

# ERN GENTURIS CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS, SURVEILLANCE AND MANAGEMENT OF PEOPLE WITH BIRT-HOGG-DUBÉ SYNDROME

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## 1. ABSTRACT

**Background:** Birt-Hogg-Dubé syndrome (BHD syndrome) is an autosomal dominant multisystem disorder with variable expression predisposing to the development of renal cell carcinoma as well as benign cutaneous fibrofolliculomas/trichodiscomas, pulmonary cysts with an associated increased risk of spontaneous pneumothorax, and renal carcinoma. International consensus on recommendations for diagnosis and surveillance is needed.

**Methods and results:** Based on a comprehensive literature review and expert consensus within the fields of respiratory medicine, urology, radiology, dermatology, clinical oncology and clinical genetics, recommendations for diagnosis and surveillance in BHD syndrome have been developed.

**Conclusion:** Awareness of BHD syndrome needs to be raised and clinical settings in which the diagnosis should be considered have been specified. Regular renal cancer surveillance is recommended in adulthood and life-long. The evidence base for additional tumour surveillance is limited and further research warranted. Outlines for future research projects have been proposed.

## 2. GUIDELINE SUMMARY

This ERN GENTURIS guideline on BHD syndrome diagnosis, genetic counselling, surveillance, quality of life and clinical management has been drawn from the best available evidence and the consensus of experts in this area and will be updated whenever deemed necessary by the experts who authored the guideline to reflect changes in available evidence. The expectation is that clinicians will follow this guideline unless there is a compelling clinical reason to undertake different management, specific to an individual patient.

**Table 1.** Key recommendations regarding diagnosing and surveillance.

The diagnosis of BHD syndrome should be considered in				Strength	Recommendation
<ul style="list-style-type: none"> <li>• Primary spontaneous pneumothorax</li> <li>• Multiple pulmonary cysts.</li> <li>• Bilateral or multifocal renal neoplasia.</li> <li>• Renal cell carcinoma, below age 50 or familial.</li> <li>• Multiple cutaneous papules consistent with fibrofolliculomas/trichodiscomas</li> <li>• Any combination of the above mentioned manifestations in an individual or in the family.</li> </ul>				Strong	1a
				Strong	1b
				Strong	1c
				Strong	1d
				Strong	1e
				Strong	1f
Genetic testing for BHD syndrome should be offered in					
<ul style="list-style-type: none"> <li>• Primary spontaneous pneumothorax, if recurrent or familial.</li> <li>• Multiple pulmonary cysts in the absence of a known cause.</li> <li>• Bilateral or multifocal renal neoplasia.</li> <li>• Early onset (usually defined as &lt;45 years) or familial renal cell carcinoma.</li> <li>• Multiple cutaneous papules consistent with fibrofolliculomas/trichodiscomas and at least one histologically confirmed.</li> <li>• Any combination of the above mentioned manifestations in an individual or in the family with or without a known family history of BHD syndrome.</li> </ul>				Strong	6a
				Strong	6b
				Strong	6c
				Strong	6d
				Strong	6e
				Strong	6f
Surveillance protocol	Exam	Age	Interval		
<ul style="list-style-type: none"> <li>• Renal cell carcinoma</li> </ul>	Renal MRI	20 y and life-long	Every 1-2 years	Strong	11, 13, 13a, 13b, 14
<ul style="list-style-type: none"> <li>• Fibrofolliculomas/trichodiscomas</li> </ul>	Consideration of the need for a dermatologic evaluation	At diagnosis	When needed	Strong	18



### 3. INTRODUCTION

#### **Birt–Hogg–Dubé syndrome and this guideline**

Birt Hogg Dubé syndrome (BHD syndrome) is a rare inherited condition caused by pathogenic germline variants in the *FLCN* gene encoding the tumour suppressor protein folliculin. Phenotypically BHD syndrome is heterogeneous with key manifestations being benign cutaneous fibrofolliculomas/trichodiscomas (FF/TD), pulmonary cysts with a subsequent increased risk of spontaneous pneumothorax (PTX) and most importantly malignant renal neoplasms (Menko et al., 2009; Schmidt & Linehan, 2015; Toro et al., 2008). Inheritance is autosomal dominant with incomplete, age-dependent penetrance and variable phenotypic expression. Exact prevalence of BHD syndrome is unknown but the condition is undoubtedly underdiagnosed, likely because of inter- and intra-familial clinical variability and lack of awareness among physicians (Muller et al., 2021).

In BHD syndrome life-time risk of renal cell carcinoma (RCC) ranges between 15-30% and spontaneous PTX is very often recurrent (Bruinsma et al., 2023; Maher, 2018; Menko & Maher, 2016). Diagnosing BHD syndrome enables regular renal cancer surveillance not only for the individual but also for relevant family members.

This guideline is based on a review of the literature conducted systematically and aims to

- Present specialty specific information on when to actively consider a potential diagnosis of BHD syndrome.
- Present organ specific guidance on the most appropriate surveillance and clinical management.

International agreement on surveillance recommendations and raised awareness of BHD syndrome will enable prospective studies of the phenotypic spectrum and cancer risks and an evidence-based evaluation of the current surveillance recommendations.

## 4. COMPOSITION OF THE GUIDELINE GROUP

The European Reference Network (ERN) for all patients with a rare genetic tumour risk syndromes (ERN GENTURIS) Guideline Group for Birt-Hogg-Dubé syndrome was established by experts in BHD syndrome encompassing the clinical care for the wide spectrum of manifestations and patient representatives. The BHD syndrome Guideline Group was supported by a Core Working Group which comprised ERN GENTURIS healthcare provider members from different Member States and other experts who are recognised experts and specialised in clinical practice and/or in the diagnosis and management of BHD syndrome. The Core Working Group met online monthly and drafted the guideline scope, clinical questions, recommendations and guideline document and obtained feedback from the BHD syndrome Guideline Group. The recommendations were finalised in a modified Delphi approach in which the Core Working Group, BHD syndrome Guideline Group (including patient representatives) and additional experts participated (see chapter 8).

### **Approach to secure views and preference of target population**

The ERN GENTURIS BHD Core Working Group was supported by patient representatives from a patient advocacy group and additional patient input was provided by including three patient representatives in the BHD syndrome Guideline Group. The role of the Core Working Group patient representative was filled consecutively by two employees of the Myrovlytis Trust, BHD Foundation.

Involving the patient representatives in the development of these guidelines and in the ERN GENTURIS BHD syndrome Guideline Group helped to ensure that:

- the questions addressed are relevant to patients with BHD syndrome and will make a positive impact on patient care
- important aspects of the experience of illness are considered
- critical clinical and patient focused outcomes are identified and prioritised
- the balance of the benefits and harms related to the intervention are appropriately considered, when recommendations are formulated in conjunction with patient values and preferences

The representatives from the patient advocacy group advised on the scope, target population and clinical questions the guideline aimed to address and rated the outcomes in terms of their importance and gave a patient perspective on the findings of the literature review and the consensus recommendations and drafted the plain language summary.

## 5. CONFLICTS OF INTEREST

All members of the ERN GENTURIS BHD syndrome Guideline Group, including the Core Working Group, have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. Core Working Group patient representatives Katie Nightingale and Jazzmin Huber were employed by the Myrovlytis Trust. Mia Gebauer Madsen reports receipt of honoraria or consultation fees from Ipsen. Cormac McCarthy reports receipt of research funding from Boehringer Ingelheim, honoraria or consultation fees from Savara Inc, Theravance, AI Therapeutics, Roche, Aerogen as well as grants from Health Research Board, LAM Foundation and Enterprise Ireland. Neil Rajan reports participation in a company sponsored speaker's bureau from Takeda UK. Maria T. A. Wetscherek reports receipt of honoraria or consultation fees from Microsoft.

All participants of the ERN GENTURIS BHD syndrome Delphi survey have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a competing interests. Patrick Benusiglio reports receipt of honoraria or consultation fees from AstraZeneca, Bristol Myers Squibb and Merck Sharp & Dohme. Raphael Borie reports receipt of grants/research support from Roche and Boehringer Ingelheim, as well as receipt of honoraria or consultation fees from Roche, Boehringer Ingelheim and Sanofi. Jesper Rømhild Davidsen reports receipt of honoraria or consultation fees from Boehringer Ingelheim. Arndt Hartmann reports receipt of grants/research support from AstraZeneca, Biocartis, Biontech, Cepheid, Gilead, Illumina, Janssen, Nanostring, Novartis, Owkin, Qiagen, QUIP GmbH, Roche and Sanofi, as well as receipt of honoraria or consultation fees from Abbvie, AstraZeneca, Biocartis, Biontech, BMS, Boehringer Ingelheim, Cepheid, Diaceutics, Gilead, Illumina, Ipsen, Janssen, Lilly, MSD, Nanostring, Novartis, Qiagen, QUIP GmbH, Roche, Sanofi and 3DHistotech. Arjan C. Houweling reports receipt of a research grant from the Myrovlytis Trust. Stefan J. Marciniak reports receipt of grants/research support from the Myrovlytis Trust, Asthma+Lung UK, Alpha 1 Foundation, the Medical Research Council (MRC) UK, and the Engineering and Physical Sciences Research Council (EPSRC). Maria Molina-Molina reports receipt of grants/research support from Boehringer Ingelheim and Roche, as well as receipt of honoraria or consultation fees from Ferrer, Chiesi, Boehringer Ingelheim, Roche and Esteve-Teijin. Charles Van Praet reports receipt of honoraria or consultation fees from Astellas, IPSEN and Baxter. Robin de Putter

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## 6. PURPOSE AND SCOPE OF THIS GUIDELINE

### 6.1 WHY WAS THIS GUIDELINE PRODUCED?

BHD syndrome is a rare multisystem disorder associated with increased risk of renal neoplasms, including renal cell carcinoma. Diagnosis may be difficult if some of the common signs, i.e. facial fibrofolliculomas/trichodiscomas, do not lead to a medical consultation or are not investigated or are overlooked. On the other hand, nowadays a genetic diagnosis may be reached even in the absence of a clear phenotype of BHD, e.g.. in patients with sporadic early onset renal cell carcinoma or with pneumothorax who are tested with gene panels, for hereditary renal cancer and for hereditary familial pneumothorax, respectively. The condition is likely underdiagnosed and, additionally, the interval between initial manifestations and the diagnosis may be long, leaving at risk individuals without cancer surveillance in the meantime. This guideline is intended to provide healthcare professionals with evidence-based advice on when a diagnosis of BHD syndrome should be considered and when genetic testing should be performed, as well as on the genetic testing approaches, surveillance for cancer and lung manifestations, and BHD syndrome specific issues concerning treatment.

### 6.2 WHO IS THE GUIDELINE FOR?

The Birt-Hogg-Dubé Guideline Group prepared this guideline document to assist healthcare professionals in the diagnosis, surveillance and treatment of individuals with a diagnosis of BHD syndrome. These guidelines are written primarily for clinicians who are more likely to care for patients who present with one or more of the main manifestations of BHD syndrome, that affects the skin, the lungs, and the kidneys with cancer. Therefore, they are addressed to clinical geneticists, urologists, dermatologists, pulmonologists, and oncologists. However, they can also be used by other physicians, patients or other interested parties. Clinical guidelines are statements to support decision making, based on systematically evaluated evidence for a specified clinical circumstance. Whilst these clinical guidelines are based on the latest published evidence, care of each individual remains primarily the responsibility of their treating medical professionals. Decisions for care should always be based on the individual needs, person preferences and individual circumstances of each patient. Clinical guidelines should support clinical decision making, but never replace clinical professional assessment and decision making. Guidelines present recommendations based

on expert opinion and published evidence and are not mandates. These guidelines do not signify nor intend to be a legal standard of care.

## 6.3 WHAT IS THE GUIDELINE ABOUT?

### 6.3.1 SCOPE

The scope of this guideline is to define clinical clues to a potential diagnosis of BHD syndrome, criteria for referral to genetic testing, that may differ depending on ascertainment mode (i.e. gene specific test versus panel testing), and surveillance and management approaches for affected patients and healthy relatives carrying a *FLCN* pathogenic (or likely pathogenic) variant.

### 6.3.2 HEALTH QUESTIONS

Key clinical questions include, but are not restricted to:

- When should a potential diagnosis of BHD syndrome be considered? The main manifestations of BHD syndrome are cutaneous fibrofolliculomas/trichodiscomas, pneumothorax/lung cysts, and renal tumours. Only a fraction of patients with one of these manifestations will have BHD syndrome. It is therefore critical to define the clinical settings in which BHD syndrome can be involved.
- When should testing of *FLCN* be considered? This can occur in different clinical scenarios, and can involve single gene testing or multigene panel testing for a single manifestation associated with BHD syndrome, i.e. renal cell carcinoma or pneumothorax.
- What is the optimal surveillance of target organs (lungs, kidneys, and skin) in people with BHD syndrome?
- Should specific tumour surveillance be offered to people with BHD syndrome other than for kidney cancer? Several other tumour types, especially colorectal cancer and polyps, have been reported in people with BHD syndrome, and an evidence based assessment is needed for this topic.
- Should any specific advice be given to people with BHD syndrome regarding the risk of pneumothorax?
- Should pneumothorax and kidney cancer in people with BHD syndrome be treated differently from the general population?

### 6.3.3 POPULATION

The guideline applies to all individuals with BHD syndrome, diagnosed based on clinical findings and/or upon the detection of a pathogenic variant in *FLCN*, and to individuals in which a diagnosis of BHD syndrome should be considered as defined in the guideline text.

### 6.3.4 CARE SETTING

This guideline has been prepared to support the decision making of health professionals involved in diagnostics, surveillance and clinical management in BHD syndrome. Patients and other interested parties can also use the guideline.

Implementation should most preferably take place through the national Direction of Health in each European Country, but the guideline could also be disseminated through relevant medical societies including respiratory medicine, urology, oncology, radiology, dermatology and clinical genetics.

### 6.3.5 EPIDEMIOLOGY & AETIOLOGY

#### **Epidemiology**

The true prevalence of BHD syndrome is unclear. It has recently been estimated to be as low as 2 in one million, according to Bayesian estimates on epidemiological data on its occurrence among patients with pneumothorax (Muller et al., 2021). However, a widely quoted figure is 1 in 200,000 (Source: [The portal for rare diseases and orphan drugs](#); (Sattler & Steinlein, 2006)), but the condition is widely considered to be underdiagnosed, and large-scale genomic studies of unselected clinical populations suggest that the prevalence of *FLCN* loss of function variants is around fortyfold higher (Savatt et al., 2022). Further research is required to establish whether the risk of manifestations in individuals with pathogenic *FLCN* variants detected as an incidental finding is similar or lower than that in families diagnosed through clinical presentation.

#### **Aetiology**

BHD syndrome is caused by monoallelic loss of function variants in the *FLCN* gene. *FLCN* is implicated in several cellular processes and in some contexts biallelic *FLCN* inactivation leads to upregulation of mTOR, which is overactivated in renal tumours from *FLCN* knockout



mouse models (Baba et al., 2008; Chen et al., 2008). A complex formed by FLCN and two interacting proteins, FNIP1 (folliculin interacting protein 1) and FNIP2 (folliculin interacting protein 2) is involved in the regulation of the protein kinases mechanistic target of rapamycin complex 1 (mTORC1) and AMP-activated protein kinase (AMPK) (Centini et al., 2018). A key role in the regulation of mTORC1 in kidney cells with FLCN inactivation is played by TFEB, that along with TFE3 belongs to the MiTF family of helix-loop-helix leucine zipper transcriptional factors (Napolitano et al., 2020; Ramirez Reyes et al., 2021). Further knowledge of the mechanistic pathways leading to the clinical manifestations of BHD syndrome will be helpful to define critical therapeutic targets.

## 7. RECOMMENDATIONS

### 7.1. DIAGNOSIS RECOMMENDATIONS

Recommendations	Strength
<p><b>Rec. 1</b></p> <p>A potential diagnosis of BHD syndrome should be <i>considered</i>* in the presence of ANY of the following:</p> <ul style="list-style-type: none"> <li>a. Primary spontaneous pneumothorax.</li> <li>b. Multiple bilateral pulmonary cysts, particularly in lower zone, in the absence of a known cause.</li> <li>c. Bilateral or multifocal renal neoplasia (i.e. renal cell carcinomas and/or oncocytomas).</li> <li>d. Renal cell carcinoma, below 50 years of age or familial.</li> <li>e. Multiple cutaneous papules clinically consistent with fibrofolliculoma/trichodiscoma.</li> <li>f. Any combination of the above mentioned cutaneous (e.g. multiple fibrofolliculomas/trichodiscomas), pulmonary (e.g. pulmonary cysts) or renal manifestations (e.g. renal cell carcinoma) presenting in the same individual or members of their family, with or without a known family history of BHD syndrome.</li> </ul> <p>* Please note that this recommendation entails to <i>consider</i> a diagnosis of BHD syndrome, indicating that other clinical features and family history should be looked for. Recommendations to perform genetic testing to diagnose BHD syndrome can differ and are detailed in recommendation 6.</p> <p>^ Criteria for early onset renal cell carcinoma might vary between countries and centres: Specific country age recommendations for early onset renal cell carcinoma might apply.</p>	<p>strong</p> <p>strong</p> <p>strong</p> <p>strong</p> <p>strong</p> <p>strong</p>

<b>Rec. 2</b>	A diagnosis of BHD syndrome should be considered at all ages (not just young persons) in the presence of suggestive features.	strong
<b>Rec. 3</b>	If BHD syndrome is considered as underlying diagnosis, appropriate further investigations, such as skin examination, CT scan of the lungs and/or genetic testing should be initiated.	strong
<b>Rec. 4</b>	A definitive diagnosis of BHD syndrome should be made when a genetic test is positive for a constitutive pathogenic/likely pathogenic variant in <i>FLCN</i> .	strong
<b>Rec. 4a</b>	Not all patients with clinical evidence of BHD syndrome will have a detectable <i>FLCN</i> pathogenic/likely pathogenic variant.	strong
<b>Rec. 4b</b>	A clinical diagnosis of BHD syndrome* can be made even in the absence of a detectable <i>FLCN</i> pathogenic/likely pathogenic variant if one major criterion (>5 fibrofolliculomas or trichodiscomas, at least one histologically confirmed, of adult onset) or two minor criteria (1. Lung: bilateral basally located pulmonary cysts with no other apparent cause; 2. Kidney: early onset (<50 years), multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology; or 3. Family history: a first-degree relative with BHD syndrome) are present.  * According to the European BHD consortium criteria (Menko et al., 2009).	strong
<b>Rec. 4c</b>	Variants of uncertain significance (VUSs) in <i>FLCN</i> should be assessed according to international guidelines (e.g. American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP)) and interpreted in the context of the clinical presentation and familial segregation studies. Additional clinical or imaging assessments in order to	strong

	detect subclinical features of BHD syndrome can also be performed.	
<b>Rec. 5</b>	Clinicians should be aware that BHD syndrome displays variable expression and that expecting classical features (skin lesions, pulmonary cysts and pneumothoraces) or only considering BHD syndrome in more extreme presentations (e.g. renal cell carcinoma at <40 years, pneumothorax at <40 years) might lead to the diagnosis being overlooked.	strong
<b>Rec. 6</b>	<p>Genetic testing for <i>FLCN</i> to diagnose BHD syndrome should be a part of the genetic evaluation offered in the presence of ANY of the following:</p> <ul style="list-style-type: none"> <li>a. Primary spontaneous pneumothorax if recurrent and/or familial.</li> <li>b. Multiple bilateral pulmonary cysts, particularly in lower zone, in the absence of a known cause.</li> <li>c. Bilateral or multifocal renal neoplasia (i.e. renal cell carcinomas and oncocytomas).</li> <li>d. Familial or early onset (45 years or under)* renal cell carcinoma.</li> <li>e. Multiple cutaneous papules clinically consistent with fibrofolliculoma/trichodiscoma with at least one histologically confirmed fibrofolliculoma.</li> <li>f. Any combination of these cutaneous (multiple fibrofolliculomas/trichodiscomas), pulmonary (e.g. pulmonary cysts) and renal manifestations (e.g. renal cell carcinoma) in the same individual or members of their family.</li> </ul> <p>* Criteria for early onset renal cell carcinoma might vary between countries and centres. From a practical perspective, specific</p>	<p>strong</p> <p>strong</p> <p>strong</p> <p>strong</p> <p>strong</p> <p>strong</p>

	country age recommendations for early onset renal cell carcinoma can be applied.	
<b>Rec. 7</b>	Predictive genetic testing for familial BHD syndrome is not generally performed until 18 years unless required for specific indications (e.g. clinical management).	strong
<b>Rec. 8</b>	First degree adult relatives of individuals with a likely pathogenic/pathogenic <i>FLCN</i> variant should be offered predictive genetic testing.	strong
<b>Rec. 9</b>	Lung ultrasound should not be used as a diagnostic test for pulmonary cysts in people with or suspected of having BHD.	strong
<b>Rec. 9a</b>	A baseline low dose high-resolution computed tomography (HRCT) scan can be offered to patients with or suspected of having BHD syndrome to diagnose pulmonary cysts. This can be offered from time of diagnosis, but not usually to asymptomatic patients before 20 years of age.	moderate

## 7.2. CLINICAL MANAGEMENT RECOMMENDATIONS

Recommendations		Strength
<b>Rec. 10</b>	<i>FLCN</i> variants should not be considered as 'pneumothorax-only' variants.	strong
<b>Rec. 11</b>	All <i>FLCN</i> variants should be considered as significantly increasing renal tumour risk and lead to appropriate renal surveillance being offered.	strong
<b>Rec. 12</b>	Currently there is not sufficient evidence of an increased risk for other tumours observed in families with BHD syndrome (e.g. colorectal cancer, malignant melanoma, thyroid cancer, etc.).	moderate

### 7.3. SURVEILLANCE RECOMMENDATIONS

Recommendations		Strength
<b>Rec. 13</b>	Surveillance for renal cell carcinoma should be lifelong.	strong
<b>Rec. 13a</b>	Surveillance for renal cell carcinoma should be started at age 20.	strong
<b>Rec. 13b</b>	Surveillance for renal cell carcinoma should be conducted every 1-2 years.	strong
<b>Rec. 14</b>	Surveillance for renal cell carcinoma should preferably be conducted using MRI, but ultrasound can be used if MRI is not available/appropriate.	strong
<b>Rec. 14a</b>	MRI with IV contrast should be used unless there are contraindications for contrast use.	strong
<b>Rec. 15</b>	Following the detection of a renal tumour, the frequency of imaging follow-up should increase in order to monitor growth rate and plan intervention.	strong
<b>Rec. 16</b>	Surveillance for colon polyps and/or cancers should follow local standard population or family history-based screening guidelines.	moderate
<b>Rec. 17</b>	Surveillance for thyroid cancers, salivary cancers and melanomas should not be performed as part of the routine follow-up of patients with BHD syndrome, but should be based on family history.	strong

#### 7.4. ORGAN-SPECIFIC RECOMMENDATIONS

Recommendations		Strength
<b>Rec. 18</b>	A formal dermatologic assessment should be considered at diagnosis.	strong
<b>Rec. 19</b>	Surgical intervention should usually be performed when the largest renal tumour reaches 3 cm in diameter.	strong
<b>Rec. 20</b>	Nephron-sparing surgery should ideally be performed whenever possible, with percutaneous thermal ablation being an alternative.	strong
<b>Rec. 21</b>	Routine lung function testing is not usually required in the follow-up of asymptomatic patients with BHD syndrome.	moderate
<b>Rec. 22</b>	Risk of pneumothoraces in flying/diving should be assessed and counselled on an individual basis with specific advice from respiratory medicine based on results of high-resolution computed tomography and previous history of pneumothoraces.	strong
<b>Rec. 23</b>	Flights on commercial airlines are generally safe but for activities that may pose a risk for pneumothorax, such as working as a pilot, flying in unpressurised aircraft or diving, expert advice should be sought so that individuals can be advised appropriately.	strong
<b>Rec. 24</b>	Surgical interventions should be considered for the treatment of recurrent pneumothorax.	strong
<b>Rec. 25</b>	Ablative procedures (e.g. electrosurgery, laser therapy) to manage fibrofolliculomas and trichodiscomas (especially facial) should be considered and discussed in patients requesting intervention, particularly if a patient states their skin lesions are affecting their quality of life.	strong

## 8. METHODS FOR GUIDELINE DEVELOPMENT

### 8.1. FORMULATING AND GRADING STATEMENTS AND CONSENSUS BUILDING

#### Literature search

The published and indexed literature [24<sup>th</sup> May 2022] that mention or reference Birt–Hogg–Dubé (BHD) syndrome was interrogated and found to total 765 papers (*Search terms - "Birt-Hogg-Dube"[All Fields]*). Subsequently, other relevant papers published after this date were included up to August 1<sup>st</sup> 2023. Of these papers, 71 form the basis of this guideline and include large studies containing extensive data, from (often single centre) retrospective case series; small, interrupted time series and case-control or cross-sectional studies (appendix 1). Of the remaining papers, 68 were simple case reports (total 76 cases; appendix 2). This collection of case-studies is a fair reflection of the heterogeneity of BHD syndrome and the ease with which it can be associated with a wide range of manifestations.

While this evidence base would rate low on a formal assessment (e.g. GRADE), its strength is that the case series cover many years and many appeared to have complete or near complete consecutive case reporting. Furthermore, with the evidence coming from multiple specialties, clinical groups and countries, and containing information on a total of several thousand unique patients, it represents a significant collection and it would likely take decades to gather additional data to meaningfully alter the guidance derived from the current series.

#### Method for formulating recommendations

In day-to-day practice, clinicians will not have the time to explore the evidence as thoroughly as a Guideline Group, nor devote as much thought to the trade-offs, or the possible underlying values and preferences in the population. Therefore, the Core Working Group has made recommendations even when confidence in effect estimate is low and/or desirable and undesirable consequences are closely balanced. Such recommendations have been classified as 'weak' and been qualified. The recommendations have been graded on the quality of evidence; balance between benefits and harms; include the values and preferences of patients; and consider the feasibility, equity & acceptability of implementation and use.



Literature was reviewed along with expert opinion to draft recommendations based on literature and experts' experiences and knowledge.

Recommendations were written in one of four stylistic formats: Should, Should Probably, Should Probably Not, Should Not

- Should & Should Not, were taken to mean: most well-informed people (those who have considered the evidence) would take this action
- Should Probably & Should Probably Not, were taken to mean: the majority of informed people would take this action, but a substantial minority would not

### **Grading of the recommendations**

As the volume of peer-reviewed evidence for rare diseases is typically limited due to the small population sizes, and it is unlikely that the evidence will ever reach a fraction of that for a more common disease, it creates a difficulty when considering the grading of the strength of evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE).

As is typical for many rare diseases, the volume of peer-reviewed evidence available to consider for these guidelines was small and came from a limited number of articles, which typically reported on small samples or series. If the evidence is categorised and then graded using standard approaches, that are designed to differentiate evidence, in circumstances when there are large numbers of papers and there are likely to be more trials, then its small volume means it would be graded as low. This is not an accurate reflection of the combination of the experts' experience and clinical consensus with the available evidence. This is further compounded as there is a low likelihood of additional volumes of evidence that could change the recommendation.

For this reason, and to balance the weight of both published evidence and quantify the wealth of expert experience and knowledge, ERN GENTURIS uses the following scale to grade the recommendations:

Strength	Grading of Recommendation
Strong	Expert consensus AND consistent evidence
Moderate	Expert consensus WITH inconsistent evidence AND/OR new evidence likely to support the recommendation
Weak	Expert majority decision WITHOUT consistent evidence

Expert consensus (an opinion or position reached by a group as whole) or expert majority decision (an opinion or position reached by the majority of the group) is established after reviewing the results of the modified Delphi approach within the Core Working Group.

In addition, strength of recommendation has been determined through a consensus-based approach (modified Delphi) and through active engagement of affected individuals and patient representatives, specifically balancing the desirable and undesirable consequences of surveillance and alternative care strategies, quality of evidence, and values and preferences held by the patient representatives.

The quantification of strength for a recommendation is a composite of harm and benefit. As a general note for these recommendations, the harms a recommendation seeks to address are often clear, however the magnitude of the benefit of a specific recommendation are often not as clear.

### **Consensus building using a modified Delphi approach**

After drafting recommendations amongst the Guideline Group these were subjected to a modified Delphi assessment. Delphi is a structured communication technique or method in which opinions of a large number of experts are asked on a topic in which there is no consensus, and this was used as a consensus building exercise. The goal is to reach consensus after several rounds of questionnaires.

Experts included in this exercise were the members of the Core Working Group (including one patient representative), the BHD syndrome Guideline Group (including three patient representatives), as well as other (external) experts identified by the Guideline Group.

The survey consisted of 2 rounds, in which the threshold for consensus was defined by a simple majority of the survey participants agree with the recommendation (>60% rated “agree” or “totally agree”). Recommendations were graded using a 4-point Likert scale (totally disagree, disagree, agree, totally agree) and a justification for the given rating was obligatory. Even if consensus was met recommendations were still modified if a higher consensus was thought achievable from written responses.

All recommendations developed by the Guideline Group were selected to proceed in the Delphi procedure. The facilitator of the Delphi survey provided anonymised summaries of the experts’ decisions after each round as well as the reasons they provided for their judgements.

We would like to thank the experts that were specifically consulted to participate in the Delphi survey:

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## 8.2. INTERNAL AND EXTERNAL REVIEW

ERN GENTURIS has actively involved external experts from different speciality areas that are relevant to the scope of the guideline to review the findings and recommendations developed in this guideline by participation in the Guideline Group or as a Delphi participant.

In addition, the BHD syndrome Guideline Group submitted a shortened version of the guideline to the European Journal of Human Genetics for independent review.

ERN GENTURIS first published the clinical practice guidelines for the diagnosis, surveillance and management of people with Birt-Hogg-Dubé syndrome on 31 July 2024.

### **8.3. TIMELINE AND PROCEDURE FOR UPDATING THE GUIDELINE**

Any new evidence that has been published will be reviewed by the ERN GENTURIS clinical leads on an annual basis to determine if the guideline should be updated. New versions will be published on the ERN GENTURIS website and circulated through the ERN GENTURIS Members.

### **8.4. FUNDING AND FINANCIAL SUPPORT**

This guideline has been supported by the European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS). ERN GENTURIS is funded by the European Union. For more information about the ERNs and the EU health strategy, please visit <http://ec.europa.eu/health/ern>. Potential conflict of interest for the individual authors and Delphi participants are listed in chapter 5.

## 9. SUMMARY OF EVIDENCE AND GUIDELINE RECOMMENDATIONS

### 9.1 DIAGNOSIS - SUMMARY OF EVIDENCE AND GUIDELINE RECOMMENDATIONS

#### Suggestive Diagnostic Criteria (Recommendations 1 and 6)

Multiple papers have suggested diagnostic criteria for BHD syndrome, though in general, these have been derived or adapted from those of the European BHD Consensus group (EBHDC) (Menko et al., 2009). However since the EBHDC Menko et al. publication (Menko et al., 2009), clinical practice has evolved, in particular, genetic testing has increasingly being used as a first-line diagnostic test for BHD syndrome rather than, for example, biopsy of cutaneous lesions to confirm fibrofolliculomas/trichodiscomas. Furthermore, access to genetic testing is no longer restricted to clinical genetics specialists. BHD syndrome may present to a wide range of clinical specialities, since its manifestations are heterogeneous, and it can mimic other disorders (e.g. lymphangioliomyomatosis (LAM) (Tomassetti et al., 2011)). Therefore, it is important to recognise in which clinical scenarios a diagnosis of BHD syndrome should be considered. In defining the clinical indicators of a possible diagnosis of BHD syndrome, a balance has to be made between high specificity/low sensitivity and higher sensitivity but low specificity that might lead to over-investigation. However, it should also be recognised that in certain clinical scenarios the chance of an underlying diagnosis of BHD syndrome is low, but that it is important to exclude it. This often occurs when genetic testing for BHD syndrome is performed as part of a specific multigene panel (e.g. genetic testing of multiple inherited cancer predisposition genes in patients with early onset renal cell carcinoma). Consideration of a diagnosis of BHD syndrome does not necessarily mean that genetic testing should be instigated. For example, in many countries a 49 year old man with unifocal unilateral clear cell renal cell carcinoma would be ineligible for routine genetic testing for hereditary kidney cancer predisposition, but if a potential diagnosis of BHD syndrome is considered, then the family history, the presence/absence of lower zone cystic lung disease and of fibrofolliculomas/trichodiscomas should be carefully investigated and this might then lead to genetic testing. Clinical scenarios in which BHD syndrome might be considered are as follows.



## Cutaneous features of BHD syndrome

### Fibrofolliculomas/trichodiscomas

Fibrofolliculomas and trichodiscomas are the most common manifestations of BHD syndrome and show age-dependent penetrance, which is 87 to 97% by age 70 years (Bruinsma et al., 2023; Lim, 2016). Fibrofolliculomas appear as raised pale or skin coloured papules typically over the nose and cheeks, neck and upper trunk (Tong et al., 2018; Toro et al., 1999). Less frequently they can appear on other parts of the torso and the scalp. Other skin lesions that occur in BHD syndrome are perifollicular fibromas and an excess of skin tags (acrochordons) (Tong et al., 2018). Comedonal fibrofolliculomas have been reported in some patients (Aivaz et al., 2015). Whilst multiple fibrofolliculomas/trichodiscomas are often considered pathognomonic of BHD syndrome there are other inherited skin conditions that may mimic BHD syndrome, e.g. familial multiple discoid fibromas (Starink et al., 2012; van de Beek et al., 2023b). In addition, there are two recent reports of cases with cutaneous fibrofolliculomas and renal cancer that were associated with rare missense variants in *PRDM10* (p.(Cys677Tyr)) and p.Cys677Arg) (Schmidt et al., 2023; van de Beek et al., 2023a). Traditionally skin biopsy has often been performed to confirm a diagnosis of fibrofolliculoma/trichodiscoma in potential new cases of BHD syndrome without non-dermatological manifestations, but nowadays genetic testing can offer an alternative route to diagnosis.

## Pulmonary features of BHD syndrome

### Spontaneous pneumothorax

It has been estimated that ~10% of patients with primary pneumothoraces have an underlying genetic cause, and BHD syndrome is the most common inherited disorder in individuals with familial pneumothorax (Abolnik et al., 1991; Muller et al., 2021; Scott et al., 2018; Toro et al., 2007). Nevertheless, the diagnosis of people with underlying BHD syndrome who first present with a pneumothorax remains an area of high unmet need. Thus, there is a longer latency to diagnosis (median 6 years) observed when pneumothorax was the first clinical feature compared to renal cell carcinoma (RCC) or skin involvement (Matsumoto et al., 2021).

Individuals diagnosed with BHD syndrome have a substantial (24%–48%) cumulative lifetime risk of pneumothorax (Lim, 2016; Zbar et al., 2002). In BHD syndrome,

primary spontaneous pneumothorax is most likely to present in the fourth and fifth decades (range 7–78 years) with the median age at first pneumothorax being around 34 years (Bessis et al., 2006; Liu et al., 2020; Matsumoto et al., 2021). Individuals with BHD syndrome who develop multiple pneumothoraces present, on average, at a younger age than those with a single occurrence (mean, 29.7 vs 38.9 years) (Sattler et al., 2020), and the risk of a pneumothorax in childhood in BHD syndrome is ~3% (Geilswijk et al., 2018). Of note, the risk of a spontaneous pneumothorax in BHD syndrome is lifelong, so advanced age *per se* is not an exclusion criterion for the possibility of BHD syndrome.

### **Multiple bilateral pulmonary cysts**

Pneumothorax in BHD syndrome is almost invariably associated with the presence of pulmonary cysts. However, multiple pulmonary cysts are also often present in BHD syndrome in individuals who do not have a history of pneumothorax (about a third of individuals with cysts have not had a pneumothorax) (Matsumoto et al., 2021). Toro et al. found an association between pneumothorax occurrence in BHD syndrome and the total number of lung cysts, total lung cyst volume and largest cyst diameter (Toro et al., 2007). A characteristic feature of BHD syndrome-associated pulmonary cysts is their tendency to be located in the basilar regions of the lungs, in contrast to emphysematous bullae which typically occur in the upper lobes (Tobino et al., 2011; Xu et al., 2020; Yang et al., 2022). Other causes of cystic lung disease include lymphangiomyomatosis (LAM), Langerhans cell histiocytosis and lymphocytic interstitial pneumonia (Arango-Diaz et al., 2021).

### **Renal features of BHD syndrome**

The major renal manifestation of BHD syndrome is RCC which occurs in 15-30% of patients. The earliest reported age onset of RCC in BHD syndrome is a single case at age 14 years (Schneider et al., 2018), but otherwise RCC occurs after age 20 years with a median age of diagnosis of 46 years, with many kidney malignancies in BHD syndrome occurring after the age of 50 years (Benusiglio et al., 2014b; Pavlovich et al., 2002; Sattler et al., 2018b). Predisposition to renal cancer appears to be lifelong, with RCC being diagnosed as late as 83 years (Benusiglio et al., 2014b). Presentation with bilateral/multicentric renal cancers is well-recognised in BHD syndrome and patients who present with a single RCC may subsequently

develop another primary tumour during follow up, so that many patients develop metachronous RCC (Benusiglio et al., 2014b; Kokorovic et al., 2020; Pavlovich et al., 2005). Tumour histopathology may be an indicator of underlying BHD syndrome. Initially most RCC in patients with BHD syndrome was classified as having overlapping features of an oncocytoma and chromophobe RCC (“hybrid oncocytic/chromophobe RCC”) (Pavlovich et al., 2002), but as the condition has been more widely recognised, the range of RCC histologies has expanded to include other subtypes, including chromophobe, papillary and clear cell (Benusiglio et al., 2014b; Pavlovich et al., 2002). Renal oncocytoma (a benign tumour) may also occur.

On average, individuals with an inherited predisposition to RCC (e.g. von Hippel-Lindau disease, BHD syndrome, Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC), Hereditary Papillary Renal Carcinoma (HPRC), Hereditary Paraganglioma-Pheochromocytoma Syndromes (SDHx-related)) develop tumours at an earlier age than non-hereditary cases. In recognition of this, in many countries it is routine to offer genetic testing for these inherited RCC syndromes to patients with young onset RCC and also those with a family history of RCC or with multiple RCC. The age threshold for offering testing to apparently sporadic non-syndromic cases of RCC has been variously suggested to be between 40 and 50 years (Bratslavsky et al., 2021; Reaume et al., 2013; Shuch et al., 2014; Yngvadottir et al., 2022) and differs between health care systems. Therefore whilst patients with early-onset RCC, multicentric or familial RCC may be routinely tested for *FLCN* pathogenic variants (as part of a panel of inherited RCC genes) some individuals with BHD syndrome and RCC may not fall into these categories. In the consensus recommendations the variability in age cut-offs for genetic testing in individuals with early-onset RCC in different health care systems was acknowledged and a cut-off for testing of 45 years or less was suggested. However, it was also suggested that consideration of a diagnosis of BHD syndrome should extend up to age 50 years (Recommendations 1 and 6) as identification of additional features of BHD syndrome (see below) could then lead to genetic testing being offered. The overall frequency of BHD syndrome in an unselected series of patients with RCC was ~1 in 300 (Yngvadottir et al., 2022).

## Multisystem and familial involvement in BHD syndrome

Many individuals apparently presenting with just a single feature of BHD syndrome (e.g. pneumothorax or RCC) will fall outside current eligibility criteria for genetic testing for BHD syndrome. Therefore, clinicians should be alert to the presence of other evidence that would suggest an underlying diagnosis of BHD syndrome. Such evidence might be elicited by careful clinical examination (e.g. presence of facial fibrofolliculomas/trichodiscomas), imaging (e.g. pulmonary cysts or renal tumours) or histopathological review (e.g. in patients with RCC). A detailed family history for possible BHD syndrome manifestations (facial fibrofolliculomas/trichodiscomas, pneumothorax or RCC) is essential as these can be overlooked unless sought specifically and the age-related penetrances of various manifestations of BHD syndrome should be considered. For example the risk of developing a pneumothorax to age 70 years was estimated at 33% and whereas the risk of cutaneous involvement was calculated to be 77% at age 70 years, 12% of mutation carriers would not have skin manifestations at age 40 years and the lifetime (age 70) risk of RCC was 36% (Bruinsma et al., 2023; Lim, 2016). Hence, the occurrence of any of the suggestive criteria (fibrofolliculomas/trichodiscomas, pneumothorax, bilateral/multifocal and/or early onset renal carcinoma) in family members should warrant careful investigation for BHD syndrome.

## BHD syndrome genetic testing

*FLCN* is the major gene associated with the BHD syndrome, though recent reports suggest that a BHD-like phenotype can rarely be associated with pathogenic variants in *PRDM10* (Schmidt et al., 2023; van de Beek et al., 2023a). Genetic testing may be performed as a targeted single gene test or be a part of a multigene panel or exome/genome sequencing. In practice, most testing is performed as part of a multigene panel for indications such as multicentric RCC or familial pneumothorax. The vast majority of pathogenic variants are truncating variants (premature stop-codon, frameshift, canonical splice site variants) detected by DNA sequencing (Sattler & Steinlein, 2006; Schmidt et al., 2005). Mutational hotspots (e.g. frameshift c.1285delC/dupC) variants have been described. The overall sensitivity of the genomic sequencing to detect SNVs/indels within the coding region of *FLCN* should be up to 100% and individuals who are negative by sequencing may have an undetected *FLCN* exonic deletion/duplication or, rarely, a chromosomal rearrangement (Benhammou et al., 2011; Smith et al., 2020). The reported detection rate of *FLCN*

pathogenic variants in individuals diagnosed with BHD syndrome is estimated to be 88-96% (Sattler et al., 2018b; Sattler & Steinlein, 2006). The interpretation of the clinical relevance of missense variants, as well as intronic and non-coding variants in *FLCN* remains challenging. Only a handful of the *FLCN* missense variants have undergone functional characterization supporting their pathogenicity (Schmidt & Linehan, 2018), and the vast majority of the identified missense variants are reported as variants of unknown significance (VUSs) (ClinVar database access March 2023: 787 missense variants, 688 uncertain; see <https://www.ncbi.nlm.nih.gov/clinvar/>). The classification of a variant as a VUS should be made according to standard international guidelines (e.g. ACMG/AMP) in a certified diagnostic laboratory and interpreted in the context of the clinical presentation and family segregation studies. BHD syndrome demonstrated age-dependent incomplete penetrance (Bruinsma et al., 2023), and additional clinical or imaging assessments to detect subclinical features of BHD syndrome can also be performed to aid variant interpretation.

Following the detection of a pathogenic *FLCN* variant, at risk family members (e.g. first degree relatives or second degree if intervening relative is unavailable) can be offered presymptomatic testing to enable those who test negative to be released from regular surveillance. In general, predictive testing is not performed before the age of 18 years unless the results would influence the management of the at risk child (Recommendation 7). Such a policy is similar to that for other adult-onset hereditary tumour predisposition syndromes (Borry et al., 2009; Borry et al., 2008; Clarke, 2014). Couples in the child-bearing age should be offered genetic counselling regarding reproductive options. Preimplantation genetic testing or prenatal invasive testing is technically available but not often requested.

### **Regional Differences in Birt–Hogg–Dubé syndrome Phenotypes**

An interesting aspect of BHD syndrome is the suggestion that there may be regional differences in phenotypes of patients with BHD syndrome. Thus lung involvement has been reported to be relatively more common, and fibrofolliculomas/trichodiscomas and RCC less common, in cohorts of individuals with BHD syndrome from Japan and China (Furuya et al., 2016; Guo et al., 2020; Hu et al., 2021). There are a number of potential explanations for these observations such as differences in phenotypic expression from allelic heterogeneity, environmental or genetic background modifying factors and/or ascertainment bias in the published literature (e.g. patient cohorts presenting to pulmonologists).

Recommendations		Strength
<b>Rec. 1</b>	<p>A potential diagnosis of BHD syndrome should be <i>considered*</i> in the presence of ANY of the following:</p> <ol style="list-style-type: none"> <li>a. Primary spontaneous pneumothorax.</li> <li>b. Multiple bilateral pulmonary cysts, particularly in lower zone, in the absence of a known cause.</li> <li>c. Bilateral or multifocal renal neoplasia (i.e. renal cell carcinomas and/or oncocytomas).</li> <li>d. Renal cell carcinoma, below 50 years of age or familial.</li> <li>e. Multiple cutaneous papules clinically consistent with fibrofolliculoma/trichodiscoma.</li> <li>f. Any combination of the above mentioned cutaneous (e.g. multiple fibrofolliculomas/trichodiscomas), pulmonary (e.g. pulmonary cysts) or renal manifestations (e.g. renal cell carcinoma) presenting in the same individual or members of their family, with or without a known family history of BHD syndrome.</li> </ol> <p>* Please note that this recommendation entails to consider a diagnosis of BHD syndrome, indicating that other clinical features and family history should be looked for.</p> <p>Recommendations to perform genetic testing to diagnose BHD syndrome can differ and are detailed in recommendation 6.</p> <p>^ Criteria for early onset renal cell carcinoma might vary between countries and centres: Specific country age recommendations for early onset renal cell carcinoma might apply.</p>	<p>strong</p> <p>strong</p> <p>strong</p> <p>strong</p> <p>strong</p> <p>strong</p>

<b>Rec. 2</b>	A diagnosis of BHD syndrome should be considered at all ages (not just young persons) in the presence of suggestive features.	strong
<b>Rec. 3</b>	If BHD syndrome is considered as underlying diagnosis, appropriate further investigations, such as skin examination, CT scan of the lungs and/or genetic testing should be initiated.	strong
<b>Rec. 4</b>	A definitive diagnosis of BHD syndrome should be made when a genetic test is positive for a constitutive pathogenic/likely pathogenic variant in <i>FLCN</i> .	strong
<b>Rec. 4a</b>	Not all patients with clinical evidence of BHD syndrome will have a detectable <i>FLCN</i> pathogenic/likely pathogenic variant.	strong
<b>Rec. 4b</b>	<p>A clinical diagnosis of BHD syndrome* can be made even in the absence of a detectable <i>FLCN</i> pathogenic/likely pathogenic variant if one major criterion (&gt;5 fibrofolliculomas or trichodiscomas, at least one histologically confirmed, of adult onset) or two minor criteria (1. Lung: bilateral basally located pulmonary cysts with no other apparent cause; 2. Kidney: early onset (&lt;50 years), multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology; or 3. Family history: a first-degree relative with BHD syndrome) are present.</p> <p>* According to the European BHD consortium criteria (Menko et al.)</p>	strong
<b>Rec. 4c</b>	Variants of uncertain significance (VUSs) in <i>FLCN</i> should be assessed according to international guidelines (e.g. ACMG/AMP) and interpreted in the context of the clinical presentation and familial segregation studies. Additional	strong

	clinical or imaging assessments in order to detect subclinical features of BHD syndrome can also be performed.	
<b>Rec. 5</b>	Clinicians should be aware that BHD syndrome displays variable expression and that expecting classical features (skin lesions, pulmonary cysts and pneumothoraces) or only considering BHD syndrome in more extreme presentations (e.g. renal cell carcinoma at <40 years, pneumothorax at <40 years) might lead to the diagnosis being overlooked.	strong
<b>Rec. 6</b>	<p>Genetic testing for <i>FLCN</i> to diagnose BHD syndrome should be a part of the genetic evaluation offered in the presence of ANY of the following:</p> <ul style="list-style-type: none"> <li>a. Primary spontaneous pneumothorax if recurrent and/or familial.</li> <li>b. Multiple bilateral pulmonary cysts, particularly in lower zone, in the absence of a known cause.</li> <li>c. Bilateral or multifocal renal neoplasia (i.e. renal cell carcinomas and oncocytomas).</li> <li>d. Familial or early onset (45 years or under)* renal cell carcinoma.</li> <li>e. Multiple cutaneous papules clinically consistent with fibrofolliculoma/trichodiscoma with at least one histologically confirmed fibrofolliculoma.</li> <li>f. Any combination of these cutaneous (multiple fibrofolliculomas/trichodiscomas), pulmonary (e.g. pulmonary cysts) and renal manifestations (e.g. renal cell carcinoma) in the same individual or members of their family.</li> </ul>	<p>strong</p> <p>strong</p> <p>strong</p> <p>strong</p> <p>strong</p> <p>strong</p>



	* Criteria for early onset renal cell carcinoma might vary between countries and centres. specific country age recommendations for early onset RCC might apply.	
<b>Rec. 7</b>	Predictive genetic testing for familial BHD syndrome is not generally performed until 18 years unless required for specific indications (e.g. clinical management).	strong
<b>Rec. 8</b>	First degree adult relatives of individuals with a likely pathogenic/pathogenic <i>FLCN</i> variant should be offered predictive genetic testing.	strong
<b>Rec. 9</b>	Lung ultrasound should not be used as a diagnostic test for pulmonary cysts in people with or suspected of having BHD.	strong
<b>Rec. 9a</b>	A baseline low dose high-resolution computed tomography (HRCT) scan can be offered to patients with or suspected of having BHD syndrome to diagnose pulmonary cysts. This can be offered from time of diagnosis, but not usually to asymptomatic patients before 20 years of age.	moderate

## 9.2 CLINICAL MANAGEMENT - SUMMARY OF EVIDENCE AND GUIDELINE RECOMMENDATIONS

Following the diagnosis of BHD syndrome in an individual, whether by clinical criteria or, more commonly, by the detection of a germline pathogenic *FLCN* variant, the focus switches towards ongoing management of any current BHD syndrome-related complications and surveillance to reduce the morbidity from complications that might develop in the future. This is exemplified by measures to ensure that any renal neoplasms are detected at an early stage (< 3 cm diameter). Reports of a germline pathogenic *FLCN* variant in kindreds with a “familial pneumothorax only” phenotype led to suggestions that BHD syndrome and isolated familial pneumothorax might be allelic (Painter et al., 2005). However, subsequently, a systematic review of the literature observed that cases of *FLCN*-related familial pneumothorax only were, on average, younger and from smaller families than individuals reported with additional manifestations of BHD syndrome. It was concluded that all

individuals with a germline pathogenic *FLCN* variant, even in the presence of a personal and family history of a pneumothorax only phenotype, should be considered to be at risk of RCC and offered appropriate renal surveillance (Matsumoto et al., 2021). In addition, no other putative genotype-phenotype correlations have been confirmed to date.

Individuals with a clinical diagnosis of BHD syndrome but no detectable *FLCN* pathogenic variant should be managed in a similar manner as those with a detectable pathogenic variant. There is little information on the management of *PRDM10*-associated BHD-like syndrome. For the time being caution should be used as applying an approach similar to patients with classical BHD might not be sufficient, particularly if there is a history of aggressive RCC in which case the “3 cm rule” for renal tumours (see below) may not be applied (Schmidt et al., 2023). Further data is needed to determine how such *PRDM10*-associated BHD-like syndrome cases should be managed.

Recommendations		Strength
<b>Rec. 10</b>	<i>FLCN</i> variants should not be considered as 'pneumothorax-only' variants.	strong
<b>Rec. 11</b>	All <i>FLCN</i> variants should be considered as significantly increasing renal tumour risk and lead to appropriate renal surveillance being offered.	strong
<b>Rec. 12</b>	Currently there is not sufficient evidence of an increased risk for other tumours observed in families with BHD syndrome (e.g. colorectal cancer, malignant melanoma, thyroid cancer, etc.).	moderate

### 9.3 SURVEILLANCE - SUMMARY OF EVIDENCE AND GUIDELINE RECOMMENDATIONS

As with other cancer predisposition syndromes, a major focus for the ongoing care of individuals with BHD syndrome is the early detection of BHD syndrome-related neoplasia. Lifetime risks (to age 70 years) of developing a RCC in BHD syndrome have been estimated

as 15-30%, which is significantly lower than in VHL disease but higher than in HLRCC. In the latter two conditions renal tumour surveillance is offered from age 16 and 10 years, respectively, by MRI scans (Maher et al., 2011; Menko et al., 2014) and a similar approach to renal surveillance has also been adopted in BHD syndrome (Menko et al., 2009). CT and MRI scans are more sensitive than ultrasonography for detecting small renal masses in inherited cancer syndromes (Choyke et al., 2003), but MRI scans avoid the radiation loads associated with annual CT scans. Though some centres routinely employ renal ultrasonography for renal surveillance in BHD syndrome, additional data is required to define if the reduced sensitivity for detecting small renal lesions compared to MRI will lead to the underdiagnosis of clinically significant RCC (Johannesma et al., 2019). Renal imaging is generally performed annually and further research is required to determine if more detailed imaging (MRI) might enable intervals to be extended to every second year. Most surveillance programmes suggest that renal imaging should commence at age 20 years (Maher, 2018; Menko et al., 2009; Schmidt & Linehan, 2015) as RCC rarely occurs earlier (Schneider et al., 2018). In the absence of another life-impairing illness, and if agreed with the patient, RCC surveillance may continue for life (RCC has been reported in the ninth decade (Benusiglio et al., 2014b)).

Whilst it has been suggested that BHD syndrome may predispose to a variety of other cancers including colorectal, thyroid, parotid tumours and melanoma, to date, none of these possible associations have been confirmed sufficiently to indicate that surveillance is required (Benusiglio et al., 2014a; Kluger et al., 2010; Lindor et al., 2012; Maffe et al., 2011; Nahorski et al., 2010; Sattler et al., 2018a; Sattler et al., 2021; Toro et al., 2008; van de Beek et al., 2020; Zbar et al., 2002). The most investigated potential association has been with colorectal neoplasia. Evidence for (Nahorski et al., 2010) and against (van de Beek et al., 2020; Zbar et al., 2002) an association between BHD syndrome and colorectal neoplasia has been reported but currently a risk for colorectal cancer is considered unproven (though there could be an increased risk of colorectal polyposis (van de Beek et al., 2020). This has led to suggestions that standard population screening guidelines for colorectal cancer should be used in BHD syndrome (rec 16) (Lattouf et al., 2016), and, when there is a positive family history of colorectal cancer, then case surveillance recommendations should be individualized according to local guidance for familial colorectal cancer. Similarly, though it has been recommended that a formal dermatologic assessment should be conducted at

diagnosis, there is no evidence to suggest that ongoing surveillance for melanoma is indicated in BHD syndrome (Lattouf et al., 2016).

Recommendations		Strength
<b>Rec. 13</b>	Surveillance for renal cell carcinoma should be lifelong.	strong
<b>Rec. 13a</b>	Surveillance for renal cell carcinoma should be started at age 20.	strong
<b>Rec. 13b</b>	Surveillance for renal cell carcinoma should be conducted every 1-2 years.	strong
<b>Rec. 14</b>	Surveillance for renal cell carcinoma should preferably be conducted using MRI, but ultrasound can be used if MRI is not available/appropriate.	strong
<b>Rec. 14a</b>	MRI with IV contrast should be used unless there are contraindications for contrast use.	strong
<b>Rec. 15</b>	Following the detection of a renal tumour, the frequency of imaging follow-up should increase in order to monitor growth rate and plan intervention.	strong
<b>Rec. 16</b>	Surveillance for colon polyps and/or cancers should follow local standard population or family history-based screening guidelines.	moderate
<b>Rec. 17</b>	Surveillance for thyroid cancers, salivary cancers and melanomas should not be performed as part of the routine follow-up of patients with BHD syndrome, but should be based on family history.	strong

## 9.4 ORGAN-SPECIFIC - SUMMARY OF EVIDENCE AND GUIDELINE RECOMMENDATIONS

### Renal Cancer Management

If renal tumours are identified, they should be followed with interval imaging studies until the largest tumour diameter reaches 3 cm, at which point nephron-sparing intervention should be pursued. This '3 cm rule' was originally formulated for renal cancer surveillance in von Hippel-Lindau disease, but has been widely adapted for other hereditary renal cancer predisposition syndromes, including BHD syndrome (Duffey et al., 2004; Schmidt & Linehan, 2015; Stamatakis et al., 2013). An alternative to surgery is image-guided percutaneous ablative therapies such as radiofrequency ablation and cryoablation (Alam et al., 2019). No studies have directly compared the use of partial nephrectomy and thermal ablation in BHD syndrome-related renal tumours, and it has been suggested that thermal ablation may complicate the interpretation of post-treatment imaging surveillance and surgical procedures in patients at high risk of new tumours (Stamatakis et al., 2013). However, recent studies have reported that percutaneous thermal ablation can be applied successfully for the treatment of RCC in people with BHD syndrome (Bodard et al., 2022; Matsui et al., 2019), and, within the limited evidence available, appears to be safe and effective. Further studies assessing the safety of thermal ablation in BHD syndrome-related renal cancer are needed.

### Lung Cysts

Some researchers have suggested that a high-resolution computed tomography (HRCT) of the chest be performed at diagnosis (Gupta et al., 2017; Lattouf et al., 2016). Number and size of cysts is related to pneumothorax and a chest HRCT may inform personal counselling regarding pneumothorax risk, for example in relation to diving. There is no evidence supporting regular repeated imaging of the chest and it should only be repeated when clinically indicated (Lattouf et al., 2016). Pulmonary cysts are best defined by HRCT scans and lung ultrasound should not be used (Recommendations g and ga) (Davidsen et al., 2017).

### Lung Function

Little has been published regarding the impact of BHD syndrome on lung function. In a retrospective study Daccord et al. (2020) assessed clinical data regarding 96 individuals and found that BHD syndrome-related cystic lung disease did not affect respiratory function at

baseline except for slightly increased RV and reduced carbon monoxide transfer factor (DLCO) (Daccord et al., 2020). No significant syndrome-specific deterioration of lung function was seen in the limited follow-up period of 6 years (Daccord et al., 2020). Currently, most experts suggest that routine lung function testing is not indicated in asymptomatic individuals with BHD syndrome. Nevertheless, lung function testing is an inexpensive and non-invasive investigation and can be considered in patients with other intercurrent lung disorders or severe cystic lung disease.

### **Pneumothorax**

Lung cysts are a main finding in BHD syndrome and give rise to an increased risk of developing spontaneous pneumothoraces. The maximum diameter of cysts is the strongest independent risk factor for spontaneous pneumothorax and the risk of recurrent pneumothorax is significantly increased (Park et al., 2019; Toro et al., 2007). Data regarding pneumothorax risk during air travel and diving is limited, although it has been estimated that BHD syndrome patients have a pneumothorax risk of 0.63% per flight and a risk of 0.33% per episode of diving (Johannesma et al., 2016). In accordance, Gupta et al. (2017) found a similar low occurrence of pneumothorax during flying and also that the risk decreases in patients who have undergone pleurodesis (Gupta et al., 2017). Anecdotally, the risk of pneumothorax may be higher in unpressurised aircraft. Individuals with BHD syndrome who plan to work as a pilot or dive regularly should seek specialised advice regarding the risks and potential preventative interventions.

Treatment of pneumothorax in BHD syndrome does not differ from that of pneumothorax for other reasons. Surgical intervention, (e.g Video Assisted Thoracoscopic Surgery (VATS) and chemical or mechanical pleurodesis or pleurectomy, or total pleural covering) should be considered in the case of recurrent pneumothorax (Gupta et al., 2013; Kurihara et al., 2010).

### **Skin fibrofolliculomas/trichodiscomas**

Self-reported alteration in Health-Related Quality of Life (HRQOL) was reported in approximately one-third of patients with BHD syndrome and fibrofolliculomas/trichodiscomas (Kluger et al., 2011). Therapeutic management is available with standard dermatological approaches, including shave excision, punch excision, ablative electrosurgery (Farrant & Emerson, 2007) and laser therapy, and should be considered as an effective intervention for

substantially improving the Quality of Life. Treatment is not curative and may need to be repeated. Topical rapamycin has been tested in a single trial and was found not to have an effect on fibrofolliculomas/trichodiscomas (Gijzen et al., 2014).

Recommendations		Strength
<b>Rec. 18</b>	A formal dermatologic assessment should be considered at diagnosis.	strong
<b>Rec. 19</b>	Surgical intervention should usually be performed when the largest renal tumour reaches 3 cm in diameter.	strong
<b>Rec. 20</b>	Nephron-sparing surgery should ideally be performed whenever possible, with percutaneous thermal ablation being an alternative.	strong
<b>Rec. 21</b>	Routine lung function testing is not usually required in the follow-up of asymptomatic patients with BHD syndrome.	moderate
<b>Rec. 22</b>	Risk of pneumothoraces in flying/diving should be assessed and counselled on an individual basis with specific advice from respiratory medicine based on results of high-resolution computed tomography and previous history of pneumothoraces.	strong
<b>Rec. 23</b>	Flights on commercial airlines are generally safe but for activities that may pose a risk for pneumothorax, such as working as a pilot, flying in unpressurised aircraft or diving, expert advice should be sought so that individuals can be advised appropriately.	strong
<b>Rec. 24</b>	Surgical interventions should be considered for the treatment of recurrent pneumothorax.	strong
<b>Rec. 25</b>	Ablative procedures (e.g. electro-surgery, laser therapy) to manage fibrofolliculomas and trichodiscomas (especially facial)	strong

	should be considered and discussed in patients requesting intervention, particularly if a patient states their skin lesions are affecting their quality of life.	
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## 10. PSYCHOLOGICAL NEEDS

BHD syndrome is a rare inherited multisystem disorder with very variable expression and severity. Though BHD syndrome is not characterized by involvement of the central nervous system, a diagnosis of BHD syndrome may be associated with psychological challenges and socioeconomic hardships, though the occurrence of these differs between individuals. Potential psychological effects include anxiety related to uncertainty about future health problems and/or fear of developing cancer. Annual cancer surveillance may be associated with heightened anxiety in the lead up to their imaging appointment. Coping with a chronic health condition may trigger or exacerbate depression. Particularly when facial fibrofolliculomas are numerous, there may be concerns about body image with self-consciousness about physical appearance. This might lead to social withdrawal and depression. When a diagnosis of BHD syndrome is delayed, a lack of a diagnostic explanation can provoke stress and repeated hospital visits and investigations can be associated with a financial burden (even in health care systems which provide free universal coverage, patients may require time off from work to attend multiple appointments etc.)

BHD syndrome, like other inherited disorders, might impact on family relationships and dynamics. Affected parents may be anxious about their untested children and feel guilty if their children become affected. Among siblings, unaffected relatives may feel guilty if their sibling is affected. Couples may feel stress and anxiety when making plans for starting a family and there may be emotional distress if there are differing perceptions of the implications of having an affected child and a lack of consensus over their reproductive options.

Addressing the psychological needs of patients and families with BHD syndrome should form a key element of holistic health care for BHD syndrome. Clinicians should be sensitive to indicators of anxiety, depression, emotional distress etc, enquire about wellbeing at each clinical contact and organise appropriate referral for professional support as required. Peer-to-peer support through patient support groups can also play a key role in maintaining wellbeing. Despite the importance of recognising and addressing the psychological burden that can be associated with BHD syndrome, there is a paucity of research addressing this issue. Consequently, the evidence base for increasing the knowledge of the psychological consequences of BHD syndrome and for approaches to ameliorate them should be addressed by future research.

## 11. WHAT DO OTHER GUIDELINES STATE?

To compare our recommendations to other similar guidelines a PubMed search was performed using the following terms: Birt-Hogg-Dube AND guidelines OR recommendations. OR (care) NOT clinical trial. A total of 46 results were obtained and these were reduced by excluding those that were not published in English or consisted of a single case report. Detailed review of the remaining articles and an additional review article not captured in the PubMed search (Menko et al., 2009) revealed that 3 articles contained relevant information relating to multiple aspects of BHD syndrome and 23 were focused on an organ-specific feature of BHD syndrome (7 on lung manifestations, 15 on renal cancer risks and one on colorectal neoplasia).

Comparison revealed that many recommendations were in common and the clinical diagnostic criteria for BHD syndrome suggested by the EBHDC (Menko et al., 2009) were adopted both for the current consensus (Recommendation 4b) and others (Gupta et al., 2013). Schmidt et al. specified that the diagnostic criteria for lung cysts should include development before 40 years of age (Schmidt & Linehan, 2015). Menko et al. also concluded that annual MRI was the best surveillance methodology for renal tumours and that surveillance should start at age 20 years (Menko et al., 2009). Similarly, other reports have adopted these recommendations though scanning intervals have been mentioned by some groups (e.g. "at least every 36 months" for MRI scans (Lattouf et al., 2016; Singh et al., 2022; Stamatakis et al., 2013). The "3 cm rule" with nephron-sparing intervention for the management of RCC in BHD syndrome has also been broadly agreed (Maher, 2018; Menko et al., 2009; Schmidt & Linehan, 2015; Singh et al., 2022; Stamatakis et al., 2013).

Sriram et al. have suggested that a chest CT scan should be performed on all patients with a primary spontaneous pneumothorax and that genetic testing for *FLCN* should then be considered in those found to have multiple pulmonary cysts (Sriram et al., 2022).

Gupta et al. suggest that patients with BHD syndrome should be reassured that BHD cystic lung disease typically does not result in respiratory failure but patients with pulmonary impairment should be followed up by a pulmonary physician with periodic assessment of pulmonary function. They also recommended evaluation by a lung specialist prior to air travel if there was evidence of pulmonary impairment or extensive cystic lung disease or prior

pneumothorax and that patients should not travel when suffering from unexplained chest pain or dyspnoea (Gupta et al., 2013). Schmidt et al. noted that the World Recreational Scuba Training Council had recommended that a history of spontaneous pneumothorax should be a contraindication to scuba diving (even if following pleurodesis) (Schmidt & Linehan, 2015). In addition it has been recommended that smoking should be discouraged in all cases (Gupta et al., 2013).

Whilst regular colonoscopy has been suggested for patients with BHD syndrome (Morrison et al., 2010), the literature is, on balance, against such a policy (van de Beek et al., 2020; Zbar et al., 2002).

## 12. SUGGESTIONS FOR FUTURE RESEARCH

### Suggestions for future research

The formulation of these guidelines for the diagnosis and management of BHD syndrome inevitably highlighted areas in which further research is required in order to guide more definitive conclusions about the most appropriate approach to diagnosis and management. Examples of topics for further research include:

#### Diagnosis

- Improved knowledge of the genetic architecture of BHD syndrome to resolve the molecular basis of patients with a clinical diagnosis of BHD syndrome but no apparent pathogenic variant in *FLCN*
- The development of clinical and biomarker based scoring systems to enable more accurate targeting of *FLCN* genetic testing of individuals with a single feature of BHD syndrome
- The development of diagnostic grade functional assays to resolve the pathogenicity of VUSs in *FLCN*
- Development of machine learning/artificial intelligence tools to identify individuals with possible BHD syndrome from presence and characteristics of lung cysts
- Better understanding of the phenotype and natural history of BHD syndrome in different populations
- Further delineation of the range of variants in *PRDM10* that can cause a BHD-like syndrome

#### Prognosis

- Approaches to better predict the likely clinical phenotype and natural history of BHD syndromes in individuals undergoing predictive testing (e.g. genotype-phenotype investigations or identification of genetic modifier alleles)
- Further characterisation of the *PRDM10* BHD syndrome-like disorder to define natural history, similarities and differences from BHD syndrome and surveillance recommendations

- Identification of environmental factors that could modify morbidity/mortality in BHD syndrome
- Increased knowledge of the natural history of cystic lung disease in BHD syndrome and better predictors of those patients who will develop recurrent pneumothoraces.
- Promote international registries to help to elucidate whether or not there is an increased risk of other cancers and to inform an evidence-based evaluation of surveillance recommendations.

### Surveillance

- Detailed comparison of the effectiveness and health economic implications of renal ultrasonography and MRI surveillance
- Development of biomarkers (e.g. ctDNA assays) that could enable more individualised approaches to renal surveillance
- Development of MRI sequences/techniques to avoid or reduce use of intravenous contrast
- Molecular characterisation of colorectal neoplasia in BHD syndrome to inform if there is a causal relationship and therefore inform if there might be a need for surveillance

### Treatment

- Development of effective topical pharmaceutical interventions for the prevention and/or treatment of fibrofolliculoma/trichodiscomas
- Identification of the optimal interventional strategy for prevention of pneumothorax and the situations when this might be considered prior to pneumothorax occurring (e.g. in a pilot with prominent cystic lung disease)
- A clinical trial to define the role of transcutaneous ablation therapies in comparison to surgical approaches (partial nephrectomy)
- Identification of optimal targeted therapies for treatment of metastatic RCC
- Formal delineation of the psychological effects of BHD syndrome and most appropriate and efficacious approaches to mitigate them
- Investigations to elucidate the molecular pathogenesis of BHD-related complications and the biochemical functions of folliculin will provide a basis to develop rational precision medicine therapies for BHD syndrome

## 13. ABBREVIATIONS

<b>ACMG/AMP</b>	<u>A</u> merican <u>C</u> ollege of <u>M</u> edical <u>G</u> enetics and Genomics/ <u>A</u> ssociation for <u>M</u> olecular <u>P</u> athology
<b>AMPK</b>	<u>A</u> denosine <u>M</u> onophosphate-activated <u>P</u> rotein <u>K</u> inase – Protein complex comprising $\alpha$ , $\beta$ , and $\gamma$ subunits.
<b>BHD syndrome</b>	<u>B</u> irt- <u>H</u> ogg- <u>D</u> ubé <u>s</u> yndrome
<b>CT</b>	Computed Tomography
<b>DLCO</b>	<u>D</u> iffusing Capacity of the <u>L</u> ungs for Carbon Monoxide ( <u>CO</u> )
<b>EBHDC</b>	<u>E</u> uropean <u>B</u> HD <u>C</u> onsensus group
<b>ERN GENTURIS</b>	<u>E</u> uropean <u>R</u> eference <u>N</u> etwork for <u>G</u> enetic <u>T</u> umour <u>R</u> isk <u>S</u> yndromes
<b>FF/TD</b>	<u>F</u> ibrofolliculomas/ <u>T</u> richodiscomas
<b>FLCN</b>	<u>F</u> olliculin - <a href="https://www.genecards.org/cgi-bin/carddisp.pl?gene=FLCN">https://www.genecards.org/cgi-bin/carddisp.pl?gene=FLCN</a>
<b>FNIP<sub>1</sub></b>	<u>F</u> olliculin <u>I</u> nteracting <u>P</u> rotein <u>1</u> - <a href="https://www.genecards.org/cgi-bin/carddisp.pl?gene=FNIP1">https://www.genecards.org/cgi-bin/carddisp.pl?gene=FNIP1</a>
<b>FNIP<sub>2</sub></b>	<u>F</u> olliculin <u>I</u> nteracting <u>P</u> rotein <u>2</u> - <a href="https://www.genecards.org/cgi-bin/carddisp.pl?gene=FNIP2">https://www.genecards.org/cgi-bin/carddisp.pl?gene=FNIP2</a>
<b>GRADE</b>	<u>G</u> radings of <u>R</u> ecommendations, <u>A</u> ssessment, <u>D</u> evelopment, and <u>E</u> valuations - <a href="https://www.gradeworkinggroup.org/">https://www.gradeworkinggroup.org/</a>
<b>HRCT</b>	<u>H</u> igh- <u>R</u> esolution <u>C</u> omputed <u>T</u> omography
<b>HRQOL</b>	Health-Related Quality of Life
<b>LAM</b>	<u>L</u> ymphangioleiomyomatosis
<b>MiTF</b>	<u>M</u> icrophthalmia family of <u>T</u> ranscription <u>F</u> actors (MITF, TFEB, TFE <sub>3</sub> , and TFEC)
<b>mTOR</b>	<u>M</u> echanistic <u>T</u> arget <u>O</u> f <u>R</u> apamycin kinase - <a href="https://www.genecards.org/cgi-bin/carddisp.pl?gene=MTOR">https://www.genecards.org/cgi-bin/carddisp.pl?gene=MTOR</a>
<b>mTORC<sub>1</sub></b>	<u>M</u> echanistic <u>T</u> arget <u>O</u> f <u>R</u> apamycin <u>C</u> omplex <u>1</u> – Protein complex comprising mTOR, raptor, GβL and dector
<b>PRDM<sub>10</sub></b>	<u>P</u> RDI-BF <sub>1</sub> and <u>R</u> IZ Homology <u>D</u> omain Containing Protein <u>10</u> <a href="https://www.genecards.org/cgi-bin/carddisp.pl?gene=PRDM10">https://www.genecards.org/cgi-bin/carddisp.pl?gene=PRDM10</a>

<b>PTX</b>	<u>P</u> neumo <u>th</u> ora <u>x</u>
<b>RCC</b>	<u>R</u> enal <u>C</u> ell <u>C</u> arcinoma
<b>TFE3</b>	<u>T</u> ranscription <u>F</u> actor Binding To IGHM <u>E</u> nhancer 3 - <a href="https://www.genecards.org/cgi-bin/carddisp.pl?gene=TFE3">https://www.genecards.org/cgi-bin/carddisp.pl?gene=TFE3</a>
<b>TFEB</b>	<u>T</u> ranscription <u>F</u> actor <u>EB</u> (Class <u>E</u> <u>B</u> asic Helix-Loop-Helix Protein) - <a href="https://www.genecards.org/cgi-bin/carddisp.pl?gene=TFEB">https://www.genecards.org/cgi-bin/carddisp.pl?gene=TFEB</a>
<b>VATS</b>	<u>V</u> ideo <u>A</u> ssisted <u>T</u> horacoscopic <u>S</u> urgery
<b>VHL</b>	<u>V</u> on <u>H</u> ippel- <u>L</u> indau disease
<b>VUS</b>	<u>V</u> ariant of <u>U</u> ncertain <u>S</u> ignificance

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