

## ABSTRACT

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





## Belgian Health Care Knowledge Centre

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

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**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.**

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**Finally, this report has been approved by common assent by the Executive Board.**

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## ■ FOREWORD

People talk a lot about health literacy today: skills enabling the patient, or even every citizen, to better understand and therefore take to heart his/her own health and the care for it. The concept is absolutely commendable, and it fits well with the prevailing call for greater empowerment, autonomy and self-determination for the patient. Yet, there are limits too. You cannot simply expect that anyone would be able to obtain, under its own power, a sufficient understanding of the - often probabilistic - diagnostic and prognostic information that he or she is being offered. Let alone to make a meaningful choice on this basis consistent with the deepest own aspirations. This will ask for guidance and all the more as the information is complex, uncertain and far-reaching.

When in May 2013 Angelina Jolie commissioned a preventive bilateral mastectomy because she proved to be a carrier of a "cancer gene" and this fact was spread worldwide in the popular press, in one single day global health literacy therewith went a step on ahead. Health educators can only dream of such an impact factor. Anyway, the issue spoke at more than one level to the imagination, but let's stay here at the medical. The fact that a movie star - female icon par excellence - chose to undergo a still very mutilating surgery to prevent worse, shows how radically introducing such genetic testing can be. And maybe it is - ironically - easier when it comes to a gene with a very high cancer risk: you know what you can do to get 'it under control'. It gets really hard, not only medical, but also and above all psychologically, and therefore ethically, when it comes to lower risks, or when there are still many uncertainties. How far to go with the prevention, investigations, informing and screening of relatives...?

We are only at the beginning of the possibilities and the 'democratization' of the genetic testing, but we already know that this evolution will be unstoppable. If, in the coming years, we want to avoid to confront thousands of patients with information they cannot handle themselves, and thus avoid to decide on their head what will happen to them, then we will, together with oncologists, geneticists and government, have to offer answers on a double challenge. In first instance we will have to determine which tests are already medically and ethically justified and which not, and regularly update this assessment. And secondly, we will have to decide how to organize the counseling, which should be inseparable from these tests. It is a debate that we must conduct independent of the interests of private professional groups or the producers of the tests and corresponding treatments, but with the patient at the centre of our concern.

This guideline on oncogenetic tests is the second in a series of four. We hope we can make a modest contribution in this complex debate.

Christian LÉONARD  
Deputy general director

Raf MERTENS  
General director



## ■ GLOSSARY

<b>Cumulative risk</b>	The absolute risk, or probability of an event occurring over a specified time period.
<b>Family History</b>	A family history of disease in an individual is the occurrence of the disease in a blood relative of that individual.
<b>Gene</b>	A gene is a molecular unit of heredity of a living organism.
<b>BRCA1 and BRCA2</b>	These two genes are involved in the repair of lesions that DNA undergoes regularly. The presence of abnormalities in one of these two genes disrupts this function and greatly increases the risk of breast and ovarian cancer.
<b>Genetic Counselling</b>	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.
<b>Genetic Counsellor</b>	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.
<b>Genetic testing</b>	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.
<b>Germline</b>	The cells from which eggs or sperm (i.e., gametes) are derived.
<b>Lifetime risk</b>	The risk of developing a disease during one's lifetime or dying of the disease.
<b>Penetrance</b>	A characteristic of a genotype; it refers to the likelihood that a clinical condition will occur when a particular genotype is present.
<b>Proband</b>	The individual through whom a family with a genetic disorder is ascertained.
<b>Relatives – First-degree relatives</b>	These are the closest blood relatives (relatives by marriage do not count). These include father, mother, son, daughter, brother, sister.
<b>Relatives – Second-degree relatives</b>	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.
<b>Relatives – Third-degree relatives</b>	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.



## ■ ABSTRACT

### 1. INTRODUCTION

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

This guideline is timely. Firstly because the new nomenclature, introduced on 1/1/2013, for genetic tests (article 33) and the agreement on genetic testing consultation led to distribute the NIHD budget between genetic counselling (€4,288 millions) and laboratory procedures (€37,795 millions)<sup>a</sup>. This new convention implies the development of genetic counselling activities by genetic centres. Secondly, because beyond a number of high-penetrance genes, BRCA 1 and 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 for breast cancer 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 (preventive mastectomy or oophorectomy) and chemoprophylaxis.

This clinical practice guideline is based on the collaborative efforts of the Belgian Health Care Knowledge Centre (KCE), the College of Human Genetics and the College of Oncology. This guideline complements the recently published practice guideline for breast cancer screening<sup>1</sup> and is the second report in a short series of oncogenetic testing guidelines.

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<sup>a</sup> 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.



## 2. OBJECTIVES AND SCOPE OF THIS GUIDELINE

This guideline provides recommendations based on current scientific evidence for the identification and referral of patients with breast and/or ovarian cancer and their family members to centres of human genetics specialised in cancer genetics for counselling, possibly followed by germline mutation analysis. Clinicians are encouraged to interpret these recommendations in the context of the individual person/patient situation, values and preferences.

This guideline concerns the oncogenetic testing aspects of breast and ovarian cancer, more specifically the hereditary breast cancer, the Li-Fraumeni syndrome and the Cowden syndrome. It does not cover other syndromes that are also associated with an increased risk for breast cancer, i.e. Peutz-Jeghers (associated with the STK11 gene), 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).<sup>2</sup> Moreover, it does not cover subsequent prophylactic treatment such as chemoprevention (e.g. Tamoxifen) or risk-reducing surgery.

## 3. METHODS

### 3.1. Clinical research questions

The current guideline addressed the following clinical questions:

- Hereditary breast cancer
  - How to identify 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 for whom a possible hereditary raised risk of breast cancer was identified those who are eligible for a genetic test?
    - What are the existing assessment tools?
    - What are their validity and their applicability in Belgian context?
  - For which genes have tests a 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?



### 3.2. Literature search

Independent searches were performed either for hereditary breast cancer, Li-Fraumeni syndrome and Cowden syndrome.

A search for published guidelines was first performed to verify if high-quality, recent guidelines are available that address the clinical research questions. Clinical practice guidelines were identified using the National Comprehensive Cancer Network (NCCN) (<http://www.nccn.org/>), the National Guideline Clearinghouse (<http://www.guideline.gov/>), NICE guidelines (<http://www.nice.org.uk>) and the Guidelines International Network ([www.g-i-n.net](http://www.g-i-n.net)). The retained guidelines were scored using the AGREE II instrument.

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.

### 3.3. Quality appraisal

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

### 3.4. Data extraction and evidence summary

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

### 3.5. Formulation of recommendations

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

Subsequently, the draft recommendations were circulated to stakeholders (associations of physicians and patient organisations) targeted by this guideline. Each association was asked to assign at least one key representative to review the draft guideline. All representatives and their association are listed in the colophon under the section stakeholders. They acted as external reviewers of the draft guideline and rated all recommendations with a score ranging from 1 ('completely disagree') to 5 ('completely agree') and discussed them at a meeting.

Finally, the report was validated by four external assessors, listed in the colophon. Their comments and questions were forwarded to the GDG in order to finalize the scientific report (November 2014).

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



## 4. CLINICAL RECOMMENDATIONS

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

### 4.1. Hereditary breast cancer

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

#### Recommendations

##### 1. GENERAL APPROACH

For women with a family history suggesting a hereditary risk of breast cancer, referral to a centre of human genetics specialised 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 specialised in cancer genetics.**



**Clinicians should seek further advice from a centre of human genetics specialised in cancer genetics 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 cancer genetics clinic 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.<sup>11</sup>



#### 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.

#### 4.2. Li-Fraumeni syndrome

##### *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.<sup>4</sup> 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.<sup>5</sup> Approximately 400 families were reported in the cumulative literature, but its actual population incidence is unknown.<sup>6</sup>

##### *Diagnostic testing criteria and follow-up 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).<sup>7</sup> Later, broader criteria were developed by Birch and Eeles to identify families which are Li-Fraumeni-like (LFL).<sup>8, 9</sup> 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.<sup>10</sup>





## 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  $\leq 30$  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.

**4.3. Cowden syndrome or PTEN hamartoma tumour syndrome (PHTS)****4.3.1. Introduction**

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). The term PTEN hamartoma<sup>b</sup> 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.<sup>5</sup> Cowden syndrome has a prevalence of about 1 in 250 000 in the Dutch population with a low mutation frequency.<sup>11</sup>

**4.3.2. Revised diagnostic criteria for Cowden syndrome**

Diagnostic criteria for Cowden syndrome, the principal PTEN-related disorder, were first established in 1996 before the identification of the PTEN gene and the ability to molecularly confirm a clinical diagnosis. These consortium criteria were based on clinical experience and case reports in the existing literature, with their inherent selection biases. A new set of PHTS diagnostic criteria is recommended to be used in making clinical diagnoses of these PTEN-related diseases. Molecular testing is recommended whenever possible, both to confirm a clinical diagnosis and to facilitate testing of at-risk relatives.<sup>12</sup>

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<sup>b</sup> Hamartoma is a benign tumor-like nodule composed of an overgrowth of mature cells and tissues normally present in the affected part, but with disorganization and often with one element predominating



### 4.3.3. Diagnostic testing criteria and follow-up for Cowden syndrome

#### Recommendations

##### 1. 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  $\geq$  three minor criteria\*\* OR
- $\geq$  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 ( $\geq 3$ )
- 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.<sup>6</sup> Recommendations listed below are suggested in the scientific literature and are 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.<sup>13</sup>



- Annual screening with ultrasound of the thyroid gland could be considered, starting at age 18 y.<sup>6</sup>
- 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)<sup>6</sup> 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.<sup>13</sup>
- If there is a family history of renal cell cancer, an annual urinalysis has been suggested, supplemented by cytology and renal ultrasound.<sup>6</sup>



## 5. ADDITIONAL CONSIDERATIONS

### 5.1. Adequate information and support for patient and relatives

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

Patients' representatives ask that a correct and understandable information be provided to individuals at increased genetic risk. Continued support in decision-making is important during the different phases of the process (referral, testing, steps after a positive or a negative test). It is important to clearly explain figures about the increased risk of (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 or prophylactic surgery). 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.

### 5.2. Role of the genetic centres and the other professionals

A uniform policy followed by all Genetic Centres in Belgium is essential. It is important that general practitioners / oncologists / 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.

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 specialised in cancer genetics for genetic counselling. They also claim that sometimes precious time is thus lost before an appropriate treatment is started. However, geneticists feel it is absolutely required to refer individuals/patients to a centre of human genetics specialised in cancer genetics for counselling and

testing rather than ordering a genetic test directly. This stepwise approach should 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 communication of the results of the test performed about the individual personal risk, and explaining 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 human genetics centre to organize a genetic consultation for patients.

### 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. PALB2 has recently shown to reach a penetrance as high as BRCA2, that means that women with a PALB2 mutation have a higher breast cancer risk equivalent to the risk of women having a BRCA2 mutation), 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.



## ■ RECOMMENDATIONS<sup>c</sup>

### *To the College of Genetics and the College of Oncology*

- The implementation of this guideline should be facilitated by the College of Genetics and the College of Oncology, preferably using a common set of (online) tools.
- A working group composed of representatives of both Colleges has to be set up to establish and regularly update a list of low- and moderate- penetrance genes that can be tested outside of a context of clinical research.
- A similar group could be composed to further streamline the procedures and professional requirements for pre-test counselling and ordering of oncogenetic tests.

### *To the associations of providers of care to these patients*

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

### *To the Human Genetics Centres and coordinators of breast cancer clinics*

- To integrate the specialised genetic counselling in the specialised care programmes for breast cancer (breast cancer clinics).

### *To the Public Federal Service Public Health*

- Consider the recognition of a professional title of 'genetics counselors' and organize with appropriate training institutes an adequate training (Master level) for these new professionals allowing them to integrate a multidisciplinary team and to collaborate with a medical geneticist in the fields of genetics and predictive medicine (genetic counselling, assessment and management of risk, elaboration of family trees, contact and information for families, integration of social, psychological, cultural, legal and ethical dimensions,...). This training for genetics counsellors could be accessible to nurses, midwives, paramedics, bachelors in biomedicine, bachelors in medicine, pharmacists, psychologists (indicative and non-exhaustive list).

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<sup>c</sup> The KCE has sole responsibility for the recommendations.





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