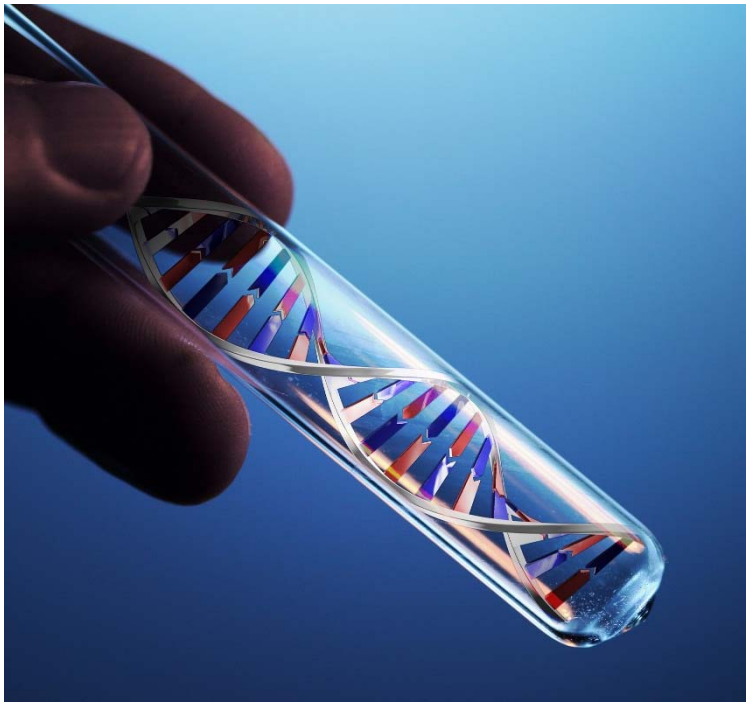
KCE REPORT 236

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

ONCOGENETIC TESTING AND FOLLOW-UP FOR WOMEN WITH FAMILIAL BREAST/OVARIAN CANCER, LI-FRAUMENI SYNDROME AND COWDEN SYNDROME



KCE REPORT 236
GOOD CLINICAL PRACTICE

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ONCOGENETIC TESTING AND FOLLOW-UP FOR WOMEN WITH FAMILIAL BREAST/OVARIAN CANCER, LI-FRAUMENI SYNDROME AND COWDEN SYNDROME

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COLOPHON

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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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This document is available on the website of the Belgian Health Care Knowledge Centre.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AGREE	Appraisal of Guidelines for Research and Evaluation
AHRQ	Agency for Healthcare Research and Quality
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
CEBAM	Belgian Centre for Evidence-Based Medicine
CI	Confidence interval
CPG	Clinical Practice Guideline
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICER	Incremental cost-effectiveness ratio
IQR	Interquartile Range
KCE	Belgian Health Care Knowledge Centre
LFS	Li-Fraumeni Syndrome
LFS criteria	Li-Fraumeni Syndrome criteria
LFL	Li-Fraumeni like (criteria)
MA	Meta-analysis
MRI	Magnetic resonance imaging
NIHDI (RIZIV/INAMI)	National Institute for Health and Disability Insurance
PICO	Participants–Interventions–Comparator–Outcomes
QALY	Quality Adjusted Life Year
RCT	Randomised controlled trial
SR	Systematic Review

GLOSSARY

Cumulative risk	The absolute risk, or probability of an event occurring over a specified time period.
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.
Lifetime risk	The risk of developing a disease during one's lifetime or dying of the disease.
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 ascertained.
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.

SCIENTIFIC REPORT

1 INTRODUCTION

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

1.1 Background

Oncogenetic tests are tests that assist in the diagnosis of specific cancers that have an important hereditary component. Such tests may also assist to identify which family members are at risk of developing specific forms of cancer when one member is diagnosed with a breast/ovarian cancer. Criteria are needed for the identification and referral of individuals and patients to genetic centres for counselling, possibly followed by germline mutation analysis.

About 5% of all breast cancers are largely attributable to inherited mutations in specific genes including BRCA1, BRCA2 and TP53 although there is considerable uncertainty around this figure, that may differ between countries. Patients may benefit from an early identification as preventive measures can be implemented, including enhanced surveillance, risk reducing surgery and chemoprophylaxis.

According to NICE (2013),[1] two key parameters are related to each other but should be clearly distinguished:

- Breast cancer risk: the risk that the individual will develop breast (or ovarian) cancer in the future. Breast cancer risk is frequently expressed as either the lifetime risk of developing the disease or as risk in the next 10 years.
- Carrier probability: the probability that the individual carries a deleterious mutation in one of the known breast (or ovarian) cancer susceptibility genes.

In the NICE guideline,[1] the genes associated with inherited breast cancer risk are listed. ‘At least five genes (BRCA1, BRCA2, TP53, E-Cadherin, STK11) are known to be associated with a high breast cancer risk (greater than 30% lifetime risk), but it is important to emphasise that these genes are not the only cause for familial breast cancer. It has been estimated that these

genes explain about 25% of the excess familial risk of breast cancer. Most of the remainder is likely to be due to low to moderate penetrance alleles. Of the known high risk genes, deleterious alleles of BRCA1 and BRCA2 are most common. Carriers of mutations in these genes have a high lifetime risk of breast cancer (variously estimated, depending on the context, as 65-85% for BRCA1 and 40-85% for BRCA2). Both genes also confer a high risk of ovarian cancer (around 40-50% for BRCA1, 10-25% for BRCA2) as well as more moderately increased risks of other cancers. BRCA1 and BRCA2 mutations explain a considerable proportion of very high risk families (that is, families with four or more close relatives with breast cancer), particularly if there is also a family history of ovarian cancer or of male breast cancer. Mutations in these genes are however rare in the general population, and probably only account for about 2% of breast cancer cases overall. Mutations in the TP53 gene predispose to a very high risk of breast cancer, such that the majority of women are affected before the age of 50. Mutations in this gene also predispose to a range of other cancers including childhood sarcomas and brain tumours, and mutations are therefore usually identified when these cancers occur together in families, a syndrome known as Li-Fraumeni syndrome. Mutations in TP53 are significantly rarer than BRCA1 or BRCA2 mutations. When considering genetic testing, as well as testing for the well known BRCA1, BRCA2 and TP53 genes, it may be important to consider other genes associated with a potentially high risk of breast cancer such as PTEN, Peutz-Jegher's syndrome and E-cadherin, where clinically appropriate. Mutations in the PTEN gene are responsible for Cowden's syndrome, a very rare inherited disorder associated with an increased risk of breast cancer. Mutations in two other genes, ATM and CHEK2, are associated with moderate risks of breast cancer; clinical genetic testing for these genes has not been implemented.'[1]

1.2 The need for a guideline

Criteria are needed for the identification and referral of patients with breast and/or ovarian cancer and their family members 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. In addition, the topic is timely. Firstly because the new nomenclature, introduced on 1/1/2013, for genetic tests (article 33) and the agreement on genetic testing consultation led to distribute the NIHDI budget between genetic counselling (€4,288 millions) and laboratory procedures (€37,795 millions)[a]. This new convention implies the development of genetic counselling activities by genetic centres. Secondly, because beyond Apart from a number of high penetrance genes, BRCA 1 and BRCA 2, TP53 for Li-Fraumeni syndrome and PTEN for Cowden syndrome, involved in familial risk for breast cancer and ovarian cancer, an increasing number of moderate- and low-penetrance genes are being identified. There is a need to standardise the use of oncogenetic tests based on the available evidence. Early identification of women at risk makes the initiation of life saving strategies possible, including enhanced surveillance, risk reducing surgery and chemoprophylaxis.

1.3 Scope

This guideline will cover following populations:

- Adult women (18 years and older) without breast cancer who may be at increased risk of developing breast cancer because of a family history of breast, ovarian or a related cancer;
- Adult women (18 years and older) with a recent diagnosis of breast cancer and a family history of breast, ovarian or a related cancer.
- Men affected with male breast cancer.

Children are not covered by this guideline.

The guideline will cover following issues:

- Who qualifies for a genetic test or criteria for genetic testing;
- Tests for which genes have clinical utility;
- What follow-up is recommended depending on test results and family history.

[a] Moreover, 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.

In two separate chapters we focused on the same issues for two more specific syndromes that are associated with an increased risk for breast cancer:

- Cowden syndrome
- Li-Fraumeni syndrome

However, we did not cover three syndromes that are also associated with an increased risk for breast cancer, i.e. Peutz-Jeghers (associated with STK11), Ataxia Telangiectasia (associated with ATM) and Hereditary Diffuse Gastric Cancer (associated with CDH1), neurofibromatosis type 1 (associated with NF1 mutations) or multiple endocrine neoplasia type 1 (caused by germline mutations in the MEN1 tumor-suppressor gene).[2] Moreover, it does not cover subsequent prophylactic treatment such as chemoprevention (e.g. Tamoxifen) or risk-reducing 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 persons at increased familial risk for breast and/or ovarian cancer. Clinicians are encouraged to interpret these recommendations in the context of the individual person situation, values and preferences.

The 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 counseling, testing and follow-up of patients with hereditary breast cancer, Li-Fraumeni syndrome and Cowden syndrome, in particular. It also contains recommendations for persons that must decide when to refer for genetic counselling and testing such as general practitioners, gynaecologists, oncologists, surgeons, radiologists and pathologists. It can also be of interest for patients and their families, hospital managers and policy makers.

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 geneticists, oncologists, gynaecologists and researchers for use within the Belgian healthcare context. It provides advice regarding the care and management of patients with hereditary breast cancer, Li-Fraumeni syndrome and Cowden syndrome to care providers involved in genetic counseling, testing and follow-up of these patients.

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

The KCE guideline is produced according to highly codified principles, based on scientific information regularly updated from the international literature. This guideline was developed using a standard methodology based on a systematic review of the evidence. Further details about KCE and the guideline development methodology are available at https://kce.fgov.be/content/kce-processes.

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 (see Appendix 1). 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. As the GRADE approach currently only applies for treatment interventions and not yet for diagnostic interventions, no grading of the recommendations was performed for this guideline.

2.2 The Guideline Development Group

This guideline was developed as a result of a collaboration between multidisciplinary groups of practising clinicians, geneticists and KCE experts. The composition of the GDG is documented in Appendix 1. The GDG consists of all authors listed 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 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

The CPG addressed the following clinical questions:

- Hereditary breast cancer
  - How to select the women who may have a hereditary risk of breast cancer based on family history?
    - What are the existing assessment tools?
    - What are their validity and their applicability in the Belgian context?
  - How to select the women where a possible hereditary raised risk of breast cancer was identified who are eligible for a genetic test?
    - What are the existing assessment tools?
    - What are their validity and their applicability in Belgian context?
  - Tests for which genes have clinical utility?
- Li-Fraumeni syndrome
  - What are the testing criteria?
  - What are the existing assessment tools?
  - What are their validity and their applicability in the Belgian context?
- Cowden syndrome
  - What are the testing criteria?
  - What are the existing assessment tools?
  - What are their validity and their applicability in the Belgian context?

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 published guidelines. If such guidelines are available, the ADAPTE methodology is followed (www.adapte.org). However, we assessed and summarized the underlying evidence where the recommendations of the guideline were based on. We only took over the recommendation if the GDG agreed with the interpretation and considered the guideline applicable to the Belgian context.

If no high-quality, recent guidelines are available, the general approach begins 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 was performed in MEDLINE and Embase. If no systematic review was available, a search for primary studies was performed in the same databases, without time restriction. Members of the guideline development group (GDG) were also consulted to identify additional relevant evidence that may have been missed by the search. The website 'Gene reviews' was consulted ad hoc for clarification as, while providing interesting background information, it is mainly based on expert opinion.

2.5 Literature search and study selection

2.5.1 Study design

- Inclusion criteria for the study design:
  - Diagnostic studies: systematic reviews, guidelines, meta-analyses, RCTs, prospective studies;
- Articles in Dutch, English, French and German were included.
- Exclusion criteria for study design
  - Narrative review
  - Cadaver/animal studies
  - Case reports
  - Studies presented as conference abstract only. If no full-text was available, the study was not taken into account for the final recommendations.
- An iterative approach was followed:
  - First, the search focused on clinical guidelines of high quality;
  - Second, a search for recently published systematic reviews and meta-analyses (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;
- search MEDLINE and at least one other electronic database;

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

To be included, a primary study had to:

- be an RCT, an observational study or a diagnostic accuracy study;
- address at least one of the research questions.

2.5.2 Databases and date limits

The following databases were included in the literature search:

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

For the guidelines the search engines were:

- G.I.N. guideline resource (http://www.g-i-n.net)
- National Comprehensive Cancer Network (NCCN) http://www.nccn.org/
- National Guideline Clearinghouse http://www.guideline.gov/
- NICE guidelines (http://www.nice.org.uk)

Members of the GDG were also consulted to identify relevant evidence that might have been missed during the search process.

2.5.3 Search strategy

A combination of appropriate MeSH terms and free text words was used. The search strategy, PICO's used to build the search strategy and number of articles per database are detailed in Appendix 2.

Studies were screened on **title and abstract** by one researcher (Jo Robays) with the PICO in- and exclusion criteria. In case of doubt, the content experts were consulted. First, the titles and abstracts of the identified studies were checked and irrelevant studies were eliminated. In a second step, the remaining papers were screened by reading their **full-text**. If no full-text was available, the study was excluded for the final recommendations. Reference

lists of the selected studies were hand-searched for additional relevant manuscripts. Due to limited resources, only articles available through the Vesalius Documentation and Information centre or Interlibrary Loan were retained.

The screening of the **guidelines** was performed on title and abstract by one researcher (Jo Robays) based on the PICO in- and exclusion criteria.

2.6 Quality appraisal

2.6.1 Clinical practice guidelines

The elements evaluating the rigour of development from the AGREE II instrument was used to evaluate the methodological quality of the identified international guidelines (www.agreetrust.org). We also took editorial independence into account. Based on an overall assessment, 2 high-quality guidelines were identified (i.e. AHRQ and NICE). The document issued by AHRQ did not contain clinical recommendations; however, we can use the systematic review done in preparation of those recommendations (to be issued by the U.S. Preventive Services Task Force Recommendation). Moreover, 1 additional guideline (NCCN) did not have a reported search strategy but was used for reference tracking and for comparison with the 2 other guidelines.

2.6.2 Systematic reviews

Selected (systematic) reviews were critically appraised by a single KCE expert (Jo Robays) using the AMSTAR checklist (http://amstar.ca/Amstar_Checklist.php).[3] In case of doubt, a second KCE expert was consulted. As AMSTAR cannot readily be used for systematic reviews of genetic association studies we complemented this with guidance from the Human Genome Epidemiology Network.[4]

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

2.7 Data extraction

For each included CPG the relevant recommendations were extracted.

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

Data extraction was performed by one researcher (Jo Robays) and entered in evidence tables using standard KCE templates. Any disagreements were resolved by discussion or, if required, by a third party. All evidence tables are reported in Appendix 3.

2.8 Grading evidence

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

2.9 Formulation of recommendations

Based on the retrieved evidence, the first draft of recommendations was prepared by a small working group (KCE experts and GDG members). This first draft was, together with the evidence tables, circulated to the guideline development group 2 weeks prior to the face-to-face meetings (30th April 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 (betwen 15th May 2014 and 2nd June 2014).

2.10 External review

2.10.1 Healthcare professionals

The recommendations prepared by the guideline development group were circulated to Professional Associations of physicians targeted by this guideline (Table 1). Each association was asked to assign one or two key representatives to act as external reviewers of the draft guideline. All representatives and their association are listed in the colophon under the section stakeholders as are their declarations of interest.

Globally, 11 external experts were involved in the evaluation of the clinical recommendations. All invited panellists received the scientific report for all research questions and were asked to indicate their level of agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' 'somewhat disagree', and '3' 'completely agree' (the panellists were also able to answer 'not applicable' if they were not familiar with the underlying evidence). If panellists disagreed with the recommendation, they were asked to provide an explanation supported by appropriate evidence and to suggest

a more appropriate formulation. Scientific arguments reported by these experts were used to adapt the formulation of the clinical recommendations.

Table 1 – List of Professional Associations invited

- Belgian Section of Breast Surgery (BSBS)
- Belgian Society for Human Genetics (BeSHG)
- Belgian Society for Surgical Oncology (BSSO)
- Belgian Society of Medical Oncology (BSMO)
- Belgian Society of Pathology - Belgische Vereniging Anatomopathologie - Société Belge d'Anatomopathologie: no representative appointed
- Belgische Genootschap voor Nucleaire Geneeskunde - Société Belge de Médecine Nucléaire: no representative appointed
- Belgische Vereniging voor Radiotherapie-Oncologie - Association Belge de Radiothérapie-Oncologie (BVRO - ABRO): no representative appointed
- College of Human Genetics
- Domus Medica
- Groupement des Gynécologues Obstétriciens de Langue Française de Belgique (GGOLFB)
- Royal Belgian Radiological Society - Koninklijke Belgische Vereniging voor Radiologie - Société Royale Belge de Radiologie (RBRS): no representative appointed
- Royal Belgian Society for Surgery (RBSS)
- Société Belge de Sénologie (SBS) – Belgische Vereniging voor Senologie (BVS)
- Société Scientifique de Médecine Générale (SSMG) : no representative appointed
- Vlaamse Vereniging voor Obstetrie en Gynaecologie (VVOG)

2.10.2 Patient representatives

Associations of patient representatives (Vlaamse Liga tegen Kanker, Fondation contre le Cancer, Europa Donna, BRCA.be) were contacted to invite patient representatives to take part in the stakeholder meeting (16th October 2014). A key role for patient representatives is to ensure that patient views and experiences inform the group's work. The patient representatives were asked to review the recommendations and add comments from a patients' perspective where needed.

For each recommendation where the patient representatives had a comment or suggestion, this was reported under 'other considerations'.

2.11 Final validation

As part of the standard KCE procedures, an external scientific evaluation of the report was conducted prior to its publication. The current guideline was reviewed by 4 independent assessors (cf. names in the colophon). Their comments and questions were forwarded to the GDG in order to finalize the scientific report (November 2014).

3 CLINICAL RECOMMENDATIONS

3.1 Hereditary breast cancer

3.1.1 Criteria for referral to a centre of human genetics specialized in cancer genetics and follow-up of women at-risk of hereditary breast cancer

In the KCE report 172 'Identifying women at risk for breast cancer/technical methods for breast cancer screening'[5] the following criteria were listed for referral of women to a centre of human genetics specialized in cancer genetics (these criteria were developed for a screening; women affected with breast cancer were out of scope):

Patients considered at high risk (that is, a 10-year risk at age 40–49 years of greater than 8% or a lifetime risk of 30% or greater):

- two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 50 years (at least one must be a first-degree relative), or
- three first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years (at least one must be a first-degree relative), or
- four relatives diagnosed with breast cancer at any age (at least one must be a first-degree relative).

OR one of the following is present in the family history

- Jewish ancestry
- bilateral breast cancer
- male breast cancer
- ovarian cancer
- sarcoma in a relative younger than 45 years of age
- glioma or childhood adrenal cortical carcinomas
- complicated patterns of multiple cancers at a young age

These recommendations were based on the NICE guideline (2005) and systematic reviews. The recommendations were made in the context of breast cancer screening.

The updated NICE guideline (2013)[1] gave similar recommendations. In addition, it reported recommendations on when to refer for counseling and testing persons affected with triple negative breast cancer under the age of 40 years.

The NICE guideline (2013)[1] also recommended the referral of patients with known cancer predisposing gene change in the family, e.g. BRCA1, BRCA2, TP53. AHRQ guideline[6] reported and endorsed the NCCN guideline, that formulated similar recommendations to those put forward in the NICE guideline.

There is no direct evidence for these criteria, all guidelines based their recommendations on observational evidence. They based their risk classification in average, moderate and high risk on data from both Claus and co-workers (1994)[7] and the Collaborative Group on Hormonal Factors in Breast Cancer study, where a meta-analysis was performed using the primary data of 52 epidemiological studies (2001).[8]

Belgian consensus based criteria were recently developed by the College for Medical Geneticists and reported in 'Guidelines for hereditary breast and/or ovarian cancer syndrome diagnostic testing criteria' (available at http://www.beshg.be).

3.1.2 Models that assess the risk of carrying a germline mutation, such as BRCA1, BRCA2 and TP53 mutations

There are two classes of models commonly used in clinical practice.

A first class of models estimates the risk of developing breast cancer, either expressed as a 5 years, 10 years or lifetime risk, i.e. risk prediction models. A second branch of models assesses the risk of carrying a germline mutation such as BRCA1, BRCA2 and TP53 mutations, i.e. 'carrier prediction models' and not the risk of developing breast cancer. They are nearly all evaluated in specialized genetic clinics and aim at reducing the need for expensive genetic testing. Some of those models have extensions that enable them to assess or estimate the breast cancer risk. These models are not tested on cohorts but in transversal studies, where the model serves as 'test' and where the results of genetic testing are applied as 'gold standard'. In the KCE report 172 'Identifying women at risk for breast cancer/technical methods for breast cancer screening'[5] we reviewed the evidence concerning both types of models focusing on both discriminative

power and calibration. Discriminative power is the ability of a model to predict which women carry a mutation.

We found moderate discriminative power with areas under the curve ranging from 0.71 to 0.85. Calibration, that is the ability of the model to give a correct prediction of the proportion of germline mutation positive patients in the tested populations, was mostly assessed in either US or British test populations and it is unclear to what degree this can be extrapolated to the Belgian context.

NICE reviewed 26 studies of carrier probability models (BOADICEA, BRCAPRO, IBIS, MYRIAD, MANCHESTER, PENN, PENN II and FHAT) but also the performance of risk counselors. They found moderate quality but consistent evidence that carrier prediction models performed significantly better than chance with typical area under the receiver operator characteristics (AUROC) curve values between 0.7 and 0.8. They did not provide proof that one model performs better than the other nor that they perform better than risk counselors. The estimated AUROC for risk counselors ranged from 0.69 to 0.70. They found that the BOADICEA model was well calibrated to the British data, but it is unclear if this also applies to the Belgian context.[9]

In UK, NICE proposed a formal cut-off point for mutation prediction models of 10%, allegedly based on a formal cost-effectiveness analysis of their own making. However, this analysis shows that a 5% cut-off point is also cost-effective and that the difference in ICER is marginal. Reason to adopt this higher threshold is the potential risk to overload the existing service by increasing the number of patients eligible for genetic testing if the threshold would be lowered to 5%.

AHRQ[6] reached similar conclusions. Both NICE and AHRQ considered FHAT and MANCHESTER suitable for use in first line or second line, but stated that other models are more difficult to use and be better suited for specialized centers. However, uncertainty on key parameters was high and it is unclear to what degree the results are applicable to the Belgian context.

3.1.3 Genes with low- and moderate-penetrance

Cancer predisposing genes can be categorized according to their relative risk of a particular type of cancer. High-penetrant genes are associated with a cancer relative risk higher than 5. Low-penetrant genes are presented with relative risk around 1.5, whereas moderate-penetrant genes confer relative cancer risks from 1.5 to 5.[10] Rare moderate-penetrant genes are CHEK2, ATM, BRIP1, and PALB2. Recent data suggest that the penetrance of PALB2 may be higher than reported before and that BRIP may be associated with increased risk of ovarian cancer only.[11]

Zang et al.[12] conducted a systematic literature search for candidate-gene association studies of breast-cancer risk. Meta-analyses were done for 279 genetic variants in 128 candidate genes or chromosomal loci. They applied the Venice criteria to all significant associations identified by meta-analysis to evaluate the epidemiological credibility of each. Credibility was defined as strong, moderate, or weak, based on grades of A, B, or C in three categories: amount of evidence, replication of the association, and protection from bias. Globally, 51 variants in 40 genes showed significant associations with breast cancer risk. Cumulative epidemiological evidence of an association was graded as strong for ten variants in six genes (ATM, CASP8, CHEK2, CTLA4, NBN and TP53), moderate for four variants in four genes (ATM, CYP19A1, TERT and XRCC3), and weak for 37 variants. Additionally, in meta-analyses that included a minimum of 10 000 cases and 10 000 controls, convincing evidence of no association with breast cancer risk was identified for 45 variants in 37 genes. Details are given in the evidence tables (Appendix 3.2).

Clinical implications of those genes remain unclear. Hostelle et al. (2010)[13] attribute this to the fact that moderate risk breast cancer susceptibility genes typically are encountered in a polygenic setting, meaning that several common low-risk breast cancer susceptibility alleles together confer increased breast cancer risks. When they do operate in a monogenic setting, their functional or clinical impact could be low.

After the search date of Zang et al. (2011),[12] we identified 59 meta-analyses showing either inconclusive or no evidence for an association, or evidence of no or protective effect and 55 meta-analyses showing a weak effect. Because of the unclear clinical meaning of these findings, we did not perform an appraisal of these meta-analyses nor a data-extraction but listed them in Appendix 4.1.

Attempts have been made to incorporate some of those genes in risk prediction models, but results were not convincing. Several authors attempted to improve models with genetic data. Wacholder (2010)[14] compared the Gail model with the modified Gail model using 10 common genetic variants associated with breast cancer and found that accuracy was only modestly improved, from an AUC of 0.580 to an AUC of 0.618. Mealiffe (2010)[15] found a similar modest improvement for a model adding single-nucleotide polymorphisms (SNP) with AUC of 0.594 compared with AUC of 0.557 for Gail risk alone ($p<0.001$).

Standard testing CHEK2 c.1100delC mutation: no consensus reached in the GDG

The question on what to recommend concerning moderate penetrance genes in general and CHEK2 in particular was extensively debated within the GDG and with some external validators. Different points of view remained. Here we try to summarize the different positions.
In 2008, a meta-analysis of 26 000 patient cases and 27 000 controls concluded that the presence of this mutation results in a three- to five-fold increased risk of breast cancer.[16] The authors of this meta-analysis argue that this increase in breast cancer risk implies that patients with a family history of breast cancer should be tested for the CHEK2 c.1100delC mutation together with BRCA1 and BRCA2 mutation screening. Others[17] immediately reacted saying that there is no compelling evidence to justify routine clinical testing for CHEK2*1100C to guide the management of families affected with breast cancer.

In the populations where it is most prevalent (Northern and Eastern Europe), CHEK2*1100delC is seen in 1 of 100 to 1 of 200 individuals. Thus, testing for CHEK2*1100C will have the highest yield in such regions as the Netherlands, Finland, and Denmark, where the allele is the most frequent.[17] Until recently, this mutation was not routinely analyzed in the Netherlands. Since September 2014, all genetic centers in the Netherlands collectively decided to systematically test for the CHEK2 c.1100delC mutation when a BRCA1 and BRCA2 mutation analysis is being performed (see http://www.vkgn.org/nieuws/279-uitbreiding-van-dna-diagnostiek-naar-erfelijke-borstkanker; accessed on November 24th 2014). The reason for the change in the attitude in the Netherlands (switching from not testing to testing) is a recent large study from Kriege et al. (2014) in which one Dutch hereditary non-BRCA1/2 breast cancer patient cohort (n=1 220) and two Dutch cohorts unselected for family history (n=1 014 and n=2 488, respectively) were genotyped for CHEK2 1100delC.[18] In total, 193 (4.1%) of the 4 722 included female breast cancer patients were tested positive for the CHEK2 1100delC mutation. The CHEK2 1100delC-associated breast cancer was associated with a higher contralateral breast cancer rate (multivariate hazard ratio 3.97, 95% CI 2.59–6.07) as well as worse breast cancer-specific survival beyond 6 years after diagnosis (multivariate hazard ratio 2.05 (95% CI 1.41–2.99). The incidence of contralateral breast cancer in CHEK2 1100delC mutation carriers found in this study was high (10-year risk 24.1%). Follow-up strategies in clinical practice are impacted, since more intensive follow-up scheme for contralateral breast cancer detection already offered for affected BRCA1/2 mutation carriers (MRI or risk-reducing contralateral mastectomy) are suggested to also be an option for CHEK2 1100delC mutation carriers after breast cancer diagnosis.

The majority of the genetic centers in Belgium, but not all of them, are currently routinely analyzing the CHEK2 c.1100delC mutation in each patient who is tested for BRCA1 and BRCA2 and are communicating the result to the patient.

3.1.4 Screening and follow-up of patients identified to be at risk

In the KCE report 172 'Identifying women at risk for breast cancer/technical methods for breast cancer screening'[5] we formulated the following recommendations: "For women at proven high-risk for breast cancer, yearly MRI and mammography is recommended from the age of 30 years onwards or starting five years before the age of the youngest diagnosed family member with breast cancer. This recommendation was based on the fact that available evidence showed a significantly increased sensitivity compared to mammography or mammography and ultrasound combined and that reported sensitivity for MRI varied between 68% and 100% in a

high-risk population. The use of ultrasound can be considered to shorten the interval or as adjunct to a positive mammography or MRI".

The NICE guideline[1] recommended to offer annual MRI surveillance to all women aged 30–49 years with a personal history of breast cancer who remain at high risk of breast cancer, including those who have a BRCA1 or BRCA2 mutation but not to offer MRI surveillance to any woman aged 50 years and over without a TP53 mutation unless mammography has shown a dense breast pattern. This recommendation is however based on a cost-effectiveness study that used an ICER threshold of 20 000 pounds per QALY with annual mammography as comparator for this group. It is unclear to what degree this cost-effectiveness analysis is applicable to the Belgian context. NICE found moderate quality evidence that surveillance using MRI has better sensitivity for breast cancer than mammography, clinical breast examination or ultrasound. Surveillance with both MRI and mammography has better sensitivity than either test alone, based on two systematic reviews. The Warner et al. (2008)[19] systematic review estimated breast cancer prevalence amongst high risk women undergoing surveillance as approximately 2%. Using their pooled sensitivities and specificities, the results from 1 000 combined MRI and mammography surveillance tests would include 17 true positives, 49 false positives, 931 true negatives and 3 false negatives. Rijnsburger et al. (2010)[20] analysed the relative sensitivity of mammography and MRI surveillance in three age groups: less than 40 years, 40 to 49 years and 50 or older. MRI had better sensitivity than mammography in all three groups: 61% versus 33%, 83% versus 39% and 67% versus 56% respectively. They found only very low level evidence of an effect on survival or quality of life for any form of intensified screening.

The review of AHRQ[6] did not identify studies that directly addressed the effectiveness of risk assessment, genetic counselling, and genetic testing in reducing cancer incidence and mortality.

The NCCN guidelines[21] recommended the combination of MRI and mammography from the age of 25 year on for high risk patients, without presenting evidence on the combination MRI and mammography compared to MRI alone that supports this combination.

Because the two guidelines, NICE and AHRQ, were very recent and dealing with this issue, we did not conduct a primary update of the evidence for this topic.

Conclusions

- There is no direct evidence from RCTs demonstrating the impact of genetic testing and counselling on mortality and morbidity. There is observational evidence however and for ethical reasons it is unlikely that such an RCT will ever be conducted.
- Family history remains the main tool for identification of persons that would benefit from genetic testing and counselling.
- Risk assessment models show moderate discriminative power, calibration was good in UK and US but may differ in the Belgian context. There is no proof that they perform better than clinical judgment of genetic counsellors however.
- Cumulative epidemiological evidence for low- and moderate-penetrance genes is variable and their clinical implications remain unclear.
- There is observational evidence for surveillance with MRI and mammography in high risk patients but no RCT assessed its effectiveness.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	The GDG insisted on the fact that testing should be done in preference in an affected individual. The GDG insisted on the fact that selection criteria are not sufficiently validated and precise and that **there needs to be room for clinical judgement** when assessing the risk and deciding on the referral to a center for cancer genetic testing and the decision to perform a test or not for hereditary breast cancer. The GDG considered that danger from radiation coming from mammography among women younger than 30 years old is too high and that a lot of prudence is necessary for the age group between 30 and 40 years. Therefore a recommendation on the use of mammography was added. The GDG considered that the recommendation put forward by NICE to take into account the youngest age at which a breast cancer is found is confusing, outdated and difficult to implement and therefore the recommendation was simplified to age 25. The GDG proposed to use a higher cut off point for triple negative breast cancer, with genetic screening in this population up to 60 years (used by NCCN) instead of 40 years of age, as proposed by NICE, based on clinical experience and considering that these cut off points are not based on hard evidence. The GDG considered that for women who are BRCA positive, MRI and mammography should not be done concomitantly but be alternated so that one examination is done every 6 months.
Quality of evidence	Although there is no evidence from RCT on the impact of genetic testing the GDG considered that such RCTs are impossible and unethical to conduct. The GDG considered that, although no formal proof of its effectiveness exists, the guideline should leave the door open for detection of interval cancers with ultrasound in high risk patients. There is no proof that one mutation prediction model is better than the other. However, some are perceived as difficult to use by the GDG. Although tested mainly in UK and USA, the GDG considers that models are sufficiently applicable in our setting as there is no reason to assume that BRCA prevalences are very different in our context. A decision can be guided or assisted by the consensus document 'Guidelines for hereditary breast and/or ovarian cancer syndrome diagnostic testing criteria' published by the College for Medical Geneticists (available at http://www.beshg.be, Guidelines, Guidelines for gene analysis for HBOC) (see Appendix 5).
Costs (resource allocation)	Within the recent laws for breast clinics (AR/KB 26.04.2007), all coordinator breast clinics should have a formal link with a genetic centre in order to make agreements on genetic consultations. NICE proposes a formal cut-off point for mutation prediction models of 10%, allegedly based on a formal cost-effectiveness analysis of their own making. However, this analysis shows that a 5% cut-off point is also cost-effective and that the difference in ICER is marginal. Moreover, it is unclear to what degree the used models, calibrated for the UK, are sufficiently comparable to the Belgian situation. In Belgium, both the GDG and the panel of stakeholders agree to use a pre-test probability of “5 to 10%” as a guidance. They argue that the cut-off point is dropping over time due to the rapid evolution in sequencing technologies (much more becomes possible at a decreasing cost), from 10% some years ago towards 5% in coming years.

Factor	Comment
	Low- and moderate-penetrance genes could also be incorporated in gene panels and this would make them more affordable. However, gene panels pose particular interpretation problems. Although it is expected that there will be a push towards the use of these panels in the near future there are too many unresolved issues to make a recommendation on them.
Patients values and preferences	Patients' representatives ask that a correct and understandable information be provided to individuals at increased genetic risk. A dedicated support in decision-making is important for 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 (breast/ovarian) cancer. Balanced and understandable information about the pros and cons of the various decisions has to be provided (e.g. about surveillance by mammography). There's a need for good 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. A uniform policy followed by all Genetic Centres in Belgium is essential. It is important that general practitioners / oncologists / gynaecologists / psychologists are well informed (or trained) about genetic mutations. Currently, a lot of people are not referred or do not receive the correct information about various mutations due to a lack of knowledge of these professionals.

Recommendations

1. GENERAL APPROACH

For women with a family history suggesting a hereditary risk of breast cancer, referral to a centre of human genetics specialized in cancer genetics for counselling and testing should be considered, whether the woman is affected by breast cancer or not. If not affected, it is advisable that the referring physician asks the unaffected patient to refer an affected family member if possible.

If possible, the genetic testing of 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 (such as BRCA1, BRCA2 or TP53). For affected women, the timing of counselling and testing should be compatible with the treatment that has to be installed.

If a mutation is identified, further testing of family members should follow a stepwise approach, based on the degree of relationship. Exceptions to the stepwise approach for testing of family members can be made if the relatives died or cannot be reached for various reasons, taking into account elements of the family history described below.

2. FAMILY HISTORY

Following elements in the patient history should be taken into account when making a judgment if the woman is at high risk, but there remains room for clinical judgement:

Individuals with an informative family are considered at high risk for hereditary breast cancer because in the family there are:

- two first-degree or second-degree relatives from the same side of the family diagnosed with breast cancer at younger age than the average age of 50 years of the relatives concerned (at least one must be a first-degree relative),

  OR
- three first-degree or second-degree relatives from the same side of the family diagnosed with breast cancer at younger age than the average age of 60 years of the relatives concerned (at least one must be a first-degree relative),

  OR
- four relatives from the same side of the family diagnosed with breast cancer at any age (at least one must be a first-degree relative).

However, not all families will prove informative. In these cases the threshold for testing is to be considered on a case by case basis after the initial assessment at a centre of human genetics specialized in cancer genetics.

Clinicians should seek further advice from a specialist cancer genetics service for individuals in families containing any of the following, in addition to breast cancer:

- ethnic groups with founder mutations,
- bilateral breast cancer,
- male breast cancer,
- ovarian cancer,
- sarcoma in a relative younger than 45 years of age,
- glioma or childhood adrenal cortical carcinomas,
- complicated patterns of multiple cancers at a young age,
- triple negative breast cancer under the age of 60 years.

Clinicians should also consider to refer their patients to a centre of human genetics specialized in cancer genetics in case of:

- breast cancer at very young age (< 35 years),
- epithelial ovarian cancer,
- pancreatic cancer and two first-degree relatives with pancreatic or ovarian or breast cancer.

3. ADDITIONAL RECOMMENDATIONS

- Women with a high breast cancer risk based on the above mentioned criteria should be offered individual risk assessment in order to give individual advice on screening strategy, genetic tests and prophylactic measures. Individual risk assessment should be done by professionals with sufficient skills and experience, and should include extensive counselling and sufficient attention to patient preferences and support.
- Use of prediction models can be considered.
- When using a formal carrier prediction model, a cut-off point for the BRCA1/BRCA2 mutation carrier probability of 5 to 10% can be used. If a prediction model is used than 5% is the lower limit for testing and otherwise the BeSHG criteria should be used (see 'Guidelines for hereditary breast and/or ovarian cancer syndrome diagnostic testing criteria' of the College for Medical Geneticists available at http://www.beshg.be).
- If there are problems with using or interpreting carrier probability calculation methods, refer to the testing criteria 'Guidelines for hereditary breast and/or ovarian cancer syndrome diagnostic testing criteria' of the College for Medical Geneticists to support your decision (available at http://www.beshg.be).
- No recommendations can be formulated concerning testing for low- and moderate-penetrance genes in routine clinical practice, as there is still debate on the clinical implications of those tests. Future data, however, may yield more insights into the clinical utility of testing for additional breast cancer predisposing genes. In this context, PALB2 was recently identified to have a penetrance that could be up to as high as BRCA2 in recent birth cohorts.[11]

4. FOLLOW-UP OF WOMEN AT HIGH RISK

- For women at proven high risk for breast cancer, yearly MRI is recommended from the age of 25 years onwards.
- Screening mammography should be used with prudence between 30 and 40 years and not before age 30.
- For women with a proven BRCA1 or BRCA2 mutation (or a similarly high risk, based on other information) and who opt for screening rather than for prophylactic bilateral mastectomy, yearly MRI and yearly mammography with an interval of six months between both examinations can be used from the age of 40 years onwards.
- Ultrasound is useful to reduce the number of false positives when MRI is difficult to interpret.

3.2 Li-Fraumeni syndrome

3.2.1 Introduction

Li-Fraumeni syndrome (LFS) is an autosomal dominant cancer syndrome caused by heterozygous germline mutations in the TP53 gene. Half of the patients with LFS develop at least one LFS-associated cancer by age 30. While many tumor types can be seen in patients with LFS, four core cancers (breast, sarcoma, brain, and adrenocortical carcinoma) make up about 80% of LFS associated tumours.[22] The next most frequently associated cancers include leukemia, lung, colorectal, skin, gastric, and ovarian.

All cancer types are diagnosed at younger than average ages. Moreover, LFS predisposes to radiation-induced malignancies as well, therefore use of radiology should be limited. It is a rare syndrome, e.g. in The Netherlands only 24 families were identified in 2009.[23] Approximately 400 families were reported in the cumulative literature, but its actual population incidence is unknown.[24]

3.2.2 Diagnostic testing criteria for Li-Fraumeni syndrome

Several sets of criteria have been developed over the past 20 years to help identify individuals with LFS who should be considered for TP53 testing. The first formal set of criteria developed in 1988 is the Classic LFS criteria; these criteria are the most stringent and are the ones used to make a clinical diagnosis of LFS (with or without the identification of a deleterious germline TP53 mutation).[25] Later, broader criteria were developed by Birch and Eeles to identify families which are Li-Fraumeni-like (LFL).[26, 27] Chompret and colleagues developed another set of criteria which were shown to provide the highest positive predictive value and, when combined with the classic LFS criteria, provided the highest sensitivity for identifying individuals with LFS.[28]

We only identified one guideline that specifically dealt with testing criteria, i.e. the NCCN guideline. Although the NCCN guideline did not have reported a formal search strategy, it proposed criteria that are widely adopted. Authors proposed to test persons either fulfilling what is called the 'classic' Li-Fraumeni criteria, and the modified Chompret criteria.[28, 29] Criteria were also proposed by Birch et al. (1994)[26] and Eeles et al. (1995)[27] often referred to as the 'Li-Fraumeni like' criteria. All are based on limited case series. The precise criteria are summarized in Appendix 6.

We looked for studies validating these criteria. Our search strategy is detailed in Appendix 2.3. No independent validation study of the testing criteria in unselected patients was found. There were some testing studies in series in preselected patients.

Ruijs et al. (2010)[30] selected 180 Dutch families referred for TP53 mutation analysis based largely on LFS, Li-Fraumeni-like (LFL) and Chompret criteria. A TP53 germline mutation was identified in 24 families. When the Chompret criteria were used 22/24 mutations were detected (sensitivity 92%, mutation detection rate 21%). In LFS and LFL families, 18/24 mutations were found (sensitivity 75%). The two mutations detected outside the 'Chompret group' were found in a child with rhabdomyosarcoma and a young woman with breast cancer.

Mitchell et al. (2013)[31] tested a clinic-based, prospective cohort of 559 adult-onset sarcoma cases, who were screened for mutations in TP53 without regard to family history and where 17 germline mutations were found, of whom only 10 met classical or Chompret criteria.

NCCN recommended testing for women with breast cancer under 35. However, evidence underpinning this recommendation is conflicting. Lalloo et al. (2003)[32] aimed to estimate the degree to which BRCA1, BRCA2 and TP53 contribute to early-onset breast cancer (age ≤30 years) and to establish use of family history in identification of mutation carriers. They tested 100 women diagnosed with breast cancer under age 30 for mutations in the BRCA1, BRCA2 and TP53 genes and found 2 TP53 mutations in 36 early onset (< 30 years) breast cancer women with a familial history. Both mutations were noted within families that fulfilled criteria for Li-Fraumeni and Li-Fraumeni-like syndrome. The high relative risk (>100) of breast cancer in women younger than 31 years led authors to recommend that TP53 be considered in very young breast-cancer patients (<30 years).

Rath et al. (2013)[33] tested 213 women with primary invasive HER2+ breast cancer age <50 years from a single centre and found 3 TP53 mutations (ages at diagnosis 23, 32, 44 years; 1.4%, 95% CI 0.3-4.1%).

Lee et al. (2012)[34] identified 4 clinically relevant TP53 mutations when testing 100 patients with early onset breast cancer, of whom 83 BRCA negative, 3 of the 4 fulfilled the LFS criteria.

Penkert et al. (2011)[35] tested 62 BRCA1/BRCA2-negative women from families fulfilling the criteria for hereditary breast and ovarian cancer. Among them, 22 women had early onset breast cancer, diagnosed at or before the age of 34 years (range 22 to 34 years). Of all, 31 women fulfilled Chompret (8) Li-Fraumeni criteria or Eeles/Birch (23) Li-Fraumeni-like criteria but did not detect TP53 mutations nor TP53 large genomic rearrangements.

Nevertheless, there are no studies that have directly addressed what the additional yield in detection of TP53 mutation carriers is when an age cut-off of 35 years is applied compared to an age cut-off of 30 years (or, in other words, what number of patients with a TP53 mutation would be missed when the age threshold is lowered from 35 yrs to 30 yrs). As there are no large studies that have directly addressed this issue, the decision on the age threshold can only be based on "expert opinion".

3.2.3 Follow-up of patients with Li-Fraumeni syndrome

NICE provided specific recommendations for the follow-up of patients with clinically relevant TP53 germline mutations.

It recommended to consider annual MRI surveillance for women aged 20–69 years with a known TP53 mutation. This recommendation is based on evidence in women at high risk of breast cancer in general. It recommended not to do mammography in this group, essentially based on theoretical risk of malignancy due to the higher susceptibility of TP53 women to radiation.

We did not identify primary studies related to breast cancer surveillance and screening in women with TP53 germline mutations.

However, we found one observational study by Villain et al. (2011)[36] where 33 TP53 mutation carriers were identified, 18 of whom underwent comprehensive cancer surveillance. The surveillance protocol detected ten asymptomatic tumours in seven patients. Median follow-up was 24 months (IQR 22-65 months). Twelve high-grade, high-stage tumours developed in 10 individuals in the non-surveillance group, of whom 2 (20%) were alive at the end of the follow-up (p=0.0417 for comparison with survival in the surveillance group). Three-year overall survival was 100% in the surveillance group and 21% (95% CI 4-48%) in the non-surveillance group (p=0.0155). However, clinical implications of this study are unclear, as follow-up time was too short to take into account lead time bias. It is also unclear if confounding was sufficiently addressed.

O' Neil et al. (2013)[37] screened 15 pediatric LFS patients with whole-body MRI (WB-MRI) twice annually but the study only demonstrated feasibility, follow-up time being too short to demonstrate effects on survival.

Masciari et al. (2008)[38] identified 3 asymptomatic cancer in 15 LFS patients using F18-fluorodeoxyglucose–positron emission tomography/computed tomography (FDG-PET/CT); clinical implications of these findings and effect on mortality or morbidity remain unclear.

Conclusions

- Evidence for testing criteria is limited
- Evidence for surveillance for breast cancer is extrapolated from evidence for surveillance among women at high risk for breast cancer in general
- There is some evidence that TP53 women may be more susceptible to radiation than others
- There is no evidence for surveillance for other cancers

Other considerations

Factor	Comment
Balance between clinical benefits and harms	In the Belgian clinical practice, geneticists see quite some patients with breast cancer between 30 years and 35 years but very rarely encounter mutations in the TP53 gene. Testing strategies differ between centres but relied on family history and BRCA1/BRCA2 mutation. The following strategy was suggested: 'In a breast cancer patient younger than 30 years negative for a BRCA1 or BRCA2 mutation, offer TP53 testing. In a breast cancer patient between 30 and 35 years with a normal BRCA1 and BRCA2 result, do not systematically offer TP53 testing; TP53 testing can be considered if there is a strong family history of breast cancer or other cancers that belong to the spectrum of the Li-Fraumeni syndrome (which probably results in a very small absolute risk of missing a de novo TP53 mutation)'. There is no proven benefit of preventive measures, therefore testing for Li-Fraumeni should only be done after extensive counselling and should only be offered under limited conditions.
Quality of evidence	• Li-Fraumeni is a rare disease. Criteria for testing are put forward but the disease is too rare to formally validate models. • For surveillance and follow-up, there are only limited data. • There is indirect proof that carriers are more sensitive to radiation, therefore the GDG does not recommend mammography in this group.
Costs (resource allocation)	Because TP53 is rare, testing should only be offered to patients that fullfill strict criteria, Classic Li-Fraumeni Syndrome, Li-Fraumeni Like Syndrome or the revised Chompret criteria. This way, cost is likely to remain acceptable.
Patients values and preferences	Patients' representatives ask that a correct and understandable information be provided to individuals at increased genetic risk. A dedicated support in decision-making is important for 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 (breast/ovarian) cancer. Balanced and understandable information about the pros and cons of the various decisions has to be provided (e.g. about surveillance by mammography). There's a need for good 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. A uniform policy followed by all Genetic Centres in Belgium is essential. It is important that general practitioners / oncologists / gynaecologists / psychologists are well informed (or trained) about genetic mutations. Currently, a lot of people are not referred or do not receive the correct information about various mutations due to a lack of knowledge of these professionals.

Recommendations

1. DIAGNOSTIC TESTING CRITERIA

A person should be only offered counseling and genetic testing if he or she fulfills either the criteria for Classic Li-Fraumeni Syndrome, Li-Fraumeni Like Syndrome or the revised Chompret criteria, or for early onset breast cancer.

Classic Li-Fraumeni Syndrome (LFS)

- A proband with a sarcoma diagnosed before age 45 years,
  AND
- A first-degree relative with any cancer before age 45 years,
  AND
- A first- or second-degree relative with any cancer before age 45 years or a sarcoma at any age.

Li-Fraumeni Like Syndrome

Birch definition:

- A proband with any childhood cancer OR with sarcoma, brain tumour, or adrenocortical carcinoma diagnosed before age 45 years,
  AND
- A first- or second-degree relative with a typical LFS cancer (sarcoma, breast cancer, brain tumor, adrenocortical carcinoma, or leukemia) at any age, AND
- A first- or second-degree relative with any cancer before age 60 years

Eeles definition:

- Two first- or second-degree relatives with LFS-related malignancies at any age.

Chompret criteria

- A proband with a tumour belonging to the LFS tumor spectrum (soft tissue sarcoma, osteosarcoma, brain tumour, pre-menopausal breast cancer, adrenocortical carcinoma, leukemia, or bronchoalveolar lung cancer) before age 46 years, AND at least one first- or second-degree relative with an LFS tumour (except breast cancer if the proband has breast cancer) before age 56 years or with multiple tumours,
  OR
- A proband with multiple tumours (except multiple breast tumours), two of which belong to the LFS tumour spectrum and the first of which occurred before age 46,
  OR
- A proband who is diagnosed with adrenocortical carcinoma or choroid plexus tumour, irrespective of family history

Early onset breast cancer

- For individual with breast cancer ≤30 years with a negative BRCA1/BRCA2 test, offer a TP53 test

2. ADDITIONAL RECOMMENDATIONS

- Individual risk assessment should be done by professionals with sufficient skills and experience, and should include extensive counselling and sufficient attention to patient preferences and support.
- Discuss with the patient the possibility to perform prophylactic bilateral mastectomy. However, the patient should be informed that there is no proof that preventive measures have a benefit overall.

3. FOLLOW-UP OF WOMEN AT HIGH RISK

- For women with a proven TP53 mutation who opt for screening rather than for prophylactic bilateral mastectomy, yearly MRI is recommended from the age of 25 years onwards.
- Yearly mammography is not recommended because of the higher susceptibility to radiation.
- Ultrasound is useful to reduce the number of false positives when MRI is difficult to interpret.

3.3 Cowden syndrome or PTEN hamartoma tumour syndrome (PHTS)

3.3.1 Introduction

The following general description of the disease is literally taken from Pilarski et al.[23] 'The term PTEN hamartoma tumour syndrome (PHTS) has been used to refer to a spectrum of disorders that have been linked to germline mutations in the phosphatase and tensin homolog (PTEN) gene, including Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), adult Lhermitte-Duclos disease (LDD), and autism spectrum disorders associated with macrocephaly. The bulk of the clinical data on these disorders comes from studies of patients with Cowden syndrome, and less commonly BRRS.

Cowden Syndrome is a rare, multisystem disease that causes increased risks for malignancies (breast, thyroid, and endometrial) as well as benign hamartomatous overgrowth of tissues (skin, colon, thyroid, etc).

CS was first described in one family in 1963 and then extended by Weary et al. who added an additional set of 5 patients and expanded the spectrum of component features.' Cowden syndrome has a prevalence of about 1 in 250 000 in the Dutch population with a low mutation frequency.[39]

3.3.2 Diagnostic testing criteria and diagnostic criteria for Cowden syndrome.

'Diagnostic criteria for CS were initially proposed by Salem and Steck in 1983[40] and later revised by consensus of an international consortium of researchers in 1996 before identification of the CS gene.[41] Clinical diagnoses since that time have been based on these consortium criteria, which were based upon early clinical experience and compilations of cases published in the literature, with their inherent selection biases, rather than on unselected series of patients.'[23] Criteria have been updated in 2000 and 2004.[42, 43] Finally, Pilarski et al.[44] proposed a new modification of the criteria based upon a systematic review and expert opinion (see Appendix 7). Note however that these are diagnostic criteria, not diagnostic testing criteria.

We only identified one guideline that specifically dealt with testing criteria, i.e. the NCCN guideline. Although the NCCN guideline did not report a formal search strategy, the criteria proposed by NCCN are widely adopted. NCCN based these criteria largely on consortium criteria combined with expert opinion and the results of 2 large cohort studies[45, 46] (testing criteria are displayed in Appendix 8).

We searched for cohort studies or transversal studies that assessed predictive values for a positive PTEN test and identified 2 cohort studies, already mentioned in the NCCN paper, that assessed prediction criteria in a prospective way.

Pilarski et al.[21] reviewed molecular and clinical data on 802 patients referred for PTEN analysis in the Ohio State University cohort and found deleterious mutations in 172 (21.4%) subjects. Among mutation carriers, significant differences from previous reports were found for the frequencies of several clinical features, including macrocephaly, uterine fibroids, benign breast disease and endometrial cancer. Logistic regression analyses indicated that female mutation carriers were best identified by the presence of macrocephaly, endometrial cancer, trichilemmomas, papillomatous papules, breast cancer, benign thyroid disease, and benign gastrointestinal (GI) lesions. For males, the most discriminating features were macrocephaly, lipomas, papillomatous papules, penile freckling, benign GI lesions, and benign thyroid disease. Age related differences were also identified. They found that the mutation frequency in patients meeting CS diagnostic criteria (34%) was significantly lower than previously reported. Based on this study, they also proposed a PTEN risk prediction calculator.

Tan et al. (2011)[45] conducted a multicenter prospective study including two independent cohorts (the Cleveland Clinic cohort and the Ohio State University cohort) in which 3 042 probands satisfied relaxed International Cowden Consortium operational criteria for CS (pathognomonic criteria, or at least two criteria, either major or minor, see also Appendix 7). PTEN mutation scanning, including promoter and large deletion analysis, was performed for all subjects. Pathogenic mutations were identified in 290 individuals (9.5%). Based on the data of these cohort studies, the authors derived a clinical score system for adults and clinical criteria for children, using complex modeling and the data from the Cleveland Clinic cohort. They then validated the score system and the criteria on the data from the Ohio State University cohort. They fixed a threshold using ROC analysis for the clinical score system and assessed the calibration with bootstrap validation that yielded an optimism-corrected concordance index of 0.91.

No independent validation of these criteria and score was done until now. Note that both cohorts concern patients in referral academic centres and selected based on the relaxed Cowden criteria, in themselves expert opinion based. This implies a double pre-selection of that patient group where the models were tested, and the results only apply to a population selected in this way. This is a population that is likely to differ in important ways from the population presenting to a typical Belgian centre for genetic testing and counseling, and it is unclear to what degree they are valid in the Belgian context.

3.3.3 Follow-up of patients with Cowden syndrome

As could be expected, given the rareness of the syndrome we did not find any studies that assessed the effectiveness of screening nor sensitivity and specificity of screening algorithms in this specific group.

We selected studies with the following inclusion criteria in order to have an idea of the cumulative cancer risk in this group: non-comparative cohort studies or case series that recruited patients in a consecutive way.

We found 5 studies assessing the cumulative risk for different cancers. Details of the studies are given in the evidence tables.

Tan et al. (2012)[47] prospectively recruited 3 399 individuals meeting relaxed International Cowden Consortium PHTS criteria and found 368 individuals with deleterious germline PTEN mutations. Estimated lifetime risks were for cancers of the breast: 85.2% (95% CI, 71.4%–99.1%), thyroid 35.2% (19.7%–50.7%), endometrium 28.2% (17.1%–39.3%), colorectum 9.0% (3.8%–14.1%), kidney 33.6% (10.4%–56.9%) and finally melanoma 6% (1.6%-9.4%).

Bubien et al. (2013),[40] van Nieuwenhuis (2012),[42, 48] Heald et al. (2010)[41] reported similar results (more details are reported in Appendix 8.1).

Riegert-Johnson (2010)[43] reported cumulative rates for patients with Cowden syndrome, either with PTEN pathogenic germline mutations or not and found similar results.

We did not find studies assessing the effects of screening for different cancers in this group, it is however unlikely that such studies will ever be conducted due to the rare nature of the disease.

Conclusions

- Evidence for testing criteria is limited.
- Evidence for surveillance for breast cancer is extrapolated from evidence for surveillance among women at high risk for breast cancer in general.
- There is evidence for an increased risk of breast cancer, endometrium cancer, renal and thyroid cancer but there is no evidence of the effectiveness of screening for those conditions.

Other considerations

Factor	Comment
Quality of evidence on the balance between clinical benefits and harms	Criteria are largely consensus based. Some predictive computer carrier prediction models are developed but not sufficiently validated. Due to the rareness of the disease there are only limited data on effectiveness of preliminary screening but there are credible studies on lifetime risk. Therefore the recommendations for breast cancer surveillance are based on the general evidence for BRCA patients, as GDG judged it sufficiently comparable. The recommendation on thyroid screening is consensus based. Elevated risk for thyroid cancer is proven, benefit of the screening not.
Costs (resource allocation)	Because PTEN is rare, testing should only be offered to patients that fullfill strict criteria. This way, cost is likely to remain acceptable.
Patients values and preferences	Patients' representatives ask that a correct and understandable information be provided to individuals at increased genetic risk. A dedicated support in decision-making is important for 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 (breast/ovarian) cancer. Balanced and understandable information about the pros and cons of the various decisions has to be provided (e.g. about surveillance by mammography). There's a need for good 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. A uniform policy followed by all Genetic Centres in Belgium is essential. It is important that general practitioners / oncologists / gynaecologists / psychologists are well informed (or trained) about genetic mutations. Currently, a lot of people are not referred or do not receive the correct information about various mutations due to a lack of knowledge of these professionals.

Recommendations

1. DIAGNOSTIC TESTING CRITERIA (NCCN TESTING CRITERIA)

The following testing criteria should be considered when deciding for counselling, genetic testing and follow-up:

Cowden Syndrome PTEN Gene Testing Criteria

Individual from a family with a known PTEN gene mutation;

Individual meeting clinical diagnostic criteria for Cowden Syndrome;

Individual with a personal history of:

- Bannayan-Riley-Ruvalcaba syndrome (BRRS) OR
- Adult Lhermitte-Duclos disease (cerebellar tumours) OR
- Autism spectrum disorder and macrocephaly OR
- Two or more biopsy-proven trichilemmomas OR
- Two or more major criteria* (one must be macrocephaly) OR
- Three major criteria*, without macrocephaly OR
- One major* and ≥ three minor criteria** OR
- ≥ Four minor criteria**

At-risk individual with a relative with a clinical diagnosis of Cowden syndrome or BRRS for whom testing has not been performed

- The at-risk individual must have the following:
  - Any one major criterion* OR
  - Two minor criteria**

*** Major criteria:**

- Breast cancer
- Endometrial cancer
- Follicular thyroid cancer
- Multiple gastrointestinal hamartomas or ganglioneuromas
- Macrocephaly
- Macular pigmentation of glans penis (a discolored area on the skin)
- Mucocutaneous lesions
  - One biopsy proven trichilemmoma
  - Multiple palmoplantar keratoses (abnormal thickening of the hands and feet)
  - Multifocal or extensive oral mucosal papillomatosis
  - Multiple cutaneous facial papules (often verrucous)

**** Minor Criteria:**

- Autism spectrum disorder
- Colon cancer
- Esophageal glycogenic acanthosis (≥3)
- Mental retardation (i.e. IQ<75)
- Papillary or follicular variant of papillary thyroid cancer
- Thyroid structural lesions (such as adenoma, nodule(s), goiter)
- Renal cell carcinoma
- Vascular anomalies (including multiple intracranial developmental venous anomalies)
- Lipomas (benign soft tissue tumour)
- Single gastrointestinal hamartoma or ganglioneuroma
- Testicular lipomatosis

2. FOLLOW-UP OF WOMEN AT HIGH RISK

The efficacy, risk, and benefits of cancer screening in Cowden syndrome are unknown.[24] Recommendations listed below are suggested in the scientific literature and were based on expert opinions.

- For women with a proven PTEN mutation who opt for screening rather than for prophylactic bilateral mastectomy, yearly MRI is recommended from the age of 25 years onwards. From the age of 40 years onwards, yearly MRI and yearly mammography with an interval of six months between both examinations can be used
- Mammography should be used with prudence between 30 and 40 years but should not be used before age 30.
- Ultrasound is useful to reduce the number of false positives when MRI is difficult to interpret.
- No studies have assessed efficacy of prophylactic mastectomy in Cowden Syndrome. Without recommending such intervention, healthcare professionals can discuss with each patient the balance benefits/harms of preventive surgery (risk-reducing mastectomy) and counsel regarding degree of protection, extent of cancer risk and reconstruction options.[21]
- Annual screening with ultrasound of the thyroid gland could be considered, starting at age 18 y.[24]
- Because data regarding lifetime risk of endometrial cancer are limited, surveillance screening (ultrasound and/or endometrial biopsy has been suggested to begin at age 35–40 or 5 years before the earliest endometrial cancer in the family)[24] and surgical intervention (hysterectomy) should be on an individual basis.
- Colonoscopy can be considered, starting at age 35 y, then every 5-10 y or more frequently if patient is symptomatic or polyps were found.[21]
- If there is a family history of renal cell cancer, an annual urinalysis has been suggested, supplemented by cytology and renal ultrasound.[24]

5 IMPLEMENTATION AND UPDATING OF THE GUIDELINE

5.1 Implementation

5.1.1 Multidisciplinary approach

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

5.1.2 Patient-centered care

The choice of an intervention, e.g. germline mutation analysis, should not only consider medical aspects but also patient preferences. Patients' 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 (breast/ovarian) cancer. Balanced and understandable information about the pros and cons of the various decisions has to be provided (e.g. about surveillance by mammography). 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. A uniform policy followed by all Genetic Centres in Belgium is essential. It is important that general practitioners / oncologists / gynaecologists / psychologists are well informed about genetic mutations. According to the patients' representatives, a lot of people are currently not referred or do not receive the correct information about various mutations due to a lack of knowledge of these professionals.

5.1.3 Barriers and facilitators for implementation of this guideline

Some medical oncologists would prefer to be able to offer the pre-test counselling and the genetic testing themselves and immediately, instead of referring their patient to a centre of human genetics specialized in cancer genetics for genetic counselling. They also claim that sometimes losing precious time is thus lost before an appropriate treatment is started.

Geneticists feel it is absolutely required to refer individuals/patients to a centre of human genetics specialized in cancer genetics for counselling and testing rather than ordering a genetic test directly. This stepwise approach allow patients to benefit from specific tests prescribed by specialists in genetics, but also to benefit from genetic counselling about the risks, benefits and consequences of testing. A specific comprehensive consultation "genetic counselling" is reimbursed by INAMI/RIZIV for this purpose. Such consultation includes personal and family history taking, the search for information on family cases, the selection of the most appropriate tests to assess the individual risk of developing the disease, the information about the tests characteristics, the results of the test performed about the individual personal risk, the measures to prevent or detect the disease as early as possible. Following the legislation on breast cancer clinics (AR/KB 26.04.2007), coordinating breast cancer clinics have to sign a written agreement with a centre of human genetics to organize a genetic consultation for patients.

Numerous barriers to refer individuals at risk of cancer to outside cancer genetics have been summarized by Prochniak et al. (2012),[49] including: lack of knowledge regarding who should be referred; doubts about the clinical utility of genetic testing; and concerns regarding insurance coverage of services, patient confidentiality, and genetic discrimination. In their own prospective study,[49] these authors found that clinicians who considered their role also includes ordering tumour testing, ordering germline testing, and interpreting genetic test results and those who felt confident doing so were more likely to report they would order their own testing than those who preferred to refer patients for testing. Physicians who preferred to refer to outside cancer genetics experts were more likely to value the counseling provided by outside genetics experts regarding the risks, benefits and consequences of the test. Authors recommended to increase referral to outside cancer genetics experts by focusing on the unique, evidence-based

benefits that genetic counselling provides to patients over and above the services received when a physician orders tests independently.

The identification of potential barriers and facilitators related to the use of this guideline is limited to a discussion held during the stakeholders meeting. More sophisticated methods could be used, but this would go beyond the scope of this project. More information on the identification of barriers and facilitators in guidelines implementation can be found in a recent KCE-report (see KCE website).

5.1.4 Actors of the implementation of this guideline

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

5.2 Monitoring the quality of care

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

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

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

5.3 Guideline update

In view of the rapidly evolving evidence due to the dynamic nature of this field, especially with regard to current risk estimations (e.g. The upper level of the lifetime breast cancer risk estimate associated with PALB2 mutations has recently shown to overlap with that for BRCA2), genetic testing capabilities, the clinical introduction of the routine analysis of a broad panel of germline DNA in at risk subjects will be monitored by the authors and this guideline should be updated when sufficient clinical evidence is available. If, in the meantime, important new evidence would become available, this should be taken into consideration in the medical decision making.

5.4 Research agenda

The use of genetic tests in oncology is a very rapidly moving field on many fronts. In particular, there is a rapid evolution in the technical capabilities to perform multiple genetic tests as a panel. Therefore, the authors will assess the clinical impact of gene panels in at risk subjects through results of ongoing research studies and regular review of the literature.

In the near future, it will be important to address certain key aspects again. In particular these three areas will need to be addressed:

1. Validation of mutation prediction models in the Belgian population.
2. Scope of testing for moderate penetrance genes in the context of Next Generation Sequencing panels
3. Plan for integrating genetic testing into oncological practice.

APPENDICES

APPENDIX 1. GDG MEMBERS

Institution/Organisation	Professional Specialty	First Name	Name
UCL	Medical oncologist	Martine	Berlière
UGent	Molecular geneticist	Kathleen	Claes
UCL	Clinical geneticist	Nicolas	Janin
UZ Leuven	Molecular geneticist	Gert	Matthijs
UGent	Clinical geneticist	Bruce	Poppe*
Institut Jules Bordet	Medical oncologist	Daphné	't Kint de Roodenbeke
UGent	Clinical geneticist	Tom	Van Maerken**
UZ Leuven	Medical oncologist	Hans	Wildiers

*Note. * President GDG; ** Vice-President GDG*

APPENDIX 2. SEARCH STRATEGIES

Appendix 2.1. Hereditary breast cancer

PICO

Project number	2013-51	
Project name	Oncogenetic testing	
Search question(s)	Systematic reviews about genetic testing in the case of breast neoplasms.	
Structured search question(s) (PICO, SPICE, ECLIPSE, ..)		and related keywords
A	Breast	Breast/ Breast? Mammary Breast.jn Breast Care.jn A&B Breast Neoplasms/
B	Cancer	Neoplasms/ KEYWORDS Neoplasm? Cancer* Malign* Tumor* Tumour* Carcinoma* Adenocarcinom*

		Metastat* Metastas* Oncolog* B&C Neoplastic syndromes, hereditary/ Clinical Breast Cancer.jn Breast Cancer Research & Treatment.jn Breast Cancer Research.jn Breast Cancer.jn Journal of Breast Cancer.jn International Journal of Breast Cancer.jn
C	Genetic	Genes, BRCA1/ Genes, BRCA2/ Genetic Predisposition to Disease/ Mutation/ Genetic counseling/ Genetic markers/ Polymorphism, genetic/ Polymorphism, single stranded conformational/ Genetic phenomena/ Genes/ B&C DNA, neoplasm/ C&D Genetic Testing/

	KEYWORDS
	heredit*
	inherit*
	famil*
	counsel*
	mutation?
	gene?
	Genet*
	Pharmacogenet*
	Genom*
	Allele?
	Genotyp*
	Phenotyp*
	Polymorphism?
	Molecular
	Transcript*
	DNA
	RNA
	Chromosom*
	Carrier?
	Counselling
	Predisposition?
	BRCA1
	BRCA2
	TP53
	STKII
	STK2
	PTEN
	CHEK2
	PALB2

		BRIP1 LKB1
D	Testing	exp Microarray Analysis/ exp Mass Screening/ Risk assessment/ Disease susceptibility/ KEYWORDS Screened, screening, sequencing, phenotyping, genotyping, detecting, detection, test, tests, testing, profile, profiling Assess* Analys* Analyz* Identif* Determin* Find Diagnos* Detect* Prevalen* Possibly: (Risk/ OR Risk Factors/) AND (KEYWORDS)
S (settings)	Systematic Review	
STRATEGY		**(((A & B) OR AB) & C) OR (A & BC))**

Appendix 2.1.1. Medline @ Ovid

Date	2014-02-05		
Database	Medline (OVID)		
Search Strategy (attention, for PubMed, check « Details »)	**#**	**Query**	**Results**
	1	exp Breast/	30786
	2	breast*.tw,kw,kf.	294163
	3	mammary.tw,kw,kf.	57836
	4	1 or 2 or 3	338970
	5	exp Neoplasms/	2485943
	6	tumor*.tw,kw,kf.	949418
	7	tumour*.tw,kw,kf.	201274
	8	cancer*.tw,kf,kw.	1049967
	9	oncolog*.tw,kf,kw.	78909
	10	metastas*.tw,kw,kf.	220957
	11	carcinom*.tw,kw,kf.	467290
	12	malign*.tw,kf,kw.	396099
	13	adenocarinom*.tw,kf,kw.	31
	14	neoplas*.tw,kw,kf.	279245
	15	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	2235125
	16	5 or 15	3014977
	17	4 and 16	260966
	18	exp Breast neoplasms/	209684
	19	17 or 18	290776
	20	exp Genetic Predisposition to Disease/	84570
	21	exp Genetics/	168290
	22	exp Genetic markers/	44142
	23	exp Polymorphism, genetic/	187939
	24	exp Polymorphism, single stranded conformational/	10287
	25	20 or 21 or 22 or 23 or 24	413726
	26	screening.tw,kw,kf.	318511
	27	screened.kw,kf,tw.	91374
	28	testing.tw,kw,kf.	333272
	29	tests.tw,kw,kf.	461505

	30	test.tw,kw,kf.	949925
	31	tested.tw,kw,kf.	646389
	32	profil*.tw,kw,kf.	449685
	33	26 or 27 or 28 or 29 or 30 or 31 or 32	2624902
	34	di.xs.	4283067
	35	diagnosis.tw,kw,kf.	1053771
	36	detection.kw,tw,kf.	572192
	37	34 or 35 or 36	4988978
	38	37 and 25	82741
	39	exp Genetic testing/	25183
	40	exp genetic counseling/	11541
	41	exp DNA mutational analysis/	45000
	42	exp Heterozygote Detection/	7957
	43	exp Genetic Techniques/	1457684
	44	exp Microarray Analysis/	70728
	45	39 or 40 or 41 or 42 or 43 or 44	1469220
	46	(genet* adj3 (test* or screened or screening or detect* or assess* or profil* or counsel?ing)).tw,kw.	42970
	47	((proteom* or genom* or gene? or sequence?) adj3 (screening or profil* or sequencing or screening or screened)).tw,kw.	67854
	48	(expression adj3 profil*).tw,kw.	46324
	49	46 or 47 or 48	129290
	50	38 or 45 or 49	1553868
	51	exp Mass Screening/	97361
	52	exp population surveillance/	48444
	53	51 or 52	143619
	54	33 or 53	2689779
	55	25 and 54	91693
	56	50 or 55	1580032
	57	19 and 56	39449
	58	exp breast neoplasms/ge	30655
	59	exp Genes, BRCA1/	4594
	60	exp Genes, BRCA2/	2691
	61	58 or 59 or 60	32204
	62	exp breast neoplasms/di	25837

	63	50 or 54 or 62	3913407
	64	61 and 63	21063
	65	exp Neoplasms/ge	274050
	66	exp Neoplastic syndromes, hereditary/	41069
	67	((hereditary or famil* or genetic* or inherited) adj3 (cancer? or tumo?r* or neoplasm* or carcinom* or adenocarcinom*)).tw,kw.	31213
	68	65 or 66 or 67	310939
	69	68 and 4	38229
	70	54 or 50	3896912
	71	69 and 70	23571
	72	57 or 64 or 71	43183
	73	limit 72 to systematic reviews	623
	74	gene?.tw,kw.	1391683
	75	genetic.tw,kw.	531502
	76	genetics.tw,kw.	69783
	77	mutation?.tw,kw.	411744
	78	allele?.tw,kw.	157196
	79	BRCA*.tw,kw.	10812
	80	TP53.tw,kw.	5201
	81	STK2.tw,kw.	10
	82	STKII.tw,kw.	1
	83	CHEK2.tw,kw.	340
	84	HER2.tw,kw.	10676
	85	('17q12-21' or '17q12-q21' or '17q12' or '17q21' or '13q12-13' or '13q12-q13' or '13q12-3').tw,kw.	1188
	86	"17p13.1".tw,kw.	308
	87	"19p13.3".tw,kw.	300
	88	"22q12.1".tw,kw.	54
	89	"11q22.3".tw,kw.	124
	90	(atm adj2 (gene or locus or loci)).tw,kw.	772
	91	(cdh1 or "16q22.1").tw,kw.	1469
	92	(pten or "10q23.3").tw,kw.	7365
	93	(palb2 or "16p12.1").tw,kw.	230
	94	(bardi or "2q34" or "2q35" or "2q34-q35" or "2q34-35" or "2q34-5").tw,kw.	342
	95	(brip1 or "17q22" or "17q23" or "17q24" or "17q22-q24" or "17q22-24" or "17q22-4").tw,kw.	637

	96	(mre11a or "11q21").tw,kw.	184
	97	(nbn or "8q21").tw,kw.	378
	98	(rad50 or "5q31").tw,kw.	1672
	99	(rad51c or "17q25.1").tw,kw.	191
	100	(xrcc2 or "7q36.1").tw,kw.	243
	101	(rad51d or "17q11").tw,kw.	270
	102	(abraxas or "4q21.23").tw,kw.	40
	103	74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102	1896256
	104	assess*.tw,kw.	1692234
	105	detect*.tw,kw.	1579990
	106	sequencing.tw,kw.	128300
	107	33 or 104 or 105 or 106	4988466
	108	(screening.tw,kw,kf. or screened.kw,kf,tw. or testing.tw,kw,kf. or tests.tw,kw,kf. or test.tw,kw,kf. or tested.tw,kw,kf. or profil*.tw,kw,kf. or assess*.tw,kw. or detect*.tw,kw. or sequencing.tw,kw.) adj3 (gene? or genetic or genetics or mutation? or allele? or BRCA* or TP53 or STK2 or STKII or CHEK2 or HER2 or ('17q12-21' or '17q12-q21' or '17q12' or '17q21' or '13q12-13' or '13q12-q13' or '13q12-3') or "17p13.1" or "19p13.3" or "22q12.1" or "11q22.3" or (atm adj2 (gene or locus or loci)) or (cdh1 or "16q22.1") or (pten or "10q23.3") or (palb2 or "16p12.1") or (bardi or "2q34" or "2q35" or "2q34-q35" or "2q34-35" or "2q34-5") or (brip1 or "17q22" or "17q23" or "17q24" or "17q22-q24" or "17q22-24" or "17q22-4") or (mre11a or "11q21") or (nbn or "8q21") or (rad50 or "5q31") or (rad51c or "17q25.1") or (xrcc2 or "7q36.1") or (rad51d or "17q11") or (abraxas or "4q21.23")).tw,kw.	701895
	109	108 and 19	25195
	110	limit 109 to systematic reviews	593
	111	EndoPredict.tw,kw.	10
	112	PAM50.tw,kw.	50
	113	"Genomic Grade Index".tw,kw.	24
	114	MammaPrint.tw,kw.	101
	115	"oncotype DX".tw,kw.	179
	116	oncotypedx.tw,kw.	18
	117	"Breast Cancer Index".tw,kw.	21
	118	111 or 112 or 113 or 114 or 115 or 116 or 117	320
	119	limit 118 to systematic reviews	16

	120	(screening.tw,kw,kf. or screened.kw,kf,tw. or testing.tw,kw,kf. or tests.tw,kw,kf. or test.tw,kw,kf. or tested.tw,kw,kf. or profil*.tw,kw,kf. or assess*.tw,kw. or detect*.tw,kw. or sequencing.tw,kw.) adj3 ((tumor* or tumour*).tw,kw,kf. or cancer*.tw,kf,kw. or oncolog*.tw,kf,kw. or metastas*.tw,kw,kf. or carcinom*.tw,kw,kf. or malign*.tw,kf,kw. or adenocarinom*.tw,kf,kw. or neoplas*.tw,kw,kf.)	663769
	121	120 and 4	94503
	122	25 or 45 or 68 or 103	2717634
	123	121 and 122	31447
	124	limit 123 to systematic reviews	679
	125	73 or 110 or 119 or 124	862
Note			

Appendix 2.1.2. Embase @ Embase.com

Date	2014-02-05		
Database	Embase (Embase.com)		
Search Strategy	**#**	**Query**	**Results**
	#1	'breast'/exp	83,921
	#2	breast*	523,538
	#3	mammary	107,156
	#4	#1 OR #2 OR #3	574,130
	#5	'neoplasm'/exp	3,360,234
	#6	neoplasm*	3,372,019
	#7	cancer*	2,817,176
	#8	malign*	2,042,448
	#9	tumor*	3,426,236
	#10	tumour*	257,374
	#11	carcinom*	941,106
	#12	adenocarcinom*	170,161
	#13	metastas*	457,613
	#14	oncolog*	1,525,312
	#15	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	4,391,625
	#16	#4 AND #15	424,264
	#17	'breast tumor'/exp	343,775
	#18	#16 OR #17	424,264

	#19	'tumor suppressor gene'/exp	44,388
	#20	'genetic predisposition'/exp	75,976
	#21	'genetic counseling'/exp	20,646
	#22	'genetic marker'/exp	54,975
	#23	'genetic polymorphism'/exp	284,048
	#24	'single strand conformation polymorphism'/exp	10,637
	#25	#19 OR #20 OR #21 OR #22 OR #23 OR #24	434,409
	#26	'genetic screening'/exp	43,332
	#27	'heterozygote detection'/exp	5,825
	#28	genet* NEAR/3 (test* OR screened OR screening OR detect* OR assess* OR profil* OR counseling OR counselling)	175,330
	#29	#26 OR #27 OR #28	175,330
	#30	#18 AND #29	10,569
	#31	(hereditary OR famil* OR genetic* OR inherited) NEAR/3 (cancer* OR tumor* OR tumour* OR neoplasm* OR carcinom* OR adenocarcinom*)	230,723
	#32	screening	643,614
	#33	screened	119,165
	#34	testing	551,278
	#35	test	2,051,766
	#36	tests	1,135,998
	#37	profile	334,086
	#38	profiling	98,050
	#39	detect*	1,953,108
	#40	assess*	2,761,457
	#41	#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	7,144,115
	#42	gene OR genes	2,931,723
	#43	genetic OR genetics	4,358,988
	#44	mutation OR mutations	840,487
	#45	allele OR alleles	210,782
	#46	brca* OR '17q12-21' OR '17q12-q21' OR '17q12' OR '17q21' OR '13q12-13' OR '13q12-q13' OR '13q12-3'	22,792
	#47	tp53 OR 17p13.1	8,066
	#48	stk2 OR 19p13.3	356
	#49	stkii	3
	#50	chek2 OR 22q12.1	532

	#51	11q22.3	212
	#53	atm NEAR/2 (gene OR locus OR loci)	1,081
	#54	cdh1 OR 16q22.1	1,983
	#55	pten OR 10q23.3	11,402
	#56	palb2 OR 16p12.1	357
	#57	bardi OR 2q34 OR 2q35 OR '2q34-q35' OR '2q34-35' OR '2q34-5'	935
	#58	brip1 OR 17q22 OR 17q23 OR 17q24 OR '17q22-q24' OR '17q22-24' OR '17q22-4'	924
	#59	mre11a OR 11q21	267
	#60	nbn OR 8q21	596
	#61	rad50 OR 5q31	2,416
	#62	rad51c OR 17q25.1	266
	#63	xrcc2 OR 7q36.1	336
	#64	rad51d OR 17q11	699
	#65	abraxas OR 4q21.23	140
	#66	her2	19,433
	#67	#42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66	4,599,489
	#68	(screening OR screened OR testing OR test OR tests OR profile OR profiling OR detect* OR assess* OR sequencing) NEAR/3 (gene OR genes OR genetic OR genetics OR mutation OR mutations OR allele OR alleles OR brca* OR tp53 OR stk2 OR stkii OR chek2 OR her2 OR abraxas OR 4q21.23 OR rad51d OR 17q11 OR xrcc2 OR 7q36.1 OR rad51c OR 17q25.1 OR rad50 OR 5q31 OR nbn OR 8q21 OR mre11a OR 11q21 OR brip1 OR 17q22 OR 17q23 OR 17q24 OR '17q22-q24' OR '17q22-24' OR '17q22-4' OR bardi OR 2q34 OR 2q35 OR '2q34-q35' OR '2q34-35' OR '2q34-5' OR palb2 OR 16p12.1 OR pten OR 10q23.3 OR cdh1 OR 16q22.1 OR 11q22.3 OR check2 OR 22q12.1 OR stkii OR stk2 OR 19p13.3 OR 17p13.1 OR '17q12-21' OR '17q12-q21' OR '17q12' OR 17q21 OR '13q12-13' OR '13q12-q13' OR '13q12-3' OR 13q13)	240,809
	#69	#18 AND #68	15,243
	#70	'familial cancer'/exp	9,475
	#71	#4 AND #70	3,377
	#72	#41 AND #71	2,205
	#73	#25 AND #41	187,429
	#74	'mass screening'/exp	150,737
	#75	'microarray analysis'/exp	36,159

	#76	'health survey'/exp	150,475
	#77	#74 OR #75 OR #76	332,748
	#78	#25 AND #77	21,677
	#79	#73 OR #78	189,146
	#80	#18 AND #79	11,007
	#81	#4 AND #31 AND #41	18,845
	#82	#30 OR #69 OR #72 OR #80 OR #81	30,560
	#83	'meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review'	159,496
	#84	#82 AND #83	762
	#85	#84 AND [embase]/lim	725
	#86	#84 AND [medline]/lim	556
	#87	#84 NOT #86	366
Note			

Appendix 2.1.3. Cochrane

Date	2014-02-07		
Database (name + access ; e.g.: Medline OVID)	Cochrane Database		
Search Strategy	**#**	**Search expression**	**Results**
	#1	MeSH descriptor: [Breast] explode all trees	591
	#2	breast*:ti,ab,kw	20645
	#3	mammary:ti,ab,kw	773
	#4	#1 or #2 or #3	21056
	#5	MeSH descriptor: [Neoplasms] explode all trees	49379
	#6	neoplasm*:ti,ab,kw	44175
	#7	cancer*:ti,ab,kw	55325
	#8	tumor*:ti,ab,kw	18655
	#9	tumour*:ti,ab,kw	4386
	#10	carcinom*:ti,ab,kw	18053
	#11	adenocarcin*:ti,ab,kw	3362
	#12	malign*:ti,ab,kw	7257
	#13	metasta*:ti,ab,kw	12967
	#14	oncolog*:ti,ab,kw	9630

	#15	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	86028
	#16	#5 or #15	91175
	#17	#4 and #16	16392
	#18	MeSH descriptor: [Breast Neoplasms] explode all trees	8274
	#19	#17 or #18	16392
	#20	MeSH descriptor: [Genetic Predisposition to Disease] explode all trees	1326
	#21	MeSH descriptor: [Genetics] explode all trees	577
	#22	MeSH descriptor: [Genetic Markers] explode all trees	213
	#23	MeSH descriptor: [Polymorphism, Genetic] explode all trees	2718
	#24	Polymorphism, single stranded conformational	52
	#25	#20 or #21 or #22 or #23 or #24	3692
	#26	screening:ti,ab,kw	18362
	#27	screened:ti,ab,kw	18522
	#28	testing:ti,ab,kw	143378
	#29	tests:ti,ab,kw	143679
	#30	tested:ti,ab,kw	143453
	#31	test:ti,ab,kw	143679
	#32	profil*:ti,ab,kw	25734
	#33	#26 or #27 or #28 or #29 or #30 or #31 or #32	174355
	#34	Any MeSH descriptor with qualifier(s): [Diagnosis - DI]	36637
	#35	diagnosis:ti,ab,kw	29655
	#36	detection:ti,ab,kw	11081
	#37	#34 or #35 or #36	67110
	#38	#37 and #25	407
	#39	MeSH descriptor: [Genetic Testing] explode all trees	464
	#40	MeSH descriptor: [Genetic Counseling] explode all trees	137
	#41	MeSH descriptor: [DNA Mutational Analysis] explode all trees	224
	#42	MeSH descriptor: [Heterozygote Detection] explode all trees	65
	#43	MeSH descriptor: [Genetic Techniques] explode all trees	4393
	#44	MeSH descriptor: [Microarray Analysis] explode all trees	237
	#45	#39 or #40 or #41 or #42 or #43 or #44	4479
	#46	(genet* near/3 (test* or screened or screening or detect* or assess* or profil* or counseling or counselling)):ti,ab,kw	1123
	#47	((proteom* or genom* or gene or genes or sequence or sequences) near/3 (screening or profil* or sequencing or screening or screened)):ti,ab,kw	9031

	#48	expression near/3 profil*:ti,ab,kw	457
	#49	#46 or #47 or #48	10052
	#50	#38 or #45 or #49	13187
	#51	MeSH descriptor: [Mass Screening] explode all trees	4732
	#52	MeSH descriptor: [Population Surveillance] explode all trees	501
	#53	#51 or #52	5164
	#54	#33 or #53	174803
	#55	#25 and #54	1264
	#56	#50 or #55	13662
	#57	#19 and #56	656
	#58	MeSH descriptor: [Breast Neoplasms] explode all trees and with qualifier(s): [Genetics - GE]	430
	#59	MeSH descriptor: [Genes, BRCA1] explode all trees	72
	#60	MeSH descriptor: [Genes, BRCA2] explode all trees	52
	#61	#58 or #59 or #60	448
	#62	MeSH descriptor: [Breast Neoplasms] explode all trees and with qualifier(s): [Diagnosis - DI]	603
	#63	#50 or #54 or #62	182317
	#64	#61 and #63	318
	#65	MeSH descriptor: [Neoplasms] explode all trees and with qualifier(s): [Genetics - GE]	1770
	#66	MeSH descriptor: [Neoplastic Syndromes, Hereditary] explode all trees	269
	#67	((hereditary or famil* or genetic* or inherited) near/3 (cancer or cancers or tumor* or tumour* or neoplasm* or carcinom* or adenocarcinom*)):ti,ab,kw	869
	#68	#65 or #66 or #67	2427
	#69	#68 and #4	566
	#70	#54 or #50	182082
	#71	#69 and #70	375
	#72	#57 or #64 or #71	729
	#73	gene:ti,ab,kw or genes:ti,ab,kw	7172
	#74	genetic:ti,ab,kw	6489
	#75	genetics:ti,ab,kw	752
	#76	mutations:ti,ab,kw or mutation:ti,ab,kw	2341
	#77	allele or alleles	1890
	#78	BRCA*:ti,ab,kw	175
	#79	TP53:ti,ab,kw	55
	#80	STK2:ti,ab,kw	0
	#81	STKII:ti,ab,kw	0

#82	CHEK2:ti,ab,kw	7
#83	HER2:ti,ab,kw	541
#84	('17q12-21' or '17q12-q21' or '17q12' or '17q21' or '13q12-13' or '13q12-q13' or '13q12-3'):ti,ab,kw	2
#85	"17p13.1":ti,ab,kw	3
#86	"19p13.3":ti,ab,kw	0
#87	"22q12.1":ti,ab,kw	0
#88	"11q22.3":ti,ab,kw	1
#89	(atm near/2 (gene or locus or loci)):ti,ab,kw	5
#90	(cdh1 or "16q22.1"):ti,ab,kw	4
#91	(palb2 or "16p12.1"):ti,ab,kw	0
#92	(pten or "10q23.3"):ti,ab,kw	36
#93	(bardi or "2q34" or "2q35" or "2q34-q35" or "2q34-35" or "2q34-5"):ti,ab,kw	2
#94	(mre11a or "11q21"):ti,ab,kw	0
#95	(brip1 or "17q22" or "17q23" or "17q24" or "17q22-q24" or "17q22-24" or "17q22-4"):ti,ab,kw	0
#96	(nbn or "8q21"):ti,ab,kw	5
#97	(rad50 or "5q31"):ti,ab,kw	2
#98	(rad51c or "17q25.1"):ti,ab,kw	0
#99	(xrcc2 or "7q36.1"):ti,ab,kw	2
#100	(rad51d or "17q11"):ti,ab,kw	0
#101	(abraxas or "4q21.23"):ti,ab,kw	0
#102	#73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101	12943
#103	assess*:ti,ab,kw	172767
#104	detect*:ti,ab,kw	35782
#105	sequencing:ti,ab,kw	8687
#106	#33 or #103 or #104 or #105	308045
#107	(screening or screened or testing or tests or test or tested or profil* or assess* or detect* or sequencing) near/3 (gene or genes or genetic or genetics or mutation or mutations or allele or alleles or BRCA* or TP53 or STK2 or STKII or CHEK2 or HER2 or ('17q12-21' or '17q12-q21' or '17q12' or '17q21' or '13q12-13' or '13q12-q13' or '13q12-3') or "17p13.1" or "19p13.3" or "22q12.1" or "11q22.3" or (atm adj2 (gene or locus or loci)) or (cdh1 or "16q22.1") or (pten or "10q23.3") or (palb2 or "16p12.1") or (bardi or "2q34" or "2q35" or "2q34-q35" or "2q34-35" or "2q34-5") or (brip1 or "17q22" or "17q23" or "17q24" or "17q22-q24" or "17q22-24" or	2168

		"17q22-4") or (mre11a or "11q21") or (nbn or "8q21") or (rad50 or "5q31") or (rad51c or "17q25.1") or (xrcc2 or "7q36.1") or (rad51d or "17q11") or (abraxas or "4q21.23")):ti,ab,kw	
	#108	#107 and #19	288
	#109	EndoPredict	1
	#110	PAM50	5
	#111	"Genomic Grade Index"	1
	#112	MammaPrint	12
	#113	oncotypedx or "oncotype dx"	20
	#114	"Breast Cancer Index"	2
	#115	#109 or #110 or #111 or #112 or #113 or #114	35
	#116	(screening or screened or testing or tests or test or tested or profil* or assess* or detect* or sequencing) near/3 ((tumor* or tumour*) or cancer* or oncolog* or metastas* or carcinom* or malign* or adenocarinom* or neoplas*)	7492
	#117	#116 and #4	1720
	#118	#25 or #45 or #68 or #102	15513
	#119	#117 and #118	246
	#120	#119 or #115 or #108 or #72	817
Note	817 results for Cochrane library split as: All Results (817) Cochrane Reviews (9) DARE (32) CENTRAL (649) Methods Studies -CMR (9) Technology Assessments – HTAD (52) Economic Evaluations NHSEED (66) Cochrane Groups – ABOUT (0)		

Appendix 2.2. Cowden

Appendix 2.2.1. Medline @ Ovid

Date	2014-03-13		
Database	Medline (OVID)		
Search Strategy	**#**	**Query**	**Results**
	1	cowden's syndrome.mp.	84
	2	Hamartoma Syndrome, Multiple/	753
	3	bannayan-ruvalcaba-riley.mp.	8
	4	cowden's disease.mp.	191
	5	myhre riley smith syndrome.mp.	0
	6	multiple hamartoma syndromes.mp.	3
	7	cerebellum dysplastic gangliocytoma?.mp.	0
	8	ruvalcaba myhre smith syndrome.mp.	14
	9	(macrocephaly pseudopapilledema and multiple hemangiomas).mp.	0
	10	dysplastic gangliocytoma of cerebellum.mp.	9
	11	cerebellum dysplastic gangliocytoma.mp.	0
	12	lhermitte duclos disease.mp.	216
	13	cowden syndrome.mp.	364
	14	hamartoma syndrome multiple.mp.	753
	15	dysplastic gangliocytoma of the cerebellum.mp.	55
	16	riley smith syndrome.mp.	4
	17	cowdens disease.mp.	191
	18	myhre-riley-smith syndrome.mp.	0
	19	myhre-riley-smith.mp.	0
	20	pten hamartoma tumor.mp.	73
	21	bannayan zonana syndrome.mp.	42
	22	hamartoma syndromes multiple.mp.	0
	23	hamartoma syndromes.mp.	44
	24	multiple hamartoma syndrome.mp.	111
	25	bannayan riley ruvalcaba syndrome.mp.	100
	26	bannayan-riley-ruvalcaba syndrome.mp.	100
	27	cowden disease.mp.	193
	28	ruvalcaba-myhre syndrome.mp.	2

	29	bannayan-zonana syndrome.mp.	42
	30	(macrocephaly multiple lipomas and hemangiomata).mp.	1
	31	(macrocephaly pseudopapilledema and multiple hemangiomata).mp.	0
	32	lhermitte-duclos disease.mp.	216
	33	ruvalcaba-myhre-smith syndrome.mp.	14
	34	riley-smith syndrome.mp.	4
	35	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34	1294
	36	(pten adj3 hamartoma).mp.	98
	37	cowden.ti,ab.	643
	38	(germline adj5 hamartom*).mp.	15
	39	(hamartoma? adj3 (syndrome? or pten or multiple)).tw.	696
	40	36 or 37 or 38 or 39	1176
	41	35 or 40	1714
	42	exp Genetic Predisposition to Disease/	88227
	43	exp Genetics/	171946
	44	exp Genetic markers/	44777
	45	exp Polymorphism, genetic/	193770
	46	exp Polymorphism, single stranded conformational/	10356
	47	42 or 43 or 44 or 45 or 46	424611
	48	(screening or screened or testing or test? or tested or profil*).tw,kw,kf.	2668335
	49	di.xs. or diagnosis.tw,kw,kf. or detection.tw,kw,kf.	5054368
	50	47 and 49	85156
	51	exp Genetic testing/	25803
	52	exp genetic counseling/	11659
	53	exp DNA mutational analysis/	46011
	54	exp Heterozygote Detection/	8036
	55	exp Genetic Techniques/	1483281
	56	exp Microarray Analysis/	72581
	57	51 or 52 or 53 or 54 or 55 or 56	1495091
	58	(genet* adj3 (test* or screened or screening or detect* or assess* or profil* or counsel?ing)).tw,kw.	43996
	59	((proteom* or genom* or gene? or sequence?) adj3 (screening or profil* or sequencing or screening or screened)).tw,kw.	69890
	60	(expression adj3 profil*).tw,kw.	47657

	61	58 or 59 or 60	132885
	62	50 or 57 or 61	1582390
	63	exp Mass Screening/	98780
	64	exp population surveillance/	49240
	65	63 or 64	145808
	66	48 or 65	2734065
	67	47 and 66	94841
	68	62 or 67	1609544
	69	41 and 68	458
	70	Hamartoma Syndrome, Multiple/ge	397
	71	70 and (48 or 49 or 57 or 61 or 65)	328
	72	69 or 71	585
	73	Hamartoma Syndrome, Multiple/di	234
	74	(73 or 66 or 62) and 70	267
	75	69 or 71 or 74	585
	76	limit 75 to systematic reviews	6
Note			

Appendix 2.2.2. Medline @ Pubmed

Date	2014-03-06		
Database	Medline (Pubmed)		
Search Strategy (attention, for PubMed, check « Details »)	**#**	**Query**	**Results**
	1	("hamartoma syndrome, multiple"[MeSH Terms] OR ("hamartoma"[All Fields] AND "syndrome"[All Fields] AND "multiple"[All Fields]) OR "multiple hamartoma syndrome"[All Fields] OR ("hamartoma"[All Fields] AND "syndromes"[All Fields] AND "multiple"[All Fields])) OR "Multiple Hamartoma Syndromes"[All Fields] OR "Multiple Hamartoma Syndrome"[All Fields] OR "Cowden's Disease"[All Fields] OR ("hamartoma syndrome, multiple"[MeSH Terms] OR ("hamartoma"[All Fields] AND "syndrome"[All Fields] AND "multiple"[All Fields]) OR "multiple hamartoma syndrome"[All Fields] OR ("cowdens"[All Fields] AND "disease"[All Fields])) OR "Cowden's Syndrome"[All Fields] OR "Cowdens Syndrome"[All Fields] OR "Cowden Disease"[All Fields] OR "Cowden Syndrome"[All Fields] OR "Lhermitte-Duclos Disease"[All Fields] OR "Lhermitte Duclos Disease"[All Fields] OR "Dysplastic Gangliocytoma of Cerebellum"[All Fields] OR ("hamartoma syndrome, multiple"[MeSH Terms] OR ("hamartoma"[All Fields] AND "syndrome"[All Fields] AND "multiple"[All Fields]) OR "multiple hamartoma syndrome"[All Fields] OR ("cerebellum"[All Fields] AND "dysplastic"[All Fields]	1848

		AND "gangliocytoma"[All Fields])) OR ("hamartoma syndrome, multiple"[MeSH Terms] OR ("hamartoma"[All Fields] AND "syndrome"[All Fields] AND "multiple"[All Fields]) OR "multiple hamartoma syndrome"[All Fields] OR ("cerebellum"[All Fields] AND "dysplastic"[All Fields] AND "gangliocytomas"[All Fields])) OR "Dysplastic Gangliocytoma of the Cerebellum"[All Fields] OR "PTEN Hamartoma Tumor Syndrome"[All Fields] OR "Bannayan-Riley-Ruvalcaba Syndrome"[All Fields] OR "Bannayan Riley Ruvalcaba Syndrome"[All Fields] OR "Macrocephaly, Multiple Lipomas, and Hemangiomata"[All Fields] OR ("hamartoma syndrome, multiple"[MeSH Terms] OR ("hamartoma"[All Fields] AND "syndrome"[All Fields] AND "multiple"[All Fields]) OR "multiple hamartoma syndrome"[All Fields] OR ("macrocephaly"[All Fields] AND "pseudopapilledema"[All Fields] AND "multiple"[All Fields] AND "hemangiomas"[All Fields])) OR "Ruvalcaba-Myhre Syndrome"[All Fields] OR ("hamartoma syndrome, multiple"[MeSH Terms] OR ("hamartoma"[All Fields] AND "syndrome"[All Fields] AND "multiple"[All Fields]) OR "multiple hamartoma syndrome"[All Fields] OR ("myhre"[All Fields] AND "riley"[All Fields] AND "smith"[All Fields] AND "syndrome"[All Fields])) OR ("hamartoma syndrome, multiple"[MeSH Terms] OR ("hamartoma"[All Fields] AND "syndrome"[All Fields] AND "multiple"[All Fields]) OR "multiple hamartoma syndrome"[All Fields] OR ("myhre"[All Fields] AND "riley"[All Fields] AND "smith"[All Fields] AND "syndrome"[All Fields])) OR "Riley-Smith Syndrome"[All Fields] OR "Riley Smith Syndrome"[All Fields] OR "Ruvalcaba-Myhre-Smith Syndrome"[All Fields] OR "Ruvalcaba Myhre Smith Syndrome"[All Fields] OR "Bannayan-Ruvalcaba-Riley Syndrome"[All Fields] OR "Bannayan-Zonana Syndrome"[All Fields] OR "Bannayan Zonana Syndrome"[All Fields] OR ("hamartoma syndrome, multiple"[MeSH Terms] OR ("hamartoma"[All Fields] AND "syndrome"[All Fields] AND "multiple"[All Fields]) OR "multiple hamartoma syndrome"[All Fields] OR ("macrocephaly"[All Fields] AND "pseudopapilledema"[All Fields] AND "multiple"[All Fields] AND "hemangiomata"[All Fields]))
	2	Limit 1 to systematic reviews	8
Note		Few reviews, no need to look for genetic testing.	

Appendix 2.2.3. Embase @ Embase.com

Date	2014-03-12		
Database	Embase (Embase.com)		
Search Strategy (attention, for PubMed, check « Details »)	**#**	**Query**	**Results**
	#1	multiple NEAR/4 hamartom*	903
	#2	hamartom* NEAR/4 syndrome	1,174
	#3	#1 AND #2	310
	#4	'bannayan ruvalcaba riley'	14
	#5	cowden NEAR/2 disease	531
	#6	cowdens NEAR/2 disease	1
	#7	myhre AND riley AND smith AND syndrome	6
	#8	cowden NEAR/2 syndrome	1,309
	#9	cowdens NEAR/2 syndrome	3
	#10	multiple AND hamartoma AND syndromes	154
	#11	cerebellum AND dysplastic AND gangliocytom*	128
	#12	ruvalcaba AND myhre AND smith AND syndrome	24
	#13	macrocephaly AND pseudopapilledema AND multiple AND hemangiomas	0
	#14	dysplastic AND gangliocytoma AND of AND cerebellum	124
	#15	cerebellum AND dysplastic AND gangliocytoma	124
	#16	lhermitte AND duclos AND disease	387
	#17	dysplastic AND gangliocytoma AND of AND the AND cerebellum	119
	#18	riley AND smith AND syndrome	53
	#19	'myhre riley smith' AND syndrome	0
	#20	'myhre riley smith'	0
	#21	pten AND hamartoma AND tumor	299
	#22	bannayan AND zonana AND syndrome	67
	#23	hamartoma AND syndromes AND multiple	154
	#24	hamartoma AND syndromes	376
	#25	multiple AND hamartoma AND syndrome	809
	#26	bannayan AND riley AND ruvalcaba AND syndrome	202
	#27	'bannayan riley ruvalcaba' AND syndrome	186
	#28	'ruvalcaba myhre' AND syndrome	32
	#29	'bannayan zonana' AND syndrome	66

	#30	macrocephaly AND multiple AND lipomas AND hemangiomata	1
	#31	macrocephaly AND pseudopapilledema AND multiple AND hemangiomata	0
	#32	'lhermitte duclos' AND disease	385
	#33	'ruvalcaba myhre smith' AND syndrome	18
	#34	'riley smith' AND syndrome	9
	#35	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	2,543
	#36	'meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review'	163,032
	#37	#35 AND #36	18
Note			

Appendix 2.2.4. Cochrane Database of Systematic Reviews

Date	2014-03-17		
Database	Cochrane		
Search Strategy (attention, for PubMed, check « Details »)	**#**	**Query**	**Results**
	#1	cowden's syndrome	0
	#2	cowden:ti	1
	#3	MeSH descriptor: [Hamartoma Syndrome, Multiple] explode all trees	1
	#4	bannayan-ruvalcaba-riley:ti,ab,kw	0
	#5	"cowden's disease":ti,ab,kw	0
	#6	"myhre riley smith syndrome":ti,ab,kw	0
	#7	"multiple hamartoma syndromes":ti,ab,kw	0
	#8	"cerebellum dysplastic gangliocytoma":ti,ab,kw	0
	#9	"cerebellum dysplastic gangliocytomas":ti,ab,kw	0
	#10	"ruvalcaba myhre smith syndrome":ti,ab,kw	0
	#11	"macrocephaly pseudopapilledema and multiple hemangiomas":ti,ab,kw	0
	#12	"dysplastic gangliocytoma of cerebellum":ti,ab,kw	0
	#13	"cerebellum dysplastic gangliocytoma":ti,ab,kw	0
	#14	"lhermitte duclos disease":ti,ab,kw	0
	#15	"cowden syndrome":ti,ab,kw	1
	#16	"hamartoma syndrome multiple":ti,ab,kw	1
	#17	"dysplastic gangliocytoma of the cerebellum":ti,ab,kw	0
	#18	"riley smith syndrome":ti,ab,kw	0
	#19	"cowdens disease":ti,ab,kw	0

	#20	"myhre-riley-smith syndrome":ti,ab,kw	0
	#21	"myhre-riley-smith":ti,ab,kw	0
	#22	"pten hamartoma tumor":ti,ab,kw	1
	#23	"bannayan zonana syndrome":ti,ab,kw	0
	#24	"hamartoma syndromes multiple":ti,ab,kw	0
	#25	"hamartoma syndromes":ti,ab,kw	0
	#26	"multiple hamartoma syndrome":ti,ab,kw	0
	#27	"bannayan riley ruvalcaba syndrome":ti,ab,kw	0
	#28	"bannayan-riley-ruvalcaba syndrome":ti,ab,kw	0
	#29	"cowden disease":ti,ab,kw	0
	#30	"ruvalcaba-myhre syndrome":ti,ab,kw	0
	#31	"bannayan-zonana syndrome":ti,ab,kw	0
	#32	"macrocephaly multiple lipomas and hemangiomata":ti,ab,kw	0
	#33	"macrocephaly pseudopapilledema and multiple hemangiomata":ti,ab,kw	0
	#34	"lhermitte-duclos disease":ti,ab,kw	0
	#35	"ruvalcaba-myhre-smith syndrome":ti,ab,kw	0
	#36	"riley-smith syndrome":ti,ab,kw	0
	#37	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36	2
	#38	(pten near/3 hamartoma):ti,ab,kw	1
	#39	cowden:ti,ab,kw	1
	#40	(germline near/5 hamartom*):ti,ab,kw	0
	#41	(hamartom* near/3 (syndrom* or pten or multiple)):ti,ab	1
	#42	#38 or #39 or #40 or #41	2
	#43	#37 or #42	2
Note		2 results: 1 Trial and 1 HTA	

Appendix 2.3. Li-Fraumeni syndrome

Appendix 2.3.1. Medline @ Ovid

Date	2014-03-13		
Database	Medline (OVID)		
Search Strategy	**#**	**Query**	**Results**
	1	cowden's syndrome.mp.	84
	2	Hamartoma Syndrome, Multiple/	753
	3	bannayan-ruvalcaba-riley.mp.	8
	4	cowden's disease.mp.	191
	5	myhre riley smith syndrome.mp.	0
	6	multiple hamartoma syndromes.mp.	3
	7	cerebellum dysplastic gangliocytoma?.mp.	0
	8	ruvalcaba myhre smith syndrome.mp.	14
	9	(macrocephaly pseudopapilledema and multiple hemangiomas).mp.	0
	10	dysplastic gangliocytoma of cerebellum.mp.	9
	11	cerebellum dysplastic gangliocytoma.mp.	0
	12	lhermitte duclos disease.mp.	216
	13	cowden syndrome.mp.	364
	14	hamartoma syndrome multiple.mp.	753
	15	dysplastic gangliocytoma of the cerebellum.mp.	55
	16	riley smith syndrome.mp.	4
	17	cowdens disease.mp.	191
	18	myhre-riley-smith syndrome.mp.	0
	19	myhre-riley-smith.mp.	0
	20	pten hamartoma tumor.mp.	73
	21	bannayan zonana syndrome.mp.	42
	22	hamartoma syndromes multiple.mp.	0
	23	hamartoma syndromes.mp.	44
	24	multiple hamartoma syndrome.mp.	111
	25	bannayan riley ruvalcaba syndrome.mp.	100
	26	bannayan-riley-ruvalcaba syndrome.mp.	100
	27	cowden disease.mp.	193
	28	ruvalcaba-myhre syndrome.mp.	2
	29	bannayan-zonana syndrome.mp.	42

	30	(macrocephaly multiple lipomas and hemangiomata).mp.	1
	31	(macrocephaly pseudopapilledema and multiple hemangiomata).mp.	0
	32	lhermitte-duclos disease.mp.	216
	33	ruvalcaba-myhre-smith syndrome.mp.	14
	34	riley-smith syndrome.mp.	4
	35	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34	1294
	36	(pten adj3 hamartoma).mp.	98
	37	cowden.ti,ab.	643
	38	(germline adj5 hamartom*).mp.	15
	39	(hamartoma? adj3 (syndrome? or pten or multiple)).tw.	696
	40	36 or 37 or 38 or 39	1176
	41	35 or 40	1714
	42	exp Genetic Predisposition to Disease/	88227
	43	exp Genetics/	171946
	44	exp Genetic markers/	44777
	45	exp Polymorphism, genetic/	193770
	46	exp Polymorphism, single stranded conformational/	10356
	47	42 or 43 or 44 or 45 or 46	424611
	48	(screening or screened or testing or test? or tested or profil*).tw,kw,kf.	2668335
	49	di.xs. or diagnosis.tw,kw,kf. or detection.tw,kw,kf.	5054368
	50	47 and 49	85156
	51	exp Genetic testing/	25803
	52	exp genetic counseling/	11659
	53	exp DNA mutational analysis/	46011
	54	exp Heterozygote Detection/	8036
	55	exp Genetic Techniques/	1483281
	56	exp Microarray Analysis/	72581
	57	51 or 52 or 53 or 54 or 55 or 56	1495091
	58	(genet* adj3 (test* or screened or screening or detect* or assess* or profil* or counsel?ing)).tw,kw.	43996
	59	((proteom* or genom* or gene? or sequence?) adj3 (screening or profil* or sequencing or screening or screened)).tw,kw.	69890
	60	(expression adj3 profil*).tw,kw.	47657
	61	58 or 59 or 60	132885

	62	50 or 57 or 61	1582390
	63	exp Mass Screening/	98780
	64	exp population surveillance/	49240
	65	63 or 64	145808
	66	48 or 65	2734065
	67	47 and 66	94841
	68	62 or 67	1609544
	69	41 and 68	458
	70	Hamartoma Syndrome, Multiple/ge	397
	71	70 and (48 or 49 or 57 or 61 or 65)	328
	72	69 or 71	585
	73	Hamartoma Syndrome, Multiple/di	234
	74	(73 or 66 or 62) and 70	267
	75	69 or 71 or 74	585
	76	limit 75 to systematic reviews	6
Note			

Appendix 2.3.2. Medline @ Pubmed

Date	2014-03-06		
Database	Medline (Pubmed)		
Search Strategy (attention, for PubMed, check « Details »)	**#**	**Query**	**Results**
	1	("hamartoma syndrome, multiple"[MeSH Terms] OR ("hamartoma"[All Fields] AND "syndrome"[All Fields] AND "multiple"[All Fields]) OR "multiple hamartoma syndrome"[All Fields] OR ("hamartoma"[All Fields] AND "syndromes"[All Fields] AND "multiple"[All Fields])) OR "Multiple Hamartoma Syndromes"[All Fields] OR "Multiple Hamartoma Syndrome"[All Fields] OR "Cowden's Disease"[All Fields] OR ("hamartoma syndrome, multiple"[MeSH Terms] OR ("hamartoma"[All Fields] AND "syndrome"[All Fields] AND "multiple"[All Fields]) OR "multiple hamartoma syndrome"[All Fields] OR ("cowdens"[All Fields] AND "disease"[All Fields])) OR "Cowden's Syndrome"[All Fields] OR "Cowdens Syndrome"[All Fields] OR "Cowden Disease"[All Fields] OR "Cowden Syndrome"[All Fields] OR "Lhermitte-Duclos Disease"[All Fields] OR "Lhermitte Duclos Disease"[All Fields] OR "Dysplastic Gangliocytoma of Cerebellum"[All Fields] OR ("hamartoma syndrome, multiple"[MeSH Terms] OR ("hamartoma"[All Fields] AND "syndrome"[All Fields] AND "multiple"[All Fields]) OR "multiple hamartoma syndrome"[All Fields] OR ("cerebellum"[All Fields] AND "dysplastic"[All Fields] AND "gangliocytoma"[All Fields])) OR ("hamartoma syndrome, multiple"[MeSH Terms] OR ("hamartoma"[All Fields] AND "syndrome"[All Fields] AND "multiple"[All Fields]) OR "multiple	1848

		hamartoma syndrome"[All Fields] OR ("cerebellum"[All Fields] AND "dysplastic"[All Fields] AND "gangliocytomas"[All Fields])) OR "Dysplastic Gangliocytoma of the Cerebellum"[All Fields] OR "PTEN Hamartoma Tumor Syndrome"[All Fields] OR "Bannayan-Riley-Ruvalcaba Syndrome"[All Fields] OR "Bannayan Riley Ruvalcaba Syndrome"[All Fields] OR "Macrocephaly, Multiple Lipomas, and Hemangiomata"[All Fields] OR ("hamartoma syndrome, multiple"[MeSH Terms] OR ("hamartoma"[All Fields] AND "syndrome"[All Fields] AND "multiple"[All Fields]) OR "multiple hamartoma syndrome"[All Fields] OR ("macrocephaly"[All Fields] AND "pseudopapilledema"[All Fields] AND "multiple"[All Fields] AND "hemangiomas"[All Fields])) OR "Ruvalcaba-Myhre Syndrome"[All Fields] OR ("hamartoma syndrome, multiple"[MeSH Terms] OR ("hamartoma"[All Fields] AND "syndrome"[All Fields] AND "multiple"[All Fields]) OR "multiple hamartoma syndrome"[All Fields] OR ("myhre"[All Fields] AND "riley"[All Fields] AND "smith"[All Fields] AND "syndrome"[All Fields])) OR ("hamartoma syndrome, multiple"[MeSH Terms] OR ("hamartoma"[All Fields] AND "syndrome"[All Fields] AND "multiple"[All Fields]) OR "multiple hamartoma syndrome"[All Fields] OR ("myhre"[All Fields] AND "riley"[All Fields] AND "smith"[All Fields] AND "syndrome"[All Fields])) OR "Riley-Smith Syndrome"[All Fields] OR "Riley Smith Syndrome"[All Fields] OR "Ruvalcaba-Myhre-Smith Syndrome"[All Fields] OR "Ruvalcaba Myhre Smith Syndrome"[All Fields] OR "Bannayan-Ruvalcaba-Riley Syndrome"[All Fields] OR "Bannayan-Zonana Syndrome"[All Fields] OR "Bannayan Zonana Syndrome"[All Fields] OR ("hamartoma syndrome, multiple"[MeSH Terms] OR ("hamartoma"[All Fields] AND "syndrome"[All Fields] AND "multiple"[All Fields]) OR "multiple hamartoma syndrome"[All Fields] OR ("macrocephaly"[All Fields] AND "pseudopapilledema"[All Fields] AND "multiple"[All Fields] AND "hemangiomata"[All Fields]))	
	2	Limit 1 to systematic reviews	8
Note		Few reviews, no need to look for genetic testing.	

Appendix 2.3.3. Embase @ Embase.com

Date	2014-03-12		
Database	Embase (Embase.com)		
Search Strategy (attention, for PubMed, check « Details »)	**#**	**Query**	**Results**
	#1	multiple NEAR/4 hamartom*	903
	#2	hamartom* NEAR/4 syndrome	1,174
	#3	#1 AND #2	310
	#4	'bannayan ruvalcaba riley'	14
	#5	cowden NEAR/2 disease	531
	#6	cowdens NEAR/2 disease	1
	#7	myhre AND riley AND smith AND syndrome	6

	#8	cowden NEAR/2 syndrome	1,309
	#9	cowdens NEAR/2 syndrome	3
	#10	multiple AND hamartoma AND syndromes	154
	#11	cerebellum AND dysplastic AND gangliocytom*	128
	#12	ruvalcaba AND myhre AND smith AND syndrome	24
	#13	macrocephaly AND pseudopapilledema AND multiple AND hemangiomas	0
	#14	dysplastic AND gangliocytoma AND of AND cerebellum	124
	#15	cerebellum AND dysplastic AND gangliocytoma	124
	#16	lhermitte AND duclos AND disease	387
	#17	dysplastic AND gangliocytoma AND of AND the AND cerebellum	119
	#18	riley AND smith AND syndrome	53
	#19	'myhre riley smith' AND syndrome	0
	#20	'myhre riley smith'	0
	#21	pten AND hamartoma AND tumor	299
	#22	bannayan AND zonana AND syndrome	67
	#23	hamartoma AND syndromes AND multiple	154
	#24	hamartoma AND syndromes	376
	#25	multiple AND hamartoma AND syndrome	809
	#26	bannayan AND riley AND ruvalcaba AND syndrome	202
	#27	'bannayan riley ruvalcaba' AND syndrome	186
	#28	'ruvalcaba myhre' AND syndrome	32
	#29	'bannayan zonana' AND syndrome	66
	#30	macrocephaly AND multiple AND lipomas AND hemangiomata	1
	#31	macrocephaly AND pseudopapilledema AND multiple AND hemangiomata	0
	#32	'lhermitte duclos' AND disease	385
	#33	'ruvalcaba myhre smith' AND syndrome	18
	#34	'riley smith' AND syndrome	9
	#35	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	2,543
	#36	'meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review'	163,032
	#37	#35 AND #36	18
Note			

Appendix 2.3.4. Cochrane Database of Systematic Reviews

Date	2014-03-17		
Database	Cochrane		
Search Strategy (attention, for PubMed, check « Details »)	**#**	**Query**	**Results**
	#1	cowden's syndrome	0
	#2	cowden:ti	1
	#3	MeSH descriptor: [Hamartoma Syndrome, Multiple] explode all trees	1
	#4	bannayan-ruvalcaba-riley:ti,ab,kw	0
	#5	"cowden's disease":ti,ab,kw	0
	#6	"myhre riley smith syndrome":ti,ab,kw	0
	#7	"multiple hamartoma syndromes":ti,ab,kw	0
	#8	"cerebellum dysplastic gangliocytoma":ti,ab,kw	0
	#9	"cerebellum dysplastic gangliocytomas":ti,ab,kw	0
	#10	"ruvalcaba myhre smith syndrome":ti,ab,kw	0
	#11	"macrocephaly pseudopapilledema and multiple hemangiomas":ti,ab,kw	0
	#12	"dysplastic gangliocytoma of cerebellum":ti,ab,kw	0
	#13	"cerebellum dysplastic gangliocytoma":ti,ab,kw	0
	#14	"lhermitte duclos disease":ti,ab,kw	0
	#15	"cowden syndrome":ti,ab,kw	1
	#16	"hamartoma syndrome multiple":ti,ab,kw	1
	#17	"dysplastic gangliocytoma of the cerebellum":ti,ab,kw	0
	#18	"riley smith syndrome":ti,ab,kw	0
	#19	"cowdens disease":ti,ab,kw	0
	#20	"myhre-riley-smith syndrome":ti,ab,kw	0
	#21	"myhre-riley-smith":ti,ab,kw	0
	#22	"pten hamartoma tumor":ti,ab,kw	1
	#23	"bannayan zonana syndrome":ti,ab,kw	0
	#24	"hamartoma syndromes multiple":ti,ab,kw	0
	#25	"hamartoma syndromes":ti,ab,kw	0
	#26	"multiple hamartoma syndrome":ti,ab,kw	0
	#27	"bannayan riley ruvalcaba syndrome":ti,ab,kw	0
	#28	"bannayan-riley-ruvalcaba syndrome":ti,ab,kw	0
	#29	"cowden disease":ti,ab,kw	0
	#30	"ruvalcaba-myhre syndrome":ti,ab,kw	0

	#31	"bannayan-zonana syndrome":ti,ab,kw	0
	#32	"macrocephaly multiple lipomas and hemangiomata":ti,ab,kw	0
	#33	"macrocephaly pseudopapilledema and multiple hemangiomata":ti,ab,kw	0
	#34	"lhermitte-duclos disease":ti,ab,kw	0
	#35	"ruvalcaba-myhre-smith syndrome":ti,ab,kw	0
	#36	"riley-smith syndrome":ti,ab,kw	0
	#37	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36	2
	#38	(pten near/3 hamartoma):ti,ab,kw	1
	#39	cowden:ti,ab,kw	1
	#40	(germline near/5 hamartom*):ti,ab,kw	0
	#41	(hamartom* near/3 (syndrom* or pten or multiple)):ti,ab	1
	#42	#38 or #39 or #40 or #41	2
	#43	#37 or #42	2
Note		2 results: 1 Trial and 1 HTA	

APPENDIX 3. EVIDENCE TABLES

Appendix 3.1. NICE recommendations for genetic testing and follow-up of familial breast cancer.

Reference CPG	Search date	Recommendations/conclusions	Evidence base	Level of evidence
NICE 2013	2013	• At least the following female breast cancers only in the family: o two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 50 years (at least one must be a first-degree relative) **[2004] or** o three first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years (at least one must be a first-degree relative) **[2004] or** o four relatives diagnosed with breast cancer at any age (at least one must be a first-degree relative). **[2004] or** • Families containing one relative with ovarian cancer at any age **and**, on the same side of the family: o one first-degree relative (including the relative with ovarian cancer) or second-degree relative diagnosed with breast cancer at younger than age 50 years **[2004] or** o two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years **[2004] or** o another ovarian cancer at any age. **[2004] or** • Families affected by bilateral cancer (each breast cancer has the same count value as one relative): o one first-degree relative with cancer diagnosed in both breasts at younger than an average age 50 years **[2004] or** o one first-degree or second-degree relative diagnosed with bilateral cancer and one first or second degree relative diagnosed with breast cancer at younger than an average age of 60 years. **[2004] or** • Families containing male breast cancer at any age **and**, on the same side of the family, at least:	Observational studies	Low

Reference CPG	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		o one first-degree or second-degree relative diagnosed with breast cancer at younger than age 50 years **[2004] or** o two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years. **[2004] or** • A formal risk assessment has given risk estimates of: o a 10% or greater chance of a gene mutation being harboured in the family **[new 2013] or** o a greater than 8% risk of developing breast cancer in the next 10 years **[2004] or** o a 30% or greater lifetime risk of developing breast cancer. **[2004]** 1.4.5 Clinicians should seek further advice from a specialist genetics service for families containing any of the following, in addition to breast cancers: • triple negative breast cancer under the age of 40 years **[new 2013]** • Jewish ancestry **[2004]** • sarcoma in a relative younger than age 45 years **[2004]** • glioma or childhood adrenal cortical carcinomas **[2004]** • complicated patterns of multiple cancers at a young age **[2004]** • very strong paternal history (four relatives diagnosed at younger than 60 years of age on the father's side of the family). **[2004]** 1.4.6 The management of high-risk people may take place in secondary care if they do not want genetic testing or risk-reducing surgery and do not wish to be referred to a specialist genetics service. **[2004]** 1.4.7 Following initial consultation in secondary care, written information should be provided to reflect the outcomes of the consultation. **[2004]**		

Reference CPG	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		1.6.4 Offer mammographic surveillance as part of the population screening program to women: • aged 50 years and over who have not had genetic testing but have a greater than 30% probability of being a *TP53* carrier • aged 60 years and over at high risk of breast cancer but with a 30% or lower probability of being a *BRCA* or *TP53* carrier • aged 60 years and over at moderate risk of breast cancer • aged 60 years and over who have not had genetic testing but have a greater than 30% probability of being a *BRCA* carrier • aged 70 years and over with a known *BRCA1* or *BRCA2* mutation. **[new 2013]** 1.6.5 Consider annual mammographic surveillance for women: • aged 30–39 years at high risk of breast cancer but with a 30% or lower probability of being a *BRCA* or *TP53* carrier • aged 30–39 years who have not had genetic testing but have a greater than 30% probability of being a *BRCA* carrier • aged 30–39 years with a known *BRCA1* or *BRCA2* mutation • aged 50–59 years at moderate risk of breast cancer. **[new 2013]** 1.6.6 Do not offer mammographic surveillance to women: aged 29 years and under • aged 30–39 years at moderate risk of breast cancer • aged 30–49 years who have not had genetic testing but have a greater than 30% probability of being a *TP53* carrier • of any age with a known *TP53* mutation. **[new 2013]** MRI surveillance		

Reference CPG	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		1.6.7 Offer annual MRI surveillance to women: • aged 30–49 years who have not had genetic testing but have a greater than 30% probability of being a *BRCA* carrier • aged 30–49 years with a known *BRCA1* or *BRCA2* mutation • aged 20–49 years who have not had genetic testing but have a greater than 30% probability of being a *TP53* carrier • aged 20–49 years with a known *TP53* mutation. **[new 2013]** 1.6.8 Consider annual MRI surveillance for women aged 50–69 years with a known *TP53* mutation. **[new 2013]** 1.6.9 Do not offer MRI to women: • of any age at moderate risk of breast cancer • of any age at high risk of breast cancer but with a 30% or lower probability of being a *BRCA* or *TP53* carrier • aged 20–29 years who have not had genetic testing but have a greater than 30% probability of being a *BRCA* carrier • aged 20–29 years with a known *BRCA1* or *BRCA2* mutation • aged 50–69 years who have not had genetic testing but have a greater than 30% probability of being a *BRCA* or a *TP53* carrier, unless mammography has shown a dense breast pattern • aged 50–69 years with a known *BRCA1* or *BRCA2* mutation, unless mammography has shown a dense breast pattern. **[new 2013]**		

Appendix 3.2. Genetic variants with a significant association with breast-cancer risk in meta-analysis[12]

Gene	Variant	Comparison*	Frequency (%)	Ethnicity	Number assessed			Breast-cancer risk		Heterogeneity	Venice criteria grade‡
					Studies	Cases	Controls	OR (95% CI)	p value		
ATM	Glu1978X	Carriers *vs* non-carriers	0·05	Caucasian	4	6593	3793	4·56 (1·35–15·42)	0·015	1·000	× A A
ATM	rs1800057 (Pro1054Arg)	(CG+GG) *vs* CC	5·06	All ancestries	9	4998	6122	1·20 (1·01–1·44)	0·038	0·466	B A A
CASP8	rs1045485 (Asp302His)	C *vs* G	13·29	Caucasian	17	18382	19?419	0·89 (0·85–0·93)	$4{\cdot}65\times10^{-78}$	0·992	A A A
CASP8	rs6435074 (A34767C)	A *vs* C	25·72	Caucasian	3	2677	3093	1·12 (1·03–1·22)	0·010	0·865	A A C
CASP8	rs6723097 (A35438C)	A *vs* C	36·33	Caucasian	3	2610	3040	1·16 (1·07–1·25)	$1{\cdot}91\times10^{-74}$	0·997	A A A
CHEK2	IVS2+1G>A	Carriers *vs* non-carriers	0·39	Caucasian	5	9970	7?526	3·07 (2·03–4·63)	$9{\cdot}82\times10^{-78}$	0·707	× A A
CHEK2	rs17879961 (Ile157Thr)	Carriers *vs* non-carriers	4·19	Caucasian	8	13311	10?817	1·52 (1·31–1·77)	$4{\cdot}76\times10^{-78}$	0·324	A A A
CHEK2	Deletion	Carriers *vs* non-carriers	0·30	Caucasian	5	10543	8447	2·53 (1·61–3·97)	$6{\cdot}33\times10^{-75}$	0·419	× A A
CHEK2	1100delC	Carriers *vs* non-carriers	0·49	All ancestries	47	41791	50?910	3·10 (2·59–3·71)	$<10^{-720}$	0·315	× A A
CTLA4	rs231775 (Thr17Ala)	A *vs* G	38·54	Asian	3	2214	2288	1·25 (1·14–1·37)	$1{\cdot}59\times10^{-76}$	0·676	A A A
CYP19A1	$(TTTA)_{10}$	R10 *vs* R7	1·76	All ancestries	13	7979	8564	1·53 (1·05–2·22)	0·027	0·044	B B A
ERCC2	rs13181 (Lys751Gln)	C *vs* A	34·62	All ancestries	33	15843	16?827	1·13 (1·05–1·22)	0·002	0·000	A C C
ESR1	rs3020314 (C5029T)	C *vs* T	31·73	Caucasian	3	5189	5614	1·12 (1·06–1·18)	$1{\cdot}09\times10^{-74}$	0·535	A A C
ESR1	rs1801132 (Pro325Pro)	G *vs* C	23·83	All ancestries	14	10836	14?685	0·95 (0·90–1·00)	0·038	0·297	A A C
GSTM1	Deletion	Null *vs* present	48·64	All ancestries	61	21289	24?850	1·11 (1·06–1·18)	$8{\cdot}86\times10^{-75}$	0·003	A B C
GSTT1	Deletion	Null *vs* present	23·37	All ancestries	43	16518	19?423	1·11 (1·03–1·20)	0·006	0·005	A B C
HSD17B1	rs676387 (C-150A)	A *vs* C	27·13	Caucasian	3	11794	14?205	1·05 (1·00–1·09)	0·050	0·278	A A C
IFNG	rs2430561 (T874A)	A *vs* T	43·32	All ancestries	3	324	397	1·25 (1·01–1·54)	0·039	0·691	B A C
IGF1	rs6220 (C84864T)	T *vs* C	29·50	All ancestries	3	6213	7192	1·06 (1·00–1·11)	0·048	0·656	A A C
LRTOMT	rs673478 (G-239A)	C *vs* T	4·51	Caucasian	3	607	587	1·53 (1·07–2·18)	0·020	0·683	B A C
MTHFR	rs1801133 (Ala222Val)	T *vs* C	32·24	All ancestries	46	21696	27?229	1·04 (1·00–1·07)	0·041	0·115	A A C
NBN	657del5	Carriers *vs* non-carriers	0·36	Caucasian	7	7082	9504	2·42 (1·54–3·80)	$1{\cdot}18\times10^{-74}$	0·736	× A A
NUMA1	rs3018301 (G-510A)	A *vs* G	5·17	Caucasian	3	606	590	1·45 (1·03–2·03)	0·033	0·911	B A C
TP53	rs12947788 (T72C)	T *vs* C	8·61	Caucasian	3	4357	5224	1·11 (1·01–1·23)	0·033	0·568	A A C
TP53	rs12951053 (T92G)	G *vs* T	8·67	Caucasian	3	4349	5247	1·12 (1·01–1·23)	0·027	0·618	A A C
TP53	rs17878362 (16 bp Del/Ins)	Insertion *vs* deletion	15·40	All ancestries	12	2961	3496	1·15 (1·04–1·26)	0·007	0·520	A A A
TYMS	28 bp tandem repeat	2R *vs* 3R	33·56	All ancestries	6	2709	3400	1·08 (1·00–1·17)	0·044	0·734	A A C
VDR	rs731236 (Ile352Met)	C *vs* T	35·85	All ancestries	14	6829	8461	1·06 (1·00–1·12)	0·034	0·357	A A C
WRN	rs1346044 (Cys1367Arg)	C *vs* T	14·16	All ancestries	3	2747	3555	1·14 (1·02–1·27)	0·019	0·330	A A C
AURKA	rs1047972 (Val57Ile)	A vs G	16·74	Caucasian	4	7309	10?158	0·93 (0·88–0·98)	0·011	0·482	A A C
ESR1	rs2234693 (PvuII T397C)	C vs T	39·78	Asian	8	4563	4503	0·94 (0·89–1·00)	0·050	0·592	A A C
GSTP1	rs1695 (Ile105Val)	G vs A	19·38	Asian	6	4634	5241	1·07 (1·00–1·15)	0·048	0·436	A A C
MTR	rs1805087 (Asp919Gly)	G vs A	21·05	Caucasian	5	5612	6671	0·92 (0·86–0·99)	0·023	0·335	A A C
NQO1	rs1800566 (Pro187Ser)	T vs C	16·58	Caucasian	5	1488	1695	1·27 (1·03–1·56)	0·023	0·049	A C C
TNF	rs1800629 (G-308A)	A vs G	17·01	Caucasian	9	10?664	13?048	0·92 (0·87–0·96)	4·48×10?4	0·436	A A C
XRCC3	rs861539 (Thr241Met)	T vs C	10·98	Asian	3	1283	1120	1·32 (1·08–1·60)	0·007	0·885	BA A

APPENDIX 4. LIST OF META-ANALYSES OF ASSOCIATIONS BETWEEN GENETIC VARIANTS AND BREAST CANCERS

Appendix 4.1. Meta-analyses that give no or insufficient evidence for an association, or evidence of no association or protective effect

Cheng, H., B. Ma, et al. (2012). "Individual and combined effects of MDM2 SNP309 and TP53 Arg72Pro on breast cancer risk: an updated meta-analysis." Mol Biol Rep **39**(9): 9265-9274.

Ding, D. P., X. F. He, et al. (2011). "Lack of association between XPG Asp1104His and XPF Arg415Gln polymorphism and breast cancer risk: a meta-analysis of case-control studies." Breast Cancer Res Treat **129**(1): 203-209.

Gao, L. B., X. M. Pan, et al. (2010). "The association between ATM D1853N polymorphism and breast cancer susceptibility: a meta-analysis." Journal of Experimental & Clinical Cancer Research **29**(117).

Gu, D. and M. Wang (2011). "VEGF 936C>T polymorphism and breast cancer risk: evidence from 5,729 cases and 5,868 controls." Breast Cancer Res Treat **125**(2): 489-493.

Gu, D., M. Wang, et al. (2010). "Lack of association between the hOGG1 Ser326Cys polymorphism and breast cancer risk: evidence from 11 case-control studies." Breast Cancer Res Treat **122**(2): 527-531.

He, J., T. Y. Shi, et al. (2013). "Associations of Lys939Gln and Ala499Val polymorphisms of the XPC gene with cancer susceptibility: a meta-analysis." Int J Cancer **133**(8): 1765-1775.

He, X. F., W. Wei, et al. (2014). "Association between the CYP1A1 T3801C polymorphism and risk of cancer: Evidence from 268 case-control studies." Gene **534**(2): 324-344.

Henegan, C., L. Moore-Smith, et al. (2013). "Decreased TGFBR1 signaling and breast cancer." J. Clin. Oncol. **31**(15).

Hou, J., Y. Jiang, et al. (2013). "p53 codon 72 polymorphism and breast cancer risk: A meta-analysis." Exp. Ther. Med. **5**(5): 1397-1402.

Hu, J., G. W. Zhou, et al. (2010). "GPX1 Pro198Leu polymorphism and breast cancer risk: a meta-analysis." Breast Cancer Res Treat **124**(2): 425-431.

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Hu, Z., X. Li, et al. (2010). "Three common TP53 polymorphisms in susceptibility to breast cancer, evidence from meta-analysis." Breast Cancer Res Treat **120**(3): 705-714.

Huang, J., J. Huang, et al. (2013). "The Cdx-2 polymorphism in the VDR gene is associated with increased risk of cancer: a meta-analysis." Mol Biol Rep **40**(7): 4219-4225.

Li, L., X. Huang, et al. (2010). "IGFBP3 polymorphisms and risk of cancer: a meta-analysis." Mol Biol Rep **37**(1): 127-140.

Lin, W. Y., I. W. Brock, et al. (2013). "Associations of ATR and CHEK1 Single Nucleotide Polymorphisms with Breast Cancer." PLoS ONE **8**(7).

Liu, C. and L. Liu (2011). "Polymorphisms in three obesity-related genes (LEP, LEPR, and PON1) and breast cancer risk: a meta-analysis." Tumour Biol **32**(6): 1233-1240.

Lu, M., F. Wang, et al. (2010). "Methionine synthase A2756G polymorphism and breast cancer risk: a meta-analysis involving 18,953 subjects." Breast Cancer Res Treat **123**(1): 213-217.

Ma, X., C. Chen, et al. (2010). "No association between SOD2 Val16Ala polymorphism and breast cancer susceptibility: a meta-analysis based on 9,710 cases and 11,041 controls." Breast Cancer Res Treat **122**(2): 509-514.

Mao, C., V. C. Chung, et al. (2012). "Association between ATM 5557G>A polymorphism and breast cancer risk: a meta-analysis." Mol Biol Rep **39**(2): 1113-1118.

Mao, C., X. W. Wang, et al. (2010). "Lack of association between CYP17 MspA1 polymorphism and breast cancer risk: a meta-analysis of 22,090 cases and 28,498 controls." Breast Cancer Res Treat **122**(1): 259-265.

Mao, Q., L. Gao, et al. (2013). "The A10389G polymorphism of ND3 gene and breast cancer: A meta-analysis." Biomed. Rep. **1**(2): 259-264.

Niu, W., Y. Qi, et al. (2010). "Association of TGFB1 -509 C>T polymorphism with breast cancer: evidence from a meta-analysis involving 23,579 subjects." Breast Cancer Res Treat **124**(1): 243-249.

Pabalan, N., O. Francisco-Pabalan, et al. (2010). "Meta-analysis of two ERCC2 (XPD) polymorphisms, Asp312Asn and Lys751Gln, in breast cancer." Breast Cancer Res Treat **124**(2): 531-541.

Pineda, B., M. A. Garcia-Perez, et al. (2013). "Associations between aromatase CYP19 rs10046 polymorphism and breast cancer risk: from a case-control to a meta-analysis of 20,098 subjects." PLoS ONE **8**(1): e53902.

Qin, X., Q. Peng, et al. (2012). "Association of COMT Val158Met polymorphism and breast cancer risk: an updated meta-analysis." Diagnostic Pathology **7**(136).

Qiu, L. X., L. Yao, et al. (2010). "Lack of association between MnSOD Val16Ala polymorphism and breast cancer risk: a meta-analysis involving 58,448 subjects." Breast Cancer Res Treat **123**(2): 543-547.

Qiu, L. X., L. Yao, et al. (2010). "Lack of association of CYP1A2-164 A/C polymorphism with breast cancer susceptibility: a meta-analysis involving 17,600 subjects." Breast Cancer Res Treat **122**(2): 521-525.

Sergentanis, T. N. and K. P. Economopoulos (2010). "Association of two CASP8 polymorphisms with breast cancer risk: a meta-analysis." Breast Cancer Res Treat **120**(1): 229-234.

Sergentanis, T. N. and K. P. Economopoulos (2010). "GSTT1 and GSTP1 polymorphisms and breast cancer risk: a meta-analysis." Breast Cancer Res Treat **121**(1): 195-202.

Shi, J., J. Tong, et al. (2013). "Correlation of the BACH1 Pro919Ser polymorphism with breast cancer risk: A literature-based meta-analysis and meta-regression analysis." Exp. Ther. Med. **6**(2): 435-444.

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Tian, Z., Y. L. Li, et al. (2013). "Role of CYP1A2 1F polymorphism in cancer risk: evidence from a meta-analysis of 46 case-control studies." Gene **524**(2): 168-174.

Wang, Y., X. Chu, et al. (2013). "Association of TGF-(beta)1 -509C/T polymorphisms with breast cancer risk: evidence from an updated meta-analysis." Tumor Biol.: 1-8.

Wei, F., J. Xu, et al. (2012). "p27(Kip1) V109G polymorphism and cancer risk: a systematic review and meta-analysis." Cancer Biother Radiopharm **27**(10): 665-671.

Win, A. K., N. M. Lindor, et al. (2013). "Risk of breast cancer in Lynch syndrome: A systematic review." Breast Cancer Res. **15**(2).

Wu, X., Q. Q. Xu, et al. (2013). "Quantitative assessment of the association between rs2046210 at 6q25.1 and breast cancer risk." PLoS ONE **8**(6): e65206.

Xiang, H., H. Li, et al. (2013). "Association of CDKN1B gene polymorphisms with susceptibility to breast cancer: a meta-analysis." Mol Biol Rep **40**(11): 6371-6377.

Xu, J., H. Li, et al. (2014). "Association between vitamin D receptor poly(A) polymorphism and breast cancer risk: a meta-analysis." Tumour Biol **35**(1): 589-593.

Yang, D. S., K. H. Park, et al. (2011). "Association of a vascular endothelial growth factor gene 936 C/T polymorphism with breast cancer risk: a meta-analysis." Breast Cancer Res Treat **125**(3): 849-853.

Yao, L., L. H. Cao, et al. (2010). "The association between HSD17B1 Ser312Gly polymorphism and breast cancer risk: a meta-analysis including 31,053 subjects." Breast Cancer Res Treat **123**(2): 577-580.

Yao, L., F. Fang, et al. (2010). "No association between CYP17 T-34C polymorphism and breast cancer risk: a meta-analysis involving 58,814 subjects." Breast Cancer Res Treat **122**(1): 221-227.

Yao, L., F. Fang, et al. (2010). "No association between CYP1B1 Val432Leu polymorphism and breast cancer risk: a meta-analysis involving 40,303 subjects." Breast Cancer Res Treat **122**(1): 237-242.

Yao, L., F. Fang, et al. (2010). "The association between two polymorphisms of eNOS and breast cancer risk: a meta-analysis." Breast Cancer Res Treat **124**(1): 223-227.

Yao, L., L. X. Qiu, et al. (2010). "The association between ERCC2 Asp312Asn polymorphism and breast cancer risk: a meta-analysis involving 22,766 subjects." Breast Cancer Res Treat **123**(1): 227-231.

Yao, L., X. Yu, et al. (2010). "Lack of significant association between CYP1A1 T3801C polymorphism and breast cancer risk: a meta-analysis involving 25,087 subjects." Breast Cancer Res Treat **122**(2): 503-507.

Yu, K. D., A. X. Chen, et al. (2010). "XRCC2 Arg188His polymorphism is not directly associated with breast cancer risk: evidence from 37,369 subjects." Breast Cancer Res Treat **123**(1): 219-225.

Yu, K. D., A. X. Chen, et al. (2010). "No association between a progesterone receptor gene promoter polymorphism (+331G>A) and breast cancer risk in Caucasian women: evidence from a literature-based meta-analysis." Breast Cancer Res Treat **122**(3): 853-858.

Yu, K. D., A. X. Chen, et al. (2012). "The associations between two polymorphisms in the interleukin-10 gene promoter and breast cancer risk." Breast Cancer Res Treat **131**(1): 27-31.

Yu, K. D., A. X. Chen, et al. (2010). "Current evidence on the relationship between polymorphisms in the COX-2 gene and breast cancer risk: a meta-analysis." Breast Cancer Res Treat **122**(1): 251-257.

Yu, K. D., G. H. Di, et al. (2010). "Lack of an association between a functional polymorphism in the interleukin-6 gene promoter and breast cancer risk: a meta-analysis involving 25,703 subjects." Breast Cancer Res Treat **122**(2): 483-488.

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Zhao, L., A. Gu, et al. (2012). "The association between ATM IVS 22-77 T>C and cancer risk: a meta-analysis." PLoS ONE **7**(1): e29479.

Zhao, M., P. Chen, et al. (2014). "Relationship between Rad51 G135C and G172T Variants and the Susceptibility to Cancer: A Meta-Analysis Involving 54 Case-Control Studies." PLoS ONE **9**(1): e87259.

Zhou, L. P., H. Luan, et al. (2012). "Association of functional polymorphisms of the XRCC4 gene with the risk of breast cancer: a meta-analysis." Asian Pac J Cancer Prev **13**(7): 3431-3436.

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Zhu, W., B. B. Wei, et al. (2010). "-765G>C and 8473T>C polymorphisms of COX-2 and cancer risk: a meta-analysis based on 33 case-control studies." Mol Biol Rep **37**(1): 277-288.

Appendix 4.2. Meta-analyses showing evidence for a weak or a moderate association

Han, F. F., C. L. Guo, et al. (2013). "The effect of CHEK2 variant I157T on cancer susceptibility: evidence from a meta-analysis." DNA Cell Biol **32**(6): 329-335.

He, X. F., W. Wei, et al. (2013). "Association between the XRCC3 T241M polymorphism and risk of cancer: evidence from 157 case-control studies." Gene **523**(1): 10-19.

Liu, C., Y. Wang, et al. (2012). "The CHEK2 I157T variant and breast cancer susceptibility: a systematic review and meta-analysis." Asian Pac J Cancer Prev **13**(4): 1355-1360.

Lu, P. H., M. X. Wei, et al. (2011). "Association between polymorphisms of the ataxia telangiectasia mutated gene and breast cancer risk: evidence from the current studies." Breast Cancer Res Treat **126**(1): 141-148.

Shen, L., Z. H. Yin, et al. (2012). "Association between ATM polymorphisms and cancer risk: a meta-analysis." Mol Biol Rep **39**(5): 5719-5725.

Wang, W., J. L. Li, et al. (2013). "Association between the RAD51 135 G>C polymorphism and risk of cancer: a meta-analysis of 19,068 cases and 22,630 controls." PLoS ONE **8**(9): e75153.

Xu, H., P. Zou, et al. (2013). "Association between the XRCC6 promoter rs2267437 polymorphism and cancer risk: Evidence based on the current literature." Gent. Test. and Mol. Biomarkers **17**(8): 607-614.

Yang, Y., F. Zhang, et al. (2012). "CHEK2 1100delC variant and breast cancer risk in Caucasians: a meta-analysis based on 25 studies with 29,154 cases and 37,064 controls." Asian Pac J Cancer Prev **13**(7): 3501-3505.

Zhang, G., Y. Zeng, et al. (2013). "Significant association between Nijmegen breakage syndrome 1 657del5 polymorphism and breast cancer risk." Tumour Biol **34**(5): 2753-2757.

Zhang, Z., M. Wang, et al. (2010). "P53 codon 72 polymorphism contributes to breast cancer risk: a meta-analysis based on 39 case-control studies." Breast Cancer Res Treat **120**(2): 509-517.

Zhang, Z. H., L. S. Yang, et al. (2012). "Current evidence on the relationship between two polymorphisms in the NBS1 gene and breast cancer risk: a meta-analysis." Asian Pac J Cancer Prev **13**(11): 5375-5379.

APPENDIX 5. GUIDELINES FOR HEREDITARY BREAST AND/OR OVARIAN CANCER SYNDROME DIAGNOSTIC TESTING CRITERIA

Woman with breast cancer + one or more of the following :

- diagnosed ≤ 35 yrs,
- diagnosed ≤ 50 yrs and one relative with bilateral, or ovarian, or breast < 50, or male breast cancer
- bilateral breast cancer and both diagnosed < 50 yrs
- ovarian cancer, any age
- triple negative breast cancer
- three individuals with breast cancer, one is a first degree relative (FDR) of the other two (excluding male transmitters) and one diagnosed ≤ 50 years
- individual of ethnicity associated with higher frequency of specific mutations (eg, Ashkenazi Jewish): eligible for founder mutation testing
- other family situations (eg multiple pancreatic cancer) with a priori chance of mutation >10% according to BRCAPRO or Evans criteria or Manchester score
- test more than one affected relative if criteria remain positive after excluding the negative case as a phenocopy

Woman with epithelial ovarian cancer

- diagnosed <70 yrs

Male with breast cancer

Individual with pancreatic cancer at any age with ≥ 2 FDR excluding male transmitters with breast where one diagnosed <50 or bilateral, or ovarian, or 2 more pancreatic cancer at any age

Family history

- First degree unaffected relative of any of the above on a case by case basis
- Testing of unaffected family members should only be considered when no affected family member is available and then the unaffected family member with the highest probability of mutation should be tested

The above mentioned guidelines were prepared by Karin Dahan and reviewed and approved by Y. Sznajer, K. Devriendt, V. Bours, M. Abramowicz, Ch. Verellen – Dumoulin, K. Keymolen, E. De Baere, G. Mortier for the High Council for Antropogenetics at the meeting of 29/03/13.

APPENDIX 6. DIFFERENT CRITERIA PUT FORWARD FOR LI-FRAUMENI SYNDROME

Classic Li-Fraumeni Syndrome

- A proband with a sarcoma diagnosed before age 45 years, AND
- A first-degree relative with any cancer before age 45 years, AND
- A first- or second-degree relative with any cancer before age 45 years or a sarcoma at any age

Li-Fraumeni Like Syndrome

Birch definition:

- A proband with any childhood cancer or sarcoma, brain tumor, or adrenocortical carcinoma diagnosed before age 45 years, AND
- A first- or second-degree relative with a typical LFS cancer (sarcoma, breast cancer, brain tumor, adrenocortical carcinoma, or leukemia) at any age, AND
- A first- or second-degree relative with any cancer before age 60 years

Eeles definition:

- Two first- or second-degree relatives with LFS-related malignancies at any age

Chompret criteria

- A proband with: a tumor belonging to the LFS tumor spectrum (soft tissue sarcoma, osteosarcoma, brain tumor, pre-menopausal breast cancer, adrenocortical carcinoma, leukemia, or bronchoalveolar lung cancer) before age 46 years, AND At least one first- or second-degree relative with an LFS tumor (except breast cancer if the proband has breast cancer) before age 56 years or with multiple tumors, OR
- A proband with multiple tumors (except multiple breast tumors), two of which belong to the LFS tumor spectrum and the first of which occurred before age 46, OR

A proband who is diagnosed with adrenocortical carcinoma or choroid plexus tumor, irrespective of family history

APPENDIX 7. REVISED DIAGNOSTIC CRITERIA FOR COWDEN SYNDROME

Revised *PTEN* hamartoma tumor syndrome clinical diagnostic criteria[44] :

Major criteria :
• Breast cancer
• Endometrial cancer (epithelial)
• Thyroid cancer (follicular)
• Gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps; ≥3)
• Lhermitte-Duclos disease (adult)
• Macrocephaly (≥97 percentile: 58cm for females, 60cm for males)
• Macular pigmentation of the glans penis
• Multiple mucocutaneous lesions (any of the following):
o Multiple trichilemmomas (≥3, at least one biopsy proven)
o Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)
o Mucocutaneous neuromas (≥3)
o Oral papillomas (particularly on tongue and gingiva), multiple (≥3) OR biopsy proven OR dermatologist diagnosed
Minor criteria
• Autism spectrum disorder
• Colon cancer
• Esophageal glycogenic acanthosis (≥3)
• Lipomas (≥ 3)
• Mental retardation (ie, IQ ≤ 75)
• Renal cell carcinoma
• Testicular lipomatosis
• Thyroid cancer (papillary or follicular variant of papillary)
• Thyroid structural lesions (e.g., adenoma, multinodular goiter)
• Vascular anomalies (including multiple intracranial developmental venous anomalies)

Operational diagnosis in an individual (either of the following)
1. Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas; or
2. Two major and three minor criteria.
Operational diagnosis in a family where one individual meets revised *PTEN* hamartoma tumor syndrome clinical diagnostic criteria or has a *PTEN* mutation:
1. Any two major criteria with or without minor criteria; or
2. One major and two minor criteria; or
3. Three minor criteria.

APPENDIX 8. NCCN TESTING CRITERIA FOR COWDEN SYNDROME

Major criteria:

- Breast cancer
- Endometrial cancer
- Follicular thyroid cancer
- Multiple gastrointestinal hamartomas or ganglioneuromas
- Macrocephaly
- Macular pigmentation of glans penis (a discolored area on the skin)
- Mucocutaneous lesions
  - One biopsy proven trichilemmoma
  - Multiple palmoplantar keratosis (abnormal thickening of the hands and feet)
  - Multifocal or extensive oral mucosal papillomatosis
  - Multiple cutaneous facial papules (often verrucous)

Minor Criteria:

- Colon cancer
- Esophageal glycogenic acanthosis (3)
- Autism spectrum disorder
- Mental retardation
- Papillary or follicular variant of papillary thyroid cancer
- Thyroid structural lesions (such as, adenoma, nodule(s), goiter)
- Renal cell kidney carcinoma
- Vascular anomalies (including multiple intracranial developmental venous anomalies)
- Lipomas (benign soft tissue tumor)
- Single gastrointestinal hamartoma or ganglioneuroma
- Testicular lipomatosis

Cowden Syndrome PTEN Gene Testing Criteria

- Individuals with a personal history of:
- A family with a known PTEN gene mutation
- Meeting clinical diagnostic criteria for CS
- Bannayan-Riley-Ruvalcaba syndrome (BRR)
- Adult Lhermitte-Duclos disease (cerebellar tumors)
- Autism spectrum disorder and macrocephaly
- Two or more biopsy-proben trichilemmomas
- Two or more major criteria (one must be macrocephaly)

CS is suspected if a person has either three major criteria without macrocephaly, one major and three minor criteria, four minor criteria, or a relative with a clinical diagnosis of CS or BRR.

Appendix 8.1. Evidence tables of cohort studies assessing cancer risk in Cowden syndrome

Table 2 – Cancer and Lhermitte-Duclos disease (LDD) risk among Cowden syndrome patients

Study ID	Method	Patient characteristics	The cumulative lifetime (age 70 years) risk (95% CI)	Critical appraisal of study quality
Riegert-Johnson 2010[43]	• **Design**: retrospective cohort study and compilation of case reports • **Source of funding**: no extramural funding • **Setting**: Mayo clinic, US • **Sample size**: 211 • **Statistical analysis**: Kaplan meyer extrapolated estimates	• **Eligibility criteria:** Person with Cowden syndrome, either with PTEN pathogenic germline mutations or not. • **Patient characteristics**: • age 44 ± 16 years, 64% female, 46% *PTEN* mutation	any cancer diagnosis 80%, breast cancer [female] 81% (66%-90%), LDD 32% (19%-49%), thyroid cancer 21% (14%-29%), endometrial cancer 19% (0%-32%), renal cancer 15% (6%-32%), colorectal cancer was identified 16% (8%-24%).	**Results critical appraisal**: Is an extrapolation from a database in the Mayo clinic and case reports. Validity and applicability to the Belgian context is unknown
Heald 2010[41]	• **Design**: subselection of a prospective cohort study • **Source of funding**: no extramural funding • **Setting**: Cleveland Clinic, US • **Sample size**: 127 • **Statistical analysis**: age- and gender-adjusted standardized incidence ratio (SIR)	• **Eligibility criteria:** out of patients who met relaxed International Cowden Consortium (ICC) criteria (N=2548) or with ≥5 GI (any location) polyps, ≥1 of which was hyperplastic or hamartomatous (N=397) were prospectively recruited. Out of these, patients having clear pathogenic PTEN mutations were included	Colorectal cancer occurred in 7.1% of our entire series and 13% of eligible subjects who underwent at least one colonoscopy (age- and gender-adjusted SIR=224)	**Results critical appraisal**: Subseries of a larger cohort, limited and unclear follow up time
Nieuwenhuis 2014[42]	• **Design**: Case series • **Source of funding**: no extramural funding • **Setting**: various countries • **Sample size**: 180 • **Statistical analysis**: Kaplan meyer extrapolated estimates	• **Eligibility criteria:** out of patients who met relaxed International Cowden Consortium (ICC) criteria (N=2548) or with ≥5 GI (any location) polyps, ≥1 of which was hyperplastic or hamartomatous (N=397) were prospectively recruited. Out of these, patients having clear pathogenic PTEN mutations were included	**Extrapolated cumulative risk per cancer (%)** *Any* Male 55.7 Female 86.6 *Breast* Male –	Extrapolated from case series, Validity of the estimation and applicability to the Belgian context unknown

			Female 67.3 *Thyroid* Male 5.7 Female 24.9 *LDD* Male 11 Female 43.5 *Melanoma* Male 2.3 Female – *Endometrial* Female 20.7 *Colorectal* Male 20 Female 16.7 *Renal* Male 2.3 Female 8.5 *Lung* Male – Female 12.2	
Tan 2012[47]	• **Design**: retrospective cohort study or case serie • **Source of funding**: no extramural funding • **Setting**: multicentre • **Sample size**: 368 • **Statistical analysis**: Kaplan meyer extrapolated estimates and age-adjusted standardized incidence ratio (SIR) calculations	• **Eligibility criteria:** 3,399 individuals meeting relaxed International Cowden Consortium • PHTS criteria were prospectively recruited; 368 individuals were found to have deleterious germline PTEN	**SIRs* for carcinomas of:** breast 25.4, [95%CI 19.8–32.0] thyroid 51.1 , [95%CI 38.1–67.1] endometrium 42.9 [95%CI 28.1–62.8] colorectum 10.3 [95%CI 5.6–17.4] kidney 30.6 [95%CI 17.8–49.4] melanoma 8.5 [95%CI 4.1–15.6] **Estimated lifetime risks** breast 85.2% [95%CI 71.4%–99.1%] thyroid 35.2% [95%CI 19.7%–50.7%] endometrium 28.2% [95%CI 17.1%–39.3%]	**Results critical appraisal**: Is an extrapolation from a multicentre case series, follow up is not entirely clear

			colorectum 9.0% [95%CI 3.8%–14.1%] kidney 33.6% [95%CI 10.4%–56.9%] melanoma 6% [95%CI 1.6%-9.4%]	
Bubien 2013[40], Riegert-Johnson 2010[43]	• **Design**: retrospective cohort study and compilation of case series • **Source of funding**: no extramural funding • **Setting**: Institut Bergonie genetic laboratory • **Sample size**:154 • **Statistical analysis**: Kaplan Meyer extrapolated estimates	• **Eligibility criteria:** PHTS individuals with a deleterious germline PTEN mutation.	**SIRs* for** **female breast cancer** [39.1, 95% CI 24.8 to 58.6], **thyroid cancer** women [43.2, 95% CI 19.7 to 82.1] men [199.5, 95% CI 106.39 to 342.03], **melanoma** women [28.3, 95% CI 7.6 to 35.4] men [39.4, 95% CI 10.6 to 100.9], and endometrial cancer [48.7, 95% CI 9.8 to 142.3]. **Cumulative cancer risks at age 70** any cancer 85% [95% CI 70% to 95%] female breast cancer 77% [95% CI 59% to 91%] thyroid cancer38% [95% CI 25% to 56%]	**Results critical appraisal**: Is an extrapolation from a case series, follow up is not entirely clear

Note. SIR = Standardized incidence ratios

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