR central)):ab,ti	**1,958**
	#5	((neuroma OR neuromas OR schwannoma OR schwannomas OR neurinoma OR neurinomas) NEAR/5 acoustic):ab,ti AND (bilateral:ab,ti OR familial:ab,ti)	**413**
	#6	#1 OR #2 OR #3 OR #4 OR #5	**17,077**
	#7	'genetic screening'/exp	**46,016**
	#8	'genetic counseling'/exp	**21,430**
	#9	'nucleotide sequence'/exp	**423,886**
	#10	'heterozygote detection'/exp	**5,881**
	#11	'microarray analysis'/exp	**39,433**
	#12	#10 OR #11 OR #12 OR #13 OR #14	**518,344**
	#13	(genet* NEAR/3 (test* OR screened OR screening OR detect* OR assess* OR profil* OR counseling or counselling)):ab,ti	**58,587**
	#14	((proteom* OR genom* OR gene OR genes OR sequence OR sequences) NEAR/3 (screening OR profil* OR sequencing OR screening OR screened)):ab,ti	**90,765**
	#15	(expression NEAR/3 profil*):ab,ti	**65,051**
	#16	#13 OR #14 OR #15	**174,610**
	#17	#15 OR #19	**632,950**
	#18	#17 AND #6	**1,230**

	#19	#18 AND [medline]/lim	**947**
	#20	#18 NOT #19	**283**
	#21	#20 AND ([editorial]/lim OR [letter]/lim OR [note]/lim)	**12**
	#22	#20 NOT #21	**271**
	#23	#39 AND [animals]/lim NOT (#39 AND [humans]/lim)	**7**
	#24	#39 NOT #40	**264**
	#25	[cochrane review]/lim OR 'systematic review'/de OR 'meta analyse' OR [meta analysis]/lim OR [systematic review]/lim OR 'meta analyses' OR 'meta analysis'/de	**142,474**
	#26	#24 AND #25	**0**
Note			

Date	**2014-07-28**		
Database	**Cochrane**		
Search Strategy (attention, for PubMed, check « Details »)	#	***Query***	*Results*
	#1	(neurofibromatos* near/3 ("2" or ii or central)):ti,ab	**3**
	#2	((neuroma or neuromas or schwannoma or schwannomas or neurinoma or neurinomas) near/5 acoustic):ti,ab and (bilateral or familial):ti,ab	**0**
	#3	nf2:ti,ab	**1**
	#4	nf2s:ti,ab	**0**
	#5	#1 or #2 or #3 or #4	**3**
	#6	MeSH descriptor: [Genetic Testing] explode all trees	**487**
	#7	MeSH descriptor: [Genetic Counseling] explode all trees	**142**
	#8	MeSH descriptor: [DNA Mutational Analysis] explode all trees	**231**
	#9	MeSH descriptor: [Heterozygote Detection] explode all trees	**65**
	#10	MeSH descriptor: [Microarray Analysis] explode all trees	**268**
	#11	#6 or #7 or #8 or #9 or #10	**1040**
	#12	(genet* near/3 (test* or screened or screening or detect* or assess* or profil* or counselling or counseling)):ti,ab	**639**

	#13	((proteom* or genom* or gene or genes or sequence or sequences) near/3 (screening or profil* or sequencing or screening or screened)):ab,ti	**8584**
	#14	(expression near/3 profil*):ti,ab	**305**
	#15	#12 or #13 or #14	**9262**
	#16	#11 or #15	**9883**
	#17	MeSH descriptor: [Neurofibromatosis 2] explode all trees	**2**
	#18	#5 or #17	**4**
	#19	#16 and #18	**0**
Note			

APPENDIX 2. BASER CRITERIA FOR DIAGNOSIS OF NF2

Table 3 The Baser criteria for diagnosis of NF2

Feature	If present at or before the age of 30 yr	If present after the age of 30 yr
First-degree relative with NF2 diagnosed by these criteria	2	2
Unilateral vestibular schwannoma	2	1[a]
Second vestibular schwannoma	4	3[a]
One meningioma	2	1
Second meningioma (no additional points for more than two meningiomas)	2	1
Cutaneous schwannoma (one or more)	2	1
Cranial nerve tumor (excluding vestibular schwannoma) (one or more)	2	1
Mononeuropathy	2	1
Cataract (one or more)	2	0

The patient is given points as shown in the table.

[a]Points are not given for unilateral or second vestibular schwannoma if age at diagnosis is more than 70 yr.

- A diagnosis of definite NF2 is established if the total number of points is 6 or more.
- *NF2* mutation testing is indicated if the total number of points is 4 or 5.
  - A diagnosis of definite NF2 is established if a constitutional pathogenic *NF2* mutation is found on mutation testing.
  - If no constitutional pathogenic *NF2* mutation is found on mutation testing:
    - A diagnosis of mosaic NF2 is established if mosaicism for a pathogenic *NF2* mutation is found in the blood or no detectable pathogenic *NF2* mutation is found in the blood but the same pathogenic *NF2* mutation is found in two separate NF2-associated tumors.
    - Otherwise, a temporary diagnosis of possible NF2 is made, pending further clarification. Clarification may occur if the patient is established to have a different condition (e.g., schwannomatosis or multiple meningiomas) by standard diagnostic criteria or if evolution of the patient's disease over time permits establishing a diagnosis of definite NF2 or mosaic NF2 according to the criteria given above.

Source: Baser et al.[43]

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