European Journal of Medical Genetics 65 (2022) 104538

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

# von Hippel-Lindau disease: Updated guideline for diagnosis and surveillance

Marie Louise M Binderup [a,1], Maja Smerdel [b], Line Borgwadt [c], Signe Sparre Beck Nielsen [d], Mia Gebauer Madsen [e], Hans Ulrik Møller [f], Jens Folke Kiilgaard [g], Lennart Friis-Hansen [h], Vibeke Harbud [i], Søren Cortnum [j], Hanne Owen [k], Steen Gimsing [l], Henning Anker Friis Juhl [m], Sune Munthe [n], Marianne Geilswijk [o], Åse Krogh Rasmussen [p], Ulla Møldrup [e], Ole Graumann [q], Frede Donskov [r,s], Henning Grønbæk [t], Brian Stausbøl-Grøn [u], Ove Schaffalitzky de Muckadell [v], Ulrich Knigge [w], Gitte Dam [t], Karin AW. Wadt [x], Lars Bøgeskov [y], Per Bagi [z], Lars Lund [aa], Kirstine Stochholm [bb,cc], Lilian Bomme Ousager [dd,ee], Lone Sunde [ff,gg,*]

[a] Department of Cellular and Molecular Medicine, University of Copenhagen, Copenhagen, Denmark
[b] Department of Clinical Genetics, Lillebælt Hospital, University Hospital of Southern Denmark, Vejle, Denmark
[c] Center for Genomics Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[d] Centre for Rare Diseases, Aarhus University Hospital, Aarhus, Denmark
[e] Department of Urology, Aarhus University Hospital, Aarhus, Denmark
[f] Department of Opthalmology, Aarhus University Hospital, Aarhus, Denmark
[g] Department of Opthalmology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[h] Department of Clinical Biochemistry, Bispebjerg Hospital, Copenhagen, Denmark
[i] The Association for vHL Patients and their Families, Denmark
[j] Department of Neurosurgery, Aarhus University Hospital, Aarhus, Denmark
[k] Ear-Nose-Throat Department, Holstebro Hospital, Holstebro, Denmark
[l] Formerly Department of Audiology, Vejle Hospital, Vejle, Denmark
[m] Department of Endocrinology and Metabolism, Odense University Hospital, Odense, Denmark
[n] Department of Neurosurgery, University Hospital of Southern Denmark, Odense, Denmark
[o] Department of Clinical Genetics, Aarhus University Hospital, Aarhus, Denmark
[p] Department of Medical Endocrinology and Metabolism, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[q] Department of Radiology, Odense University Hospital, Odense, Denmark
[r] Department of Oncology, University Hospital of Southern Denmark, Esbjerg, Denmark
[s] Department of Regional Health Research, University of Southern Denmark, Odense, Denmark
[t] Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark
[u] Department of Radiology, Aarhus University Hospital, Aarhus, Denmark
[v] Department of Medical Gastroenterology S, Odense University Hospital, Odense, Denmark
[w] Department of Endocrinology and Surgery, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[x] Department of Clinical Genetics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[y] Department of Neurosurgery, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[z] Department of Urology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[aa] Department of Urology, University Hospital of Southern Denmark, Odense, Denmark
[bb] Department of Internal Medicine and Endocrinology, Aarhus University Hosiptal, Aarhus, Denmark
[cc] Center for Rare Diseases, Aarhus University Hospital, Aarhus, Denmark
[dd] Department of Clinical Genetics, Odense University Hospital, Odense, Denmark
[ee] Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[ff] Department of Clinical Genetics, Aalborg University Hospital, Aalborg, Denmark
[gg] Department of Biomedicine, Aarhus University, Aarhus, Denmark

* Corresponding author. Department of Clinical Genetics, Aalborg University Hospital, Department of Clinical Genetics, Aalborg University Hospital, Ladegaardsgade 5, DK-9000, Aalborg, Denmark.
*E-mail address:* l.sunde@rn.dk (L. Sunde).
[1] Present affiliation: H. Lundbeck A/S, Valby, Denmark.

https://doi.org/10.1016/j.ejmg.2022.104538
Received 18 March 2021; Received in revised form 29 May 2022; Accepted 6 June 2022
Available online 13 June 2022

ARTICLE INFO

*Keywords:*
von Hippel-Lindau disease
Guideline
Surveillance
Hemangioblastoma
Renal cell carcinoma
Pheochromocytoma

ABSTRACT

von Hippel Lindau disease (vHL) is caused by a hereditary predisposition to multiple neoplasms, especially hemangioblastomas in the retina and CNS, renal cell carcinomas (RCC), pheochromocytomas, neuroendocrine pancreatic tumours (PNET) and endolymphatic sac tumours. Evidence based approaches are needed to ensure an optimal clinical care, while minimizing the burden for the patients and their families.

This guideline is based on evidence from the international vHL literature and extensive research of geno- and phenotypic characteristics, disease progression and surveillance effect in the national Danish vHL cohort. We included the views and preferences of the Danish vHL patients, ensured consensus among Danish experts and compared with international recommendations.

*Recommendations:* vHL can be diagnosed on clinical criteria, only; however, in most cases the diagnosis can be supported by identification of a pathogenic or likely pathogenic variant in *VHL*. Surveillance should be initiated in childhood in persons with, or at risk of, vHL, and include regular examination of the retina, CNS, inner ear, kidneys, neuroendocrine glands, and pancreas. Treatment of vHL manifestations should be planned to optimize the chance of cure, without unnecessary sequelae. Most manifestations are currently treated by surgery. However, belzutifan, that targets HIF-2α was recently approved by the U.S. Food and Drug Administration (FDA) for adult patients with vHL-associated RCC, CNS hemangioblastomas, or PNETs, not requiring immediate surgery. Diagnostics, surveillance, and treatment of vHL can be undertaken successfully by experts collaborating in multidisciplinary teams. Systematic registration, collaboration with patient organisations, and research are fundamental for the continuous improvement of clinical care and optimization of outcome with minimal patient inconvenience.

## 1. Introduction

von Hippel-Lindau disease (vHL) (OMIM number 193300) is caused by a hereditary multi-organ tumour predisposition, usually related to heterozygosity for a variant in the tumour suppressor gene *VHL* located on chromosome 3p (Gossage et al., 2015).

Predisposed individuals are at risk of developing multiple benign as well as malignant neoplasms, especially hemangioblastomas in the retina and the cerebellum, as well as renal cysts and renal cell carcinoma (RCC), which are often bilateral. Neoplasms also occur in other locations in the CNS, in the adrenal glands (pheochromocytomas), pancreas (neuroendocrine tumours, PNETs), the endolymphatic sac in the inner ear, and the epididymis/the broad uterine ligament (cystic adenomas). Supplementary Table 1 gives the frequencies of vHL-associated manifestations, mean ages at manifestation onset, and the frequencies of vHL among patients with the various manifestation types, based on a systematic review of published vHL cohort studies. The prevalence of vHL has been found to be 1:46,900 in Denmark and has internationally been reported to be 1: 36,000–91,000 (Binderup et al., 2016; Evans et al., 2010; Maddock et al., 1996; Maher et al., 1991; Neumann and Wiestler, 1991). No founder effects were identified in the Danish vHL cohort (Binderup et al., 2016).

The vHL phenotype is highly variable, both in terms of manifestation types, age at onset, and tumour burden. Patients with vHL and individuals predisposed for vHL are recommended to undergo regular surveillance to ensure early diagnosis and timely treatment (Glasker et al., 2020; Maher et al., 2011). Surgical treatment has been the cornerstone in the treatment of most vHL-associated tumours. However, the understanding of accumulation of hypoxia-inducible factor 2α (HIF-2α) within the cell as a result of *VHL* inactivation has led to the development of the HIF-2α inhibitor drug belzutifan (previously known as PT2977 or MK6482) (Jonasch et al., 2021). In 2021, the U.S. Food and Drug Administration (FDA) approved belzutifan for adult patients with vHL associated RCC, CNS hemangioblastomas, or PNETs, not requiring immediate surgery; thereby providing a medical treatment option.

Apart from recently published papers on diagnosis and surveillance of individual vHL manifestation types (Chahoud et al., 2020; Huntoon et al., 2021; Laks et al., 2021; Mehta et al., 2021), guidelines for vHL management have largely been based on expert opinions and clinical assessments (Andersen et al., 2005; Glasker et al., 2020; Hes et al., 2005; Maher et al., 2011; The Alliance, 2015). In Denmark, we have had comprehensive national guidelines for diagnostics and clinical care of patients with, or at risk of, vHL since 2002. Furthermore, we have systematically and prospectively registered data on the Danish vHL patients. We here present the fourth version of our guidelines, adjusted by the results from research on the Danish vHL cohort and from international studies as well as our experiences with a multidisciplinary approach and long-standing collaboration with the Danish patient association.

Based on our work we recommend that diagnostics, including thorough clinical examination in combination with genetic screening, as well as surveillance and treatment of manifestations are handled in a dedicated multidisciplinary team setting. Surveillance should include lifelong annual focused clinical/neurological and retinal examination from as young an age as possible, hearing examination and annual biochemical screening from age 5 years, and MRI of the abdomen and CNS every second years from age 15 with a baseline MRI of the CNS at age 10 years.

The present version of this guideline was endorsed by the European Reference Network for patients with a genetic tumour risk syndrome (ERN Genturis) (www.genturis.eu).

## 2. Objectives

Our objectives were to outline the current knowledge and share the Danish guidelines and experience with vHL management set-up concerning 1) the diagnostic strategy for patients suspected of vHL, and 2) surveillance of patients with, or predisposed to, vHL.

## 3. Methods

The first edition of this clinical guideline was published in 2002 by a group of medical specialists managing vHL patient care in Denmark and was primarily based on their clinical experience with vHL, as well as perspectives from vHL families. The second and third revised editions were published in 2005 and 2013 (Andersen et al., 2005; Binderup et al., 2013). The Danish vHL coordination group was formalized during this period, and currently consists of vHL researchers, representatives of the Danish vHL patient association, as well as the leading national experts within all relevant medical specialities and representing all hospitals involved in vHL management in Denmark.

The Danish vHL coordination group established a nationwide database, the vHL database, in May 2012, comprising clinical and genetic data about families diagnosed with vHL. Since then, all clinical geneticists and other specialists working with vHL have asked patients diagnosed with vHL for permission to registration, which has also been

encouraged by the patient association, allowing prospective studies. Furthermore, data about vHL families from previous Danish research projects dated as far back as 1930, have been included (Moller, 1930; Moller, 1952), allowing for observation periods of more than 100 years in some vHL families (Binderup et al., 2016, 2017). The database is continuously updated in collaboration with the departments of clinical genetics/genomic medicine. In January 2022, the vHL database comprised data on 103 living persons from 41 families. Of these, 93 living individuals were registered as carrying a clinically actionable variant in VHL, while 10 living individuals from 6 different families fulfilled the diagnostic criteria even though no *VHL* variant had been identified in their family.

The main basis for this fourth version of the guideline is our recent extensive mapping of geno- and phenotypic characteristics, disease progression and effect of surveillance in the national Danish vHL research cohort that comprises 91% of all known Danish vHL families (Binderup, 2018). In addition, we have performed systematic literature searches using PubMed as described in the 3rd edition of the guideline (Binderup et al., 2013). These searches were last updated in December 2021, and we further searched for combinations of "vHL", "von Hippel-Lindau disease", "diagnostic criteria", "surveillance", "management", and "screening". We screened abstracts for evidence regarding vHL diagnostic criteria and surveillance of vHL-associated manifestations. Studies in which vHL cohorts were included and in which diagnostic criteria, natural history of manifestation development, and/or screening/surveillance were specifically described or assessed, were evaluated. In addition, we have related our guideline to recent consensus statements regarding CNS hemangioblastoma, ELST, pancreatic and renal manifestations made by the American VHL Alliance (Chahoud et al., 2020; Huntoon et al., 2021; Laks et al., 2021; Mehta et al., 2021).The Danish vHL coordination group will continue to monitor the literature as well as new technologies in the relevant areas of vHL diagnosis and surveillance. The group will evaluate the need for revision at least yearly at the annual group meetings.

We have included the views and preferences of vHL patients and their families through close collaboration with the Danish vHL patient association (https://vhl.dk) in guideline discussions. The chairperson of the patient association has been actively engaged in the work behind these guidelines as a co-author. Furthermore, we have collected views and opinions regarding surveillance approaches voiced by patients in the outpatient's clinics and at The Nordic vHL symposium 26th April 2019 where vHL patients from Denmark, Sweden and Norway participated.

## 4. Formulating surveillance recommendations

We used the best available research evidence to develop the recommendations.

Our analysis of available evidence identified through the described literature searches mainly focused on relevant age at screening initiation, as well as screening modality and frequency for each vHL-related type of manifestation. In addition, we have taken the clinical accessibility and the acceptability by patients of a screening modality, as well as the clinical relevance, i.e. potential clinical consequences of a finding, into account. The quality of the available evidence supporting a given surveillance, as well as the appropriate strength of the surveillance recommendations were assessed using the principles of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines (Guyatt et al., 2008): "High level of evidence": Further research is very unlikely to change our confidence in the estimate of effect; "Moderate level of evidence": Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; "Low level of evidence": Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; "Very low level of evidence": Any estimate of effect is very uncertain. Based on an overall assessment of all relevant identified evidence, we then characterized the strength of each recommendation according to GRADE definitions, as "strong" when the level of evidence was assessed to be "high" or "moderate", and "conditional" when the level of evidence was assessed to be "low" or "very low". To describe strength of a recommendation in a consistent language, we used the phrase "we recommend" when describing strong recommendations, and "we suggest" when describing conditional recommendations. The strength and level of evidence for each recommendation are described in the section "Recommended surveillance", and an overview is given in Supplementary Table 3.

**Table 1**
Diagnostic criteria for vHL.

| A clinically actionable *VHL* variant[a] has been detected in the family | No clinically actionable *VHL* variant[a] has been detected in the family | |
|---|---|---|
| The patient carries the variant and has (had) at least 1 vHL manifestation | No first-degree relatives with vHL<br>The patient has (had) at least 2 vHL manifestations; at least one of these was a hemangioblastoma | The patient has at least one first-degree relative with vHL<br>The patient has (had) at least 1 vHL manifestation |
| **vHL manifestations included in the criteria[b]:**<br>Hemangioblastoma in the retina or the CNS<br>Renal cell carcinoma (RCC)<br>Pheochromocytoma<br>Pancreatic neuroendocrine tumour (PNET)<br>Endolymphatic sac tumour (ELST) | | |

[a] A clinically actionable variant is a variant that can be used for predicting the risk of the phenotype seen in the affected members, in his/her unaffected relatives. Most often variants classified as class 5 (pathogenic) or class 4 (likely pathogenic) by using the criteria published by ACMG (Richards et al., 2008), are regarded as clinically actionable. However, some variants that fulfil the criteria for class 5 or 4 do not have a high penetrance. Thus, in addition to estimating the likelihood of a given variant being pathogenic, it is also important to evaluate the likelihood that the variant is causing the phenotype observed.

[b] Some vHL manifestations are so common in the general population that they are not a part of the diagnostic criteria; but observation of these can support the diagnosis of vHL: Simple pancreatic cysts, kidney cysts (dependent on screening modality (US/CT/MRI) and age distribution of the examined population, as frequency increases with age). Multiple pancreatic or renal cysts strongly support the vHL diagnosis. Further, papillary cystadenoma in the epididymis/papillary cystadenoma of the broad uterine ligament are highly indicative of vHL, especially in patients with bilateral affection, but there is not enough evidence to support inclusion in the current diagnostic criteria.

## 5. The gene: *VHL*

*VHL* is located in 3p25.3. (Gossage et al., 2015; Nordstrom-O'Brien et al., 2010). A main action of the protein encoded by *VHL* (pVHL) is its E3 ubiquitin ligase activity that leads to proteasome-mediated degradation of HIFs (Hypoxia Inducible Factors) that mediates angiogenesis.

In most patients diagnosed with vHL due to clinical findings, heterozygosity for a pathogenic or likely pathogenic variant in *VHL* can be demonstrated. Approximately 80% of these patients have an affected parent, whereas in 20% of the patients the variant has arisen *de novo* (Nordstrom-O'Brien et al., 2010; Sgambati et al., 2000).

The observed frequencies of the various variant types in 34 Danish vHL families are comparable to internationally reported frequencies (Nordstrom-O'Brien et al., 2010): Missense variants: 44%, frameshift variants: 6%, nonsense variants: 12%, in frame deletions/insertions: 35%, and splice site variants: 3% (Binderup, 2018).

Homozygosity and compound heterozygosity for some variants in *VHL* cause the phenotype familial erythrocytosis 2 (Gossage et al., 2015). Although a few patients with both the vHL and the erythroblastosis phenotypes have been described, generally, the variants identified in patients with erythroblastosis are not associated with an increased tumour risk (Gossage et al., 2015).

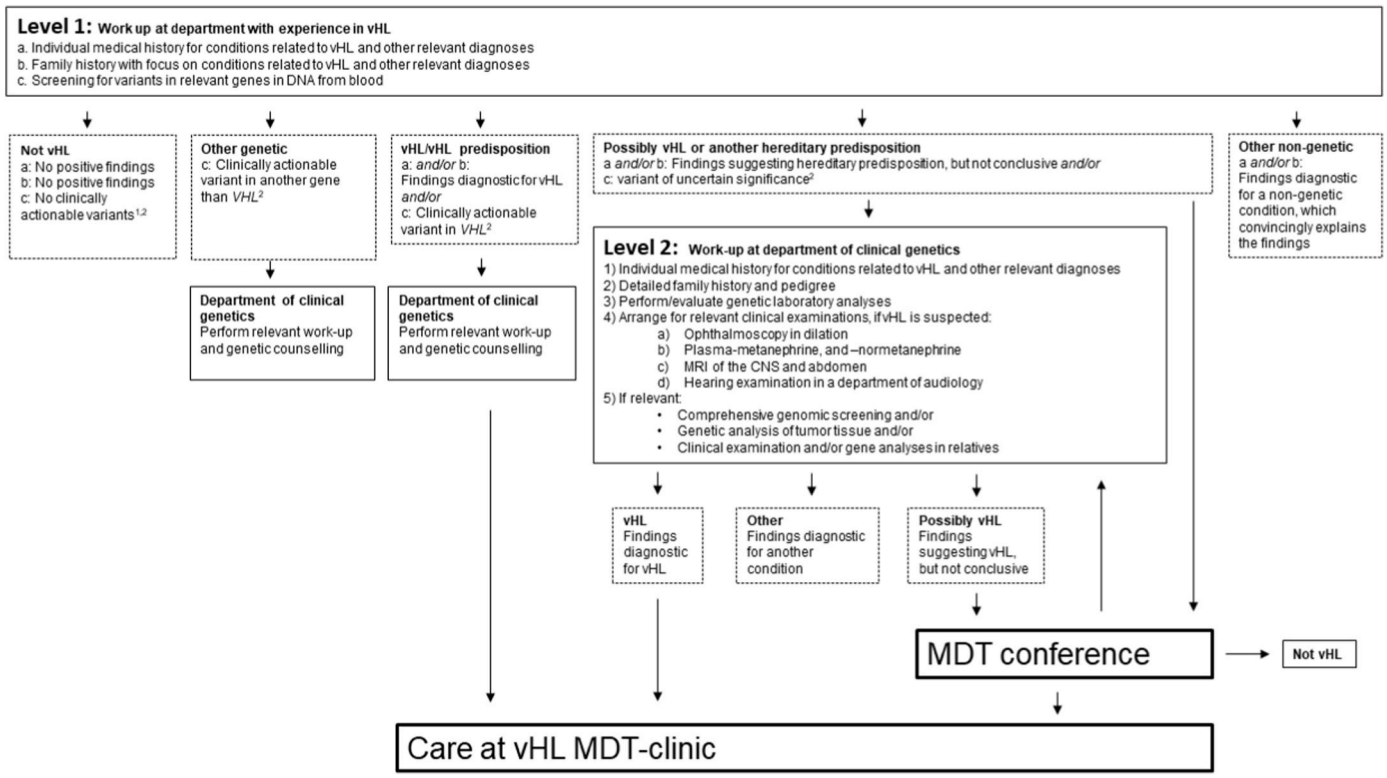


**Fig. 1.** Recommended clinical and genetic work-up in persons suspected of vHL
1: The screening should be "sufficient", i.e. with a sensitive technique (for example, NGS should be preferred for Sanger sequencing), and mosaicism should be unlikely. 2: A clinically actionable variant is a variant that can be used for predicting the risk of the phenotype seen in the affected family members, in their unaffected relatives. Most often variants classified as class 5 (pathogenic) or class 4 (likely pathogenic) by using the criteria published by the American College of Medical Genetics (ACMG) [23]), are regarded as clinically actionable. ACMG variant categories: Class 5: pathogenic, Class 4: likely pathogenic, Class 3: variant of uncertain significance, Class 2: likely benign, Class 1: benign (Richards et al., 2015).

### 5.1. Diagnostic criteria

The diagnosis vHL is based on clinical findings, however in most patient a pathogenic or likely pathogenic variant is identified (Decker et al., 2014). In a small proportion of patients, the diagnosis vHL is made because the patient fulfils the clinical diagnostic criteria although no pathogenic or likely pathogenic variant in *VHL* is identified (Cybulski et al., 2002; Hes et al., 2007). The consensus in the literature states that, in individuals with a first-degree relative with vHL, a clinical diagnosis can be made when the individual has at least one vHL manifestation, and that in a patient without a family history of vHL, the diagnosis vHL can be confirmed in patients with two different vHL manifestations of which at least one is a hemangioblastoma (Table 1), (Lonser et al., 2003; Maher et al., 2011; MELMON and ROSEN, 1964; Nordstrom-O'Brien et al., 2010). We support this recommendation, as this will promote a broader diagnostic approach in patients with abdominal neoplasms only, in order to explore differential diagnoses. We estimate that in a vHL patient who by chance only has abdominal manifestations at the time of the initial presentation, the risk of missing the diagnosis is low: With a modern diagnostic approach, such individuals would be screened for *VHL* variants during the diagnostic process. Furthermore, in a large Danish vHL cohort, we recently found that only 7% of patients who were later found to be *VHL* variant carriers fell into this category at initial presentation (Binderup et al., 2016).

## 6. Diagnostic strategy

The diagnostic strategy differs with clinical situations. Some patients are unaffected, but a vHL predisposition is suspected due to family members being diagnosed with vHL. Other patients are affected by one

**Table 2**
Actions recommended in patients suspected of vHL.

| Clinical situation | Action |
|---|---|
| The patient has a solitary pheochromocytoma/paraganglioma | Start at work up level 1 (Fig. 1) |
| The patient has ≥1 hemangioblastoma in the retina or in the CNS | Start at work up level 2 (Fig. 1) |
| The patient has multiple or early onset (≤40 years) RCC | |
| The patient has ≥2 PNETs[a] | |
| The patient has ≥2 different abdominal manifestations (RCC, pheochromocytoma/paraganglioma/PNET) | |
| The patient has ≥1 endolymphatic sac tumour | |
| The patient has a first-degree relative who fulfils the diagnostic criteria for vHL, or a family history with at least 2 first-degree relatives[b] with ≥1 of the vHL manifestations included in the diagnostic criteria (Table 1), and the patient is affected or first-degree relative to one of the affected patients. | |
| The patient has a first-degree relative with a clinically actionable variant in *VHL* | Predictive gene test at department of clinical genetics |
| The patient fulfils the diagnostic criteria for vHL (Table 1) | Genetic counselling and relevant work-up at department of clinical genetics |
| The patient has a clinically actionable variant in *VHL* detected incidentally | |

RCC: Renal cell carcinoma, PNET: Pancreatic neuroendocrine tumour.
[a] In the case of patients with ≥2 PNETs, MRI or somatostatin-receptor PET-imaging should be performed.
[b] E.g. two siblings, a parent and a sibling, a parent and his/her sibling, or a parent and his/her parent.

or more vHL manifestations. Some vHL-associated manifestations are more frequent in the general population than others, and the prior risk of vHL varies accordingly. Furthermore, the likelihood of vHL in a patient with a vHL-associated manifestation varies with the age of the patient at presentation. As the suggested work-up varies with the clinical presentation, we introduce two levels of diagnostic work-up, see Fig. 1. For examples, see Table 2.

We suggest that the following medical specialists with expertise in vHL should participate in the multidisciplinary team (MDT) handling vHL diagnostics and management: clinical geneticist, urologist, neurosurgeon/neurologist, endocrinologist, ophthalmologist, gastroenterologist, radiologist, audiologist, paediatrician, and oncologist.

### 6.1. Genetic work-up and counselling at a department of clinical genetics

In patients suspected of vHL due to a solitary phaeochromocytoma or paraganglioma, the genetic work-up can be initiated at a department with experience in vHL; all other patients suspected of vHL are recommended to be referred to the local department of clinical genetics (Fig. 1 and Table 2).

If a clinically actionable variant in *VHL* has previously been identified in a relative, predictive testing for this variant is performed. If an appropriate genetic work-up has previously been performed in the family, no clinically actionable variant has been detected in *VHL*, and the diagnosis vHL was made using the clinical criteria, the patient is counselled according to his/her relation to the affected relative(s). In all other cases a genetic work-up is performed. The medical history of the patient and relevant relatives is obtained by interviewing the patient and reviewing medical records and other relevant sources and documented in a pedigree. Relevant clinical examinations and gene analysis of a blood sample from the patient are arranged (Fig. 1, Level 2). If vHL is the only condition suspected, *VHL* is sequenced. If several diagnoses are possible, a relevant panel of genes is analysed. A variant classified as pathogenic or likely pathogenic, e.g. according to the guidelines by American College of Medical Genetics and Genomics and the Association for Molecular Pathology (Richards et al., 2015), and that likely is the major cause of the vHL manifestations in the family, is regarded as clinically actionable.

In families where a clinically actionable variant is identified, predictive testing is recommended to relevant family members. Some variant carriers stay unaffected even at high ages (Maddock et al., 1996; Maher et al., 1991). In the Danish vHL cohort, the average penetrance at the age of 60 was 87%, and among those who did not attend surveillance prior to the diagnosis of their first manifestation, the penetrance was as low as 80% (Binderup et al., 2016). Furthermore, vHL manifestations are seen in childhood. We therefore recommend predictive testing to all first-degree relatives to a carrier of a clinically actionable *VHL* variant, regardless of age. Predictive testing can also be performed prenatally on cells obtained by chorionic villus biopsy or as preimplantation genetic testing. If no clinically actionable variant is identified, relevant differential diagnoses should be considered, see Supplementary Table 2. If this leaves vHL as the most likely diagnosis, and the individual analysed is the only affected in the family, mosaicism should be suspected. If the patient has children, these should be recommended genetic counselling and analysis of *VHL*. Furthermore, gene analysis could be repeated on biopsies from two vHL manifestation, e.g. two tumours.

In families where all relevant gene screenings have been performed and no clinically actionable variant has been identified, no differential diagnoses are more likely, and the clinical criteria for vHL are fulfilled, affected family members and their first-degree relatives should be recommended surveillance according to the guidelines below. If the clinical criteria are not fulfilled, but the diagnosis vHL is the most likely diagnosis, affected family members and their first-degree relatives can be advised to attend surveillance. It might be indicated to refer families which fulfil the diagnostic criteria or do not, but are still suspected of vHL, to a renewed risk assessment some years after the initial genetic work-up. This may especially be relevant in first-degree relatives attending the surveillance programme without positive findings after repeated examinations.

All patients with a possible diagnosis of vHL after the diagnostic work-up (i.e. Level 2 in Fig. 1) should be discussed within a multidisciplinary team of vHL experts. For instance, this would be relevant for some patients with two or three vHL manifestations (e.g. combinations of renal cell carcinoma, pheochromocytoma, endolymphatic sac tumour and/or pancreatic cysts).

When considering if a patient suspected for vHL because he/she had one vHL manifestation only and in whom no further findings at the work-up supported the diagnosis vHL, should enter a surveillance programme, it may be helpful to estimate the risk that he/she will develop certain vHL manifestations.[2]

With the increased use of gene-panel screenings, variants of uncertain significance (VUSs) are identified more and more frequently. To which extend it is indicated to explore the significance of a VUS, depends on the phenotype of the patient and his/her family, a.o.: It is clearly more indicated to perform further work-up if the variant is identified in a patient with a phenotype that clearly suggests vHL, and no actionable variant is identified, than if the variant is identified in a patient suspected of a predisposition to breast cancer, where neither the history nor the family history suggest vHL. In case a VUS in *VHL* is identified in a patient with a phenotype that is consistent with, but not suggesting, vHL, it may be worth trying to estimate the chance of helping, versus the risk of harming, the patient and his/her relatives, by performing further work-up (e.g. clinical examinations). In these estimations, the probability of vHL, the age of the patient, the number of relatives potentially at risk etc., should be considered.

We suggest nationwide registration of vHL families, as is currently being done in Denmark in the vHL database. The database can allow easy access to information about genetic work-up performed in family members, useful when a patient is referred for genetic work-up. Furthermore, the database can be used to monitor the outcome of the nationally recommended surveillance and management and allow research with minimal bias.

## 7. vHL management

### 7.1. Clinical variability and natural history of vHL

The clinical presentation of vHL varies markedly, both with regards to when in life manifestations develop, and with regards to organ involvement and tumour burden. In the Danish vHL cohort, the median age at diagnosis of first manifestation was 23 years (range: 6–73 years) (Binderup et al., 2016), and almost 30% (25 of 85 patients) had at least one manifestation diagnosed before the age of 18 years (Launbjerg et al., 2017). The most common manifestations in childhood were

[2] As an example: In an individual, who a) was suspected of vHL based on a single manifestation, b) underwent the diagnostic investigations described without having additional manifestations detected, c) is without a family history, and d) had no variant detected in VHL, we estimate the risk of developing RCC due to vHL to be less than 0.05% based on the following assumptions: 1) The probability that the manifestation is caused by a clinically actionable *VHL* variant is 50%, 2) The probability that a carrier of a clinically actionable variant has no family history of vHL equals the probability that a variant in *VHL* arose *de novo*, which is approximately 20% (Nordstrom-O'Brien et al., 2010), 3) The probability that a variant caused by *de novo* mutation is not detected is 5% (Sgambati et al., 2000), 4) Among vHL patients, the frequency of RCC is approximately 30% (Supplementary Table 1).The risk that such an individual will develop renal cell carcinoma due to vHL in his/her lifetime is 0.30 x 0.50 x 0.20 x 0.05/(0.50 x 0.20 x 0.05 + 0.50) = 0.00037. Accordingly, such an individual is not recommended to undergo surveillance, but is encouraged to contact the department of clinical genetics immediately if he/she/a relative should experience vHL-associated symptoms.

**Table 3**
Surveillance recommendations.

| Age interval | Recommendation | | | | |
|---|---|---|---|---|---|
| | Eye clinical exam. | CNS clinical exam. | Hearing exam.[b] | Imaging[c] | Biochemistry |
| **0–4 years** | **Annual retinal inspection:** | **Annual general paediatric examination** including growth parameters | – | – | – |
| **5–14 years** | 1. Ophthalmoscopy and/or 2. Wide angle funduscopy or fundus photography and/or 3. Optos photography® and/or 4. Goldmann three mirror examination[a] | | **Annual hearing examination** | **MRI of the CNS (brain and neuroaxis) including the inner ear with contrast:** Baseline scan at age 10 years | **Annual plasma metanephrine and plasma normetanephrine** |
| **From 15 years** | | **Annual neurological evaluation:** systematic questioning about general health and any neurological symptoms + focused neurological examination based on symptoms/imaging findings | **Every second year: Hearing examination** | **Every second year: MRI of the CNS (brain and neuroaxis) including the inner ear with contrast AND Imaging of the abdomen** (kidneys, adrenal glands, pancreas): MRI with contrast is preferred, while CT and US may be considered based on special indications[d] | |

CT: Computerized Tomography, MRI: Magnetic Resonance Imaging, PET: Positron Emission Tomography, US: Ultrasound examination.

[a] None of the four modalities, is the superior one; the combination of the four modalities is believed to provide a more thorough evaluation. Ophthalmoscopy twice a year can be considered in young children who have difficulties in cooperation to the examination.

[b] The hearing examination should be performed at a department of audiology and consist of: A) Pure tone audiometry (Screening audiometry, classifying the individuals hearing ability as "within/outside normal hearing limits" is not sufficiently sensitive as very small manifestations can be of significance): As far as possible a threshold determination (testing both air and bone conduction on each ear) should be done, even if the hearing level is within normal limits. B) Speech audiometry: Determination of Speech Reception Threshold (SRT) and Speech Discrimination test. C) Impedance audiometry: Tympanometry and stapedial reflex determination (both contra- and ipsilateral reflexes).

[c] All imaging results should be assessed at a department of radiology, and preferable also be discussed at a MDT conference by radiologists as well as specialists in the organ of interest.

[d] US can only be recommended to screen for kidney manifestations, not pancreatic or adrenal manifestations. As it can be hard to differentiate between a simple pancreatic cyst and a cystic PNET, we suggest that any apparently simple pancreatic cyst is further examined using Ga-DOTATOC-PET/CT or Cu-DOTATATE-PET/CT.

hemangioblastomas in the retina (20% of *VHL* variant carriers) and CNS (13% of *VHL* variant carriers) (Launbjerg et al., 2017). Mean life expectancy for male and female vHL patients in Denmark was 67 and 60 years, respectively (Binderup et al., 2017), which is consistent with reported median life expectancy of 62–66 years in Chinese vHL patients (Wang et al., 2018; Zhang et al., 2021). Life expectancy is continuously improving, as risk of vHL-related death decreases (Binderup et al., 2017), but the main causes of death are still CNS hemangioblastoma (51–76%) and RCC (16–36%) (Binderup et al., 2017; Wang et al., 2018; Zhang et al., 2021). A higher risk of pheochromocytoma is associated with missense *VHL* variants, which typically result in functionally altered VHL proteins (Gossage et al., 2015). Carriers of a truncating variant have been found to have a higher risk of developing tumours, especially CNS hemangioblastoma (Binderup et al., 2015b; Cybulski et al., 2002; Glasker et al., 1999; Lonser et al., 2014; Salama et al., 2019; Wang et al., 2017). Furthermore, carriers of truncating *VHL* variants may have a poorer survival than carriers of missense variants (Binderup et al., 2017; Wang et al., 2018; Zhang et al., 2021). In contrast, carriers of missense variants may have a higher risk of hemangioblastoma in the retina (Binderup et al., 2015b). The type of *VHL* variant is however not the only modulator of phenotype, as both inter- and intrafamilial variation is great. Variants in other genes than *VHL* may influence disease risk. For instance, loss of the *VHL*-adjacent gene, *BRK1,* which may be caused by a large deletion involving both *VHL* exon 1 and adjacent areas, is associated with lower retinal hemangioblastoma and RCC risks (Cascon et al., 2007; Franke et al., 2009; Maranchie et al., 2004; McNeill et al., 2009). In the Danish vHL cohort study we found that male vHL patients tend to develop new tumours, especially CNS hemangioblastoma, at a higher frequency than female patients (Binderup et al., 2015b). An American cohort study similarly found that male patients developed more new CNS hemangioblastomas than female patients, and that the male patients' tumours grew significantly faster (Lonser et al., 2014). At present, surveillance recommendations are neither stratified on genotype nor sex. Further research is needed regarding individual risk factors that may modify the vHL phenotype before surveillance can be individualized.

## 8. Recommended surveillance

Surveillance is recommended for:

A) Individuals who fulfil the diagnostic criteria mentioned in Table 1.
B) Unaffected individuals who carry a clinically actionable *VHL* variant.
C) First-degree relatives of an individual who fulfils the diagnostic criteria, but in whom an underlying genetic cause cannot be identified. If no vHL manifestations are identified, surveillance need not be lifelong. The choice of whether and when to stop surveillance may be guided by the age at which manifestation(s) first appeared in the affected family member(s). However, there are no available data that supports a specific age to stop surveillance.
D) First-degree relatives of carriers of a clinically actionable variant in the *VHL* gene, who have not had a predictive gene test.

Clinical as well as paraclinical examinations should be performed by medical specialists with a special interest and experience in vHL. In Denmark, previously the surveillance was recommended to be organized by a clinical-coordinator, i.e. a physician from one of the relevant specialities (for example a neurosurgeon), coordinating the examinations by the physicians from the relevant specialities, and being the primary physician to communicate with the patient. In 2015 the first MDT vHL clinic, where patients see all relevant specialists on the same day, was established, and by 2022 most Danish individuals who have, or are predisposed for vHL are cared for in such clinics. In a multidisciplinary approach, the coordination of surveillance is facilitated and when the patient shows symptoms or an examination disclose finding(s), all relevant specialities are involved in the discussion of test results and evaluation of the patient. The MDT clinics and the accompanying MDT

conferences are held 2–5 times a year, dependent on the number of patients managed in the individual clinics. However, due to the network established in the clinics, supplementary ad hoc conferences are easily arranged, in case a patient needs care with a short notice. Furthermore, living with a life-long tumour pre-disposition and attending surveillance can be a heavy psychological burden for vHL patients/families, which can influence compliance. Surveillance examinations may be associated with anxiety regardless of the test result, as has been reported in other patients scanned for cancer (Bui et al., 2021). Similarly, patients have reported fear and worry associated with surveillance for vHL (Kasparian et al., 2015; Lammens et al., 2011), and one study found a significantly higher frequency of self-reported pre-test anxiety in patients who discontinued their surveillance program within the first 5 years after their vHL diagnosis (N = 36 vHL patients, of these 17 were asymptomatic at the time of genetic diagnosis) (Rasmussen et al., 2010).

We suggest using the MDT one-day clinic approach, as in our experience, patient and physician satisfaction as well as compliance to surveillance are higher compared to the clinical-coordinator approach. At the Nordic VHL symposium in 2019, surveillance approaches were discussed with patients. Through these discussions, it was clear that the vast majority of vHL patients, both those currently attending MDT one-day clinics and those that did not, preferred the one-day MDT clinic approach. Even though the patients/families attending the MDT one-day clinic face the risk of having to process several unpleasant test results on the same day, many expressed that the fewer hospital visits saved them both time and multiple periods with worry about test results. Consistently, more and more Danish vHL families opt for this surveillance approach. A British and a Korean study reported significantly higher compliance with surveillance in a MDT-like approach compared to a multiple visit approach (Fraser et al., 2007; Yoon et al., 2022). The clinical co-ordinator and MDT-approaches have not been directly compared in the Danish vHL cohort, however low compliance and wide regional variation in the recommended surveillance frequency before the MDT approach was introduced, were observed in two studies (Bertelsen and Kosteljanetz, 2010; Poulsen et al., 2010).

The surveillance recommendations are listed in Table 3. The recommendations apply for organs in which the individual does not have any manifestations. Once an organ is affected, a specific follow-up programme for this organ should be composed. Besides the routine surveillance examinations, symptoms which occur in between these, should reported to the MDT, and if relevant a targeted examination should be performed. Any positive findings should be reported to the relevant specialist.

The surveillance recommendations are age-dependent, as the frequency of new tumour development as well as the growth of existing tumours vary significantly with age (Lonser et al., 2014;Binderup et al., 2015b). In the Danish vHL cohort, new vHL tumours, regardless of type, developed at the highest rate in patients' thirties, corresponding to almost one new tumour every year (Binderup et al., 2015b).

## 9. Retinal hemangioblastoma

We recommend annual retinal inspection from as early an age as possible (Strong recommendation based on a moderate level of evidence).

In the Danish vHL cohort, a high frequency of these tumours was found in patients' childhood and teenage years (Binderup et al., 2015b; Launbjerg et al., 2017). A recent systematic review of the literature for paediatric patients diagnosed with vHL during childhood found that retinal hemangioblastoma was the most frequent type of manifestation to be diagnosed in childhood (34% of all the 99 reported paediatric patients)(Launbjerg et al., 2017). In the Danish cohort, retinal hemangioblastomas have been diagnosed in children as young as 6 years, and in other cohorts, patients as young as 2 years have been diagnosed with retinal hemangioblastomas (Kruizinga et al., 2014; Singh et al., 2001). Applying a mathematical model on a Dutch vHL cohort and based on a low frequency of retinal hemangioblastoma below the age of 7, it has been suggested that the starting age of retinal surveillance could be as high as 7 years of age (very low level of evidence)(Kruizinga et al., 2014). However, we and others suggest to start as early as possible due to the good accessibility and high acceptability by the patients of this assessment type (Hes et al., 2001; Rednam et al., 2017; TheAlliance, 2015). It may be difficult to examine young children (<3 years) thoroughly. However, since the frequency of retinal hemangioblastomas is low at an early age, indirect ophthalmoscopy is usually sufficient. If the examination of a child is difficult to perform, one could consider examining the child every six months. General anaesthesia for the sole purpose of opthalmoscopy is not recommended - however, if general anaesthesia is planned for the child for any reason, we suggest coordinating this with an ophthalmologic examination. Once the child can cooperate to Optos® photography, this may be the best option during childhood.

Retinal surveillance is important to ensure early diagnosis, as most smaller retinal hemangioblastomas can be treated successfully and with minimal risk of vision loss with photo coagulation, while they are still asymptomatic (Feletti et al., 2016). In the Danish vHL cohort (N = 52), we previously estimated that retinal inspection once a year was the most optimal frequency, as this was associated with a very low risk of symptomatic new retinal lesions (1.7%) in the period between two surveillance examinations (Poulsen et al., 2010).

Compliance to the annual examinations is especially crucial in patients' teenage years and twenties due to the high risk of new tumours in this period (Binderup et al., 2015b). In the Danish cohort (N = 52), the rate at which new retinal hemangioblastomas were diagnosed was highest from 15 years to patients' mid-twenties, corresponding to almost one new retinal tumour diagnosed every second year (Binderup et al., 2015a). Surveillance frequency could possibly be decreased later in life, as the rate of new retinal tumours after patients' thirties corresponds to about one new tumour every ten years (Binderup et al., 2015b). However, this conclusion is based on data from only 22 vHL patients over the age of 40 years, and further studies should be performed.

## 10. CNS hemangioblastoma

In childhood, we suggest annual paediatric examinations, which should include an age-adjusted neurological examination as well as assessment of growth parameters (Conditional recommendation based on low level of evidence). From the age of 15 years, annual neurological evaluation including systematic questioning about general health and any neurological symptoms are suggested (Conditional recommendation based on low level of evidence).

Indication for surgical treatment of CNS hemangioblastomas can be complex and should be based on specific symptoms and/or findings confirmed by imaging such as tumour location, growth rate, associated cyst formation, and total CNS tumour burden (Wind and Lonser, 2011). We therefore suggest that the neurological examinations performed at surveillance visits should be focused based on symptoms and/or imaging findings and not necessarily an extensive neurological examination.

We suggest a baseline MRI scan of the CNS at 10 years of age (Conditional recommendation based on low level of evidence). From the age of 15 years, we recommend MRI of the CNS every second year (Strong recommendation based on moderate level of evidence). As soon as a CNS lesion is diagnosed, the frequency of CNS surveillance should be designed on an individual basis by the neurologist or neurosurgeon.

The starting age of 10 years for a baseline scan is chosen on one hand to minimize the potential burden of performing MRI scans in young children, who may need general anaesthesia, while on the other hand to optimize the chance of identifying any asymptomatic CNS tumours that require treatment before 15 years of age, when the regular surveillance screening by CNS MRI is initiated. These recommendations are in line with those recently proposed in consensus statement by the CNS Subcommittee of the VHL Alliance Surveillance Guidelines Consortium

(Huntoon et al., 2021), with one exception for paediatric patients: In the asymptomatic patients the consensus statement recommends two MRIs before the age of 15 (at age 11 and 13). Instead, we suggest one MRI at the age of 10, to balance the risks and burden of performing MRI scans in young children, who may require general anaesthesia, with the chance of identifying an asymptomatic CNS tumour that may require treatment before 15 years of age, taking the low risk of asymptomatic CNS tumours needing treatment in childhood into consideration. Others have suggested even earlier start ages of regular MRIs of the CNS (Rednam et al., 2017) or later start ages (14–16 years) (Hes et al., 2001; Kruizinga et al., 2014; TheAlliance, 2015). In the Danish cohort, when only considering vHL patients and unaffected carriers of a clinically actionable *VHL* variant before 18 years of age, 30% (11 of 37) had at least one CNS hemangioblastoma diagnosed before 18 years (median age at diagnosis: 13 years (range: 6–17 years)). This corresponds to reported age at diagnosis among vHL patients with CNS hemangioblastoma in childhood in international vHL cohorts (median age: 14 years, range: 10–17 years (N = 16)) (Launbjerg et al., 2017). In the Danish cohort, neurosurgical treatment before the age of 15 years was indicated in three of the 11 patients with at least one CNS hemangioblastomas in childhood, one of these was asymptomatic at diagnosis.

A prospective American study including a selected group of vHL patients with at least one symptomatic CNS hemangioblastoma, found that new CNS tumour development was associated with a younger age as well as the tumour burden at age 20 years (Lonser et al., 2014). In the Danish vHL cohort, the rate of detection of a new cerebellar hemangioblastoma was found to increase during vHL patients' teenage years with a marked increase and the highest rates in patients' thirties to forties, corresponding to about one new cerebellar tumour every second year at 35–40 years of age. The consensus statement by the CNS Subcommittee of the VHL Alliance Surveillance Guidelines Consortium proposes that MRIs can be stopped at the age of 65 based on low level evidence of a reduced frequency of CNS hemangioblastomas in older vHL patients (Huntoon et al., 2021). However, consistent with the reduced mean life expectancy of vHL patients diagnosed in the previous decades, data did not allow for an accurate conclusion on the tumour development rate at later ages (Binderup et al., 2015b). Therefore, we suggest that CNS surveillance should be continued until comorbidity, life expectancy and/or the patient preferences indicate cessation (Conditional recommendation based on a very low level of evidence). Knowledge about vHL tumour development and growth in older vHL patients will likely be increased as the life expectancy improves among vHL patients (Binderup et al., 2017; Wang et al., 2018; Zhang et al., 2021).

## 11. Renal lesions (RCC and complex renal cysts)

For renal screening, imaging of the abdomen is recommended every second year from the age of 15 years (Strong recommendation based on moderate evidence level).

RCC rarely develops during childhood in patients with the vHL predisposition. In a study of manifestations in patients diagnosed and screened for vHL lesions in childhood (N = 99), no RCCs were diagnosed before the age of 18 years (Launbjerg et al., 2017). Nevertheless, in patients with vHL RCC has previously been reported as early as 16 years of age, while the mean age of RCC diagnosis is reported to be 37 years (Chahoud et al., 2020).

As an update of the previous edition of the Danish clinical vHL guideline, we have removed the recommendation of an ultrasound examination (US) of the abdomen every second year (Binderup et al., 2013). This was done mainly to limit the burden of multiple examinations for asymptomatic individuals with no known renal lesions. In a Danish study, we previously found a similar risk of having an abdominal lesion diagnosed in the period between surveillance examinations with abdominal imaging preformed every second year and annually (Poulsen et al., 2010). Due to the accuracy of MRI of the abdomen as well as better potential for evaluation in the MDT team, we now suggest MRI as the first line surveillance tool. MRI of the abdomen may be replaced by CT or US of abdomen in individual patients based on an assessment by a specialist. A systematic meta-analysis of renal surveillance in vHL by a group of experts from a VHL Alliance surveillance recommendations subcommittee recently evaluated the current vHL guidelines and the literature, and in line with our recommendations, evaluated MRI every second year from the age of 15 years to be the preferred approach in asymptomatic individuals (Chahoud et al., 2020). Once a renal lesion is diagnosed, a urologist should estimate of the nature and frequency of the patient's renal surveillance based on the characteristics, size and growth rate of the lesion (Chahoud et al., 2020).

## 12. Pancreatic lesions

From the age of 15 years, we recommend surveillance of the abdomen by contrast-enhanced MRI every second year (Strong recommendation based on moderate evidence level).

Pancreatic lesions are diagnosed in approximately two thirds of vHL patients. The majority of these lesions are benign cysts (simple pancreatic cysts and serous cystadenomas) (Hammel et al., 2000). These cystic lesions are generally asymptomatic and the cysts do not require treatment unless they cause pancreatitis, or result in bile duct compression and exocrine dysfunction (Hammel et al., 2000). PNETs are seen in about 11% of patients with vHL and the mean age at diagnosis is between 30 and 39 years (Supplementary Table 1). Because PNETs in vHL most often are non-functioning and have a malignant potential, early diagnosis is crucial. PNETs rarely develop during childhood although PNET has been reported as early as 16 years of age in vHL patients (Blansfield et al., 2007). Our recommendations are in line with a recent consensus statement from the Pancreatic Manifestation Subcommittee of the VHL Alliance Surveillance Guidelines Consortium who recommend gadolinium enhanced MRI every second year from of the age of 15 (Laks et al., 2021), and with most previous vHL surveillance guidelines (Kruizinga et al., 2014; TheAlliance, 2015), although some have proposed even lower starting ages of regular abdominal imaging (Hes et al., 2001; Rednam et al., 2017). In the previous edition of this guideline, we recommended measurement of plasma-chromogranin A (Binderup et al., 2013). In the present edition we have removed the recommendation of chromogranin A use due to lack of evidence for a predictive value.

The Pancreatic Manifestation Subcommittee of the VHL Alliance Surveillance Guidelines Consortium recommends cessation of abdominal surveillance at the age of 65 years, in patients that has shown no sign of pancreatic tumours based on median level evidence of low frequency among older vHL patients (Laks et al., 2021). With the same arguments as for CNS tumours, we suggest that surveillance continue until comorbidity and/or life expectancy indicates this, or the individual prefers to stop (Conditional recommendation based on a very low level of evidence).

## 13. Pheochromocytoma, paraganglioma

In addition to the imaging of the abdomen, we suggest annual measurement of plasma-metanephrine and plasma-normetanephrine from 5 years of age (Strong recommendation based on a moderate level of evidence)

In individuals with fear of needles, urine-catecholamines can be measured instead. This corresponds with most other surveillance recommendations (Hes et al., 2001; Rednam et al., 2017; TheAlliance, 2015). A Dutch group indicate that biochemical surveillance for pheochromocytomas may be initiated as early as 0 years of age, mainly based on case reports of pheochromocytoma development before the age of 5 years (very low level evidence) (Kruizinga et al., 2014). In individuals with, or predisposed for, vHL, pheochromocytomas are especially prevalent in childhood, but may occur throughout life. The mean age of onset reported in vHL cohorts is 20–29 years (Supplementary Table 1).

In the Danish cohort, when only considering patients diagnosed with vHL or known to be at risk due to a clinically actionable *VHL* variant before 18 years of age, 18% (11 of 37; median age of diagnosis: 13 years, range: 8–15 years) had at least one pheochromocytoma diagnosed before 18 years, which corresponded to the frequency diagnosed in pediatric vHL patients reported in the literature (Launbjerg et al., 2017).

In patients with indications of a lesion, relevant functional imaging should be performed as part of the diagnostic work-up.

## 14. Endolymphatic sac tumours

In adults, we recommend thin-slice MRI of the inner ear, which is recommended to be performed as part of the MRI of the CNS (strong recommendation based on a moderate level of evidence). In addition, we suggest a hearing examination every second year (conditional recommendation based on low level of evidence). Although MRI is a gold standard for ELST screening, there are strong indications that a characteristic low-frequency hearing loss demonstrated by audiometry correlates to ELST development at early stages, even before the patient experiences subjective symptoms (Poulsen et al., 2011).

Early diagnosis of ELSTs is crucial: Surgical resection is indicated even for small asymptomatic ELSTs, as these may cause sudden and irreversible hearing loss (Wind and Lonser, 2011). In children, in whom regular CNS imaging is not routinely performed, we suggest annual hearing examination.

In a recent consensus statement from a the ELST Subcommittee of the VHL Alliance Surveillance Guidelines Consortium, ELST surveillance was recommended to start at the age of 10 and end at the age of 60 (Mehta et al., 2021). We acknowledge that our recommendations are not substantiated by evidence that the surveillance will reduce morbidity or mortality. However, in the lack of knowledge about which age interval is optimal, and acknowledging that the feasibility of surveillance in other countries may suggest something else, we will continue our suggestion that hearing examinations are started at age 5, as this examination is without side effects, and feasible in Denmark. As for a the age at cessation, we suggest that until we have more valid data on the frequency of ELST in elderly people, the surveillance is continued until comorbidity, life expectancy or the individual's preferences indicates cessation.

## 15. Surveillance in relation to pregnancy

Several studies have investigated the effect of pregnancy on vHL manifestation development, with conflicting results (Binderup et al., 2015a; Frantzen et al., 2012; Ye et al., 2012). Case reports and one cohort study (N = 12 pregnancies in vHL patients) have described increased growth of CNS hemangioblastoma during pregnancy (Frantzen et al., 2012), and intensified surveillance during pregnancy has been included in some surveillance recommendations (TheAlliance, 2015). Both one prospective study (N = 36 female vHL patients) (Ye et al., 2012) and we found no indications that pregnancy aggravated tumour development (Binderup et al., 2015a). Neither of the two studies of pregnancy effect in vHL cohorts published in 2012 took the age of the studied females into consideration and both studies had short follow-up periods (mean 18.7 and 18.4 months after delivery) (Frantzen et al., 2012; Ye et al., 2012). Our study of the Danish cohort is the only study to include an age-matched control group, as we compared tumour risk in pregnancy with age-matched non-pregnant periods in the same female cohort (Binderup et al., 2015a), and we studied the potential long-term effect of pregnancy for up to 5 years after conception (Binderup et al., 2015a). We actually found the rate of tumour development to be lower during and following pregnancy compared to age-matched controls, even when controlling for the women's genotype and tumour burden before twenty years of age (Binderup et al., 2015a). Based on these results, we do not suggest intensified surveillance during pregnancy (conditional recommendation based on a low level of evidence). A

**Table 4**
**Overview of treatment strategies for vHL manifestations.**

| Manifestation | Most commonly used treatment strategy and methods |
|---|---|
| **Retinal hemangioblastomas** | Most extrapapillary and small retinal hbs can be treated with laser photocoagulation. For hbs which are juxtapapillary, large, or refractory to photocoagulation, the treatment approach should be chosen taking the risk of vision loss and the risk of associated sequelae into consideration (Wiley et al., 2019). |
| **CNS hemangioblastomas** | Surgical removal is the main treatment for CNS hbs. The surgical approach and the timing of surgery depends on multiple factors, especially the tumour location, tumour size, growth rate, and symptom development (Wind and Lonser, 2011). Belzutifan could be considered (Jonasch et al., 2021). |
| **Endolymphatic sac tumour (ELST)** | Surgical resection is the main treatment for ELST. As even small and asymptomatic ELST can cause sudden and irreversible hearing loss, resection is recommended for ELSTs of all sizes at the time of diagnosis (Wind and Lonser, 2011). |
| **Renal lesions** | |
| Renal cysts | In vHL patients, apparently simple cysts may contain malignant characteristics in the wall. Thus, simple cysts as well as solid tumours should undergo active surveillance. Typically, both cysts and tumours are multiple, bilateral and recurring after treatment; thus nephron sparing treatment is currently considered the standard treatment ( Bausch et al., 2013). |
| Renal tumours | To reduce the number of times a kidney is operated on, indications for surgery should be considered very carefully. A correlation between tumour size and risk for spread is well documented in vHL, and active surveillance is therefore recommended for RCCs less than 3 cm in diameter. When a tumour grows larger, intervention should be considered. Even if the RCC is larger than this size, nephron sparing treatment should always be considered whenever technically feasible. Only if no functional capacity remains, radical nephrectomy should be performed (Bausch et al., 2013). Belzutifan could be considered (Jonasch et al., 2021). |
| **Pancreas neuroendocrine tumours (PNET)** | PNETs must be evaluated in a dedicated NET MDT. Surgical resection of PNET in vHL patients should be considered in the case of tumours > 2–3 cm and in the case of growth in smaller tumours (Falconi et al., 2016). Medical treatment should follow the guidelines for non-functioning PNETs. Patients with disseminated disease, NET grade 1 and 2 and Ki67 index <10% can be treated with somatostatin analogues. Patients with disseminated disease, NET grade 2 (Ki67 10–20%) may be treated with everolimus, sunitinib, temozolomide + capecitabine or streptozotocin + 5FU. Patients with NET grade 3 and patients with neuroendocrine carcinomas (NEC - Ki67 > 20%) should be offered treatment with carboplatin + etoposide or temozolomide + capecitabine. Radionuclide treatment should be offered to patients with grade 1–3 NETs with progression after first/second line treatment and high uptake at somatostatin receptor imaging ( Pavel et al., 2016). Belzutifan could be considered (Jonasch et al., 2021). |
| **Pheochromocytoma/ paraganglioma** | Surgical resection after medical treatment with α-blocker (Lenders et al., 2014). If relevant, partial adrenalectomy should be discussed with the patient. After partial adrenalectomy, recurrence rate is 10–15% (Lenders et al., 2014). Radionuclide treatment should be considered in patients with inoperable metastases (Jasim and Jimenez, 2020). |

recent consensus statement from the CNS Subcommittee of the VHL Alliance Surveillance Guidelines Consortium recommend MRI of the CNS prior to any planned pregnancy in a female vHL patient, as consistent surveillance during pregnancy may not be feasible; however in line with us, the subcommittee did not find evidence to support intensified surveillance during pregnancy (Huntoon et al., 2021).

## 16. Treatment of vHL manifestations

Surgical removal is the cornerstone in the treatment of most vHL tumours to minimize the risk of sequelae. The timing of surgery and choice of surgical method vary with clinical presentation, tumour location, and any concurrent tumours the patient may have in the same organ/area. Although now approved by the FDA, the appropriate use of belzutifan in patients with vHL remains to be determined (Jonasch et al., 2021). For each diagnosed manifestation, a specific clinical and/or imaging follow-up programme should be planned to allow for the most optimal treatment planning. Table 4 gives an overview of the most frequently used treatment methods for various manifestations. We refer to speciality-specific literature for more detailed descriptions of the treatments.

CNS: Central Nervous System; hbs: hemangioblastomas; MDT: MultiDisciplinary Team; NEC: Neuroendocrine carcinoma; PNET: Pancreatic Neuroendocrine Tumour; RCC: Renal Cell Carcinoma; 5-FU: Fluorouracil.

In recent years, there has been an increased focus on the development of systemic treatment for vHL manifestations. Drugs evaluated and approved for metastatic RCC, VEGF receptor inhibitors such as sunitinib or pazopanib, have been used in patients with vHL manifestations with only limited effect (Glasker et al., 2020). The non-selective β-blocker propanolol has been designated as an orphan drug to treat retinal hemangioblastomas in vHL patients, after a phase III clinical trial found retinal lesions to remain stable in number and size during propanolol treatment in a small number vHL patients (Gonzalez-Rodriguez et al., 2019). Recently, the understanding of accumulation of hypoxia-inducible factor 2α (HIF2α) within the cell as a result of VHL inactivation has led to the development of the HIF-2α inhibitor drug belzutifan (previously known as PT2977 or MK6482) (Yu et al., 2019). Belzutifan was approved by the FDA in 2021 for treatment of adult patients with vHL associated RCC, CNS hemangioblastomas, or PNETs, not requiring immediate surgery. The approval was based on a pivotal phase II trial of 61 patients with vHL-associated RCC, with a *VHL* germline variant and with at least one measurable solid tumour localized to the kidney (Jonasch et al., 2021). Patients received belzutifan 120 mg once daily until disease progression or unacceptable toxicity. After a median follow-up of 21.8 months (range, 20.2 to 30.1), the percentage of patients with renal cell carcinoma who had an objective response was 49% (95% confidence interval, 36 to 62). Responses were also observed in patients with pancreatic lesions (47 of 61 patients [77%]) and CNS hemangioblastomas (15 of 50 patients [30%]). Among the 16 eyes that could be evaluated in 12 patients with retinal hemangioblastomas at baseline, all (100%) were graded as showing improvement. The most common adverse events were anemia, fatigue, headache, dizziness, and nausea; anemia and hypoxia could be severe (Jonasch et al., 2021).

## Funding sources

This work was not financially supported by external sources.

## Declaration of competing interest

Dr. Binderup has been employed by H. Lundbeck A/S from 1. September 2019 to present. The employment is unrelated to the present work. The other authors declare no conflicts of interest.

## Acknowledgements

This work represents a joint effort of the national von Hippel-Lindau coordination group in Denmark. We especially would like to acknowledge the great ongoing collaboration between the coordination group and the Danish association for vHL patients and their families to ensure optimized guidelines for vHL management. We thank the many vHL families who participate in ongoing national research in the Danish vHL cohort. Aarhus Universitetshospital, Odense Universitetshospital and Rigshospitalet Copenhagen are Affiliated Partners of the European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS, https://www.genturis.eu/). This guideline has been endorsed by the European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS), Project ID No 739547. ERN GENTURIS is partly co-funded by the European Union within the framework of the Third Health Programme "ERN-2016—Framework Partnership Agreement 2017–2021".

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2022.104538.

## References

Andersen, M.K., Bisgaard, M.L., Brandt, C., Friis-Hansen, L., Gerdes, A.M., Harbud, V., Kjærgaard, S., Kosteljanetz, M., Rosenberg, T., Schwartz, M., Sunde, L., 2005. Von Hippel-Lindaus Reference Program Vedr. Udredning Og Kontrol. Ugeskr Laeger version 2.0.

Bausch, B., Jilg, C., Glasker, S., Vortmeyer, A., Lutzen, N., Anton, A., Eng, C., Neumann, H.P., 2013. Renal cancer in von Hippel-Lindau disease and related syndromes. Nat. Rev. Nephrol. 9 (9), 529–538.

Bertelsen, M., Kosteljanetz, M., 2010. An Evaluation of the Danish National Clinical Guidelines for Von Hippel-Lindau (VHL), , 1st153. Acta Neurochir, Wien, pp. 35–41.

Binderup, M.L., Bisgaard, M.L., Harbud, V., Moller, H.U., Gimsing, S., Friis-Hansen, L., Hansen, T., Bagi, P., Knigge, U., Kosteljanetz, M., Bogeskov, L., Thomsen, C., Gerdes, A.M., Ousager, L.B., Sunde, L., 2013. Von Hippel-Lindau disease (vHL). National clinical guideline for diagnosis and surveillance in Denmark. Dan Med J 60 (12), B4763, 3rd edition.

Binderup, M.L., Budtz-Jorgensen, E., Bisgaard, M.L., 2015a. New von Hippel-Lindau manifestations develop at the same or decreased rates in pregnancy. Neurology 85 (17), 1500–1503.

Binderup, M.L., Budtz-Jorgensen, E., Bisgaard, M.L., 2015b. Risk of new tumors in von Hippel-Lindau patients depends on age and genotype. Genet. Med. 18 (1), 89–97.

Binderup, M.L., Galanakis, M., Budtz-Jorgensen, E., Kosteljanetz, M., Luise, B.M., 2016. Prevalence, birth incidence, and penetrance of von Hippel-Lindau disease (vHL) in Denmark. Eur. J. Hum. Genet. 25 (3), 301–307. https://doi.org/10.1038/ejhg.2016.173.

Binderup, M.L., Jensen, A.M., Budtz-Jorgensen, E., Bisgaard, M.L., 2017. Survival and causes of death in patients with von Hippel-Lindau disease. J. Med. Genet. 54 (1), 11–18. https://doi.org/10.1136/jmedgenet-2016-104058.

Binderup, M.L.M., 2018. von Hippel-Lindau disease: diagnosis and factors influencing disease outcome. Dan Med J 65 (3).

Blansfield, J.A., Choyke, L., Morita, S.Y., Choyke, P.L., Pingpank, J.F., Alexander, H.R., Seidel, G., Shutack, Y., Yuldasheva, N., Eugeni, M., Bartlett, D.L., Glenn, G.M., Middelton, L., Linehan, W.M., Libutti, S.K., 2007. Clinical, genetic and radiographic analysis of 108 patients with von Hippel-Lindau disease (VHL) manifested by pancreatic neuroendocrine neoplasms (PNETs). Surgery 142 (6), 814–818.

Bui, K.T., Liang, R., Kiely, B.E., Brown, C., Dhillon, H.M., Blinman, P., 2021. Scanxiety: a scoping review about scan-associated anxiety. BMJ Open 11 (5), e043215.

Cascon, A., Escobar, B., Montero-Conde, C., Rodriguez-Antona, C., Ruiz-Llorente, S., Osorio, A., Mercadillo, F., Leton, R., Campos, J.M., Garcia-Sagredo, J.M., Benitez, J., Malumbres, M., Robledo, M., 2007. Loss of the actin regulator HSPC300 results in clear cell renal cell carcinoma protection in Von Hippel-Lindau patients. Hum. Mutat. 28 (6), 613–621.

Chahoud, J., McGettigan, M., Parikh, N., Boris, R.S., Iliopoulos, O., Rathmell, W.K., Daniels, A.B., Jonasch, E., Spiess, P.E., 2020. Evaluation, diagnosis and surveillance of renal masses in the setting of VHL disease. World J. Urol. 39 (7), 2409–2415.

Cybulski, C., Krzystolik, K., Murgia, A., Gorski, B., Debniak, T., Jakubowska, A., Martella, M., Kurzawski, G., Prost, M., Kojder, I., Limon, J., Nowacki, P., Sagan, L., Bialas, B., Kaluza, J., Zdunek, M., Omulecka, A., Jaskolski, D., Kostyk, E., Koraszewska-Matuszewska, B., Haus, O., Janiszewska, H., Pecold, K., Starzycka, M., Slomski, R., Cwirko, M., Sikorski, A., Gliniewicz, B., Cyrylowski, L., Fiszer-Maliszewska, L., Gronwald, J., Toloczko-Grabarek, A., Zajaczek, S., Lubinski, J., 2002. Germline mutations in the von Hippel-Lindau (VHL) gene in patients from Poland: disease presentation in patients with deletions of the entire VHL gene. J. Med. Genet. 39 (7), E38.

Decker, J., Neuhaus, C., MacDonald, F., Brauch, H., Maher, E.R., 2014. Clinical utility gene card for: von Hippel-Lindau (VHL). Eur. J. Hum. Genet. 22 (4).
Evans, D.G., Howard, E., Giblin, C., Clancy, T., Spencer, H., Huson, S.M., Lalloo, F., 2010. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am. J. Med. Genet. 152A (2), 327–332.
Falconi, M., Eriksson, B., Kaltsas, G., Bartsch, D.K., Capdevila, J., Caplin, M., Kos-Kudla, B., Kwekkeboom, D., Rindi, G., Kloppel, G., Reed, N., Kianmanesh, R., Jensen, R.T., 2016. ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. Neuroendocrinology 103 (2), 153–171.
Feletti, A., Anglani, M., Scarpa, B., Schiavi, F., Boaretto, F., Zovato, S., Taschin, E., Gardi, M., Zanoletti, E., Piermarocchi, S., Murgia, A., Pavesi, G., Opocher, G., 2016. Von Hippel-Lindau disease: an evaluation of natural history and functional disability. Neuro Oncol. 18 (7), 1011–1020.
Franke, G., Bausch, B., Hoffmann, M.M., Cybulla, M., Wilhelm, C., Kohlhase, J., Scherer, G., Neumann, H.P., 2009. Alu-Alu recombination underlies the vast majority of large VHL germline deletions: molecular characterization and genotype-phenotype correlations in VHL patients. Hum. Mutat. 30 (5), 776–786.
Frantzen, C., Kruizinga, R.C., van Asselt, S.J., Zonnenberg, B.A., Lenders, J.W., de Herder, W.W., Walenkamp, A.M., Giles, R.H., Hes, F.J., Sluiter, W.J., van Pampus, M. G., Links, T.P., 2012. Pregnancy-related hemangioblastoma progression and complications in von Hippel-Lindau disease. Neurology 79 (8), 793–796.
Fraser, L., Watts, S., Cargill, A., Sutton, S., Hodgson, S., 2007. Study comparing two types of screening provision for people with von Hippel-Lindau disease. Fam. Cancer 6 (1), 103–111.
Glasker, S., Bender, B.U., Apel, T.W., Natt, E., van, V., V, Scheremet, R., Zentner, J., Neumann, H.P., 1999. The impact of molecular genetic analysis of the VHL gene in patients with haemangioblastomas of the central nervous system. J. Neurol. Neurosurg. Psychiatry 67 (6), 758–762.
Glasker, S., Vergauwen, E., Koch, C.A., Kutikov, A., Vortmeyer, A.O., 2020. Von hippel-lindau disease: current challenges and future prospects. OncoTargets Ther. 13, 5669–5690.
Gonzalez-Rodriguez, B., Gomez de Las Heras, Villar, Aguirre, D.T., Rodriguez-Padial, L., Albinana, V., Recio-Poveda, L., Cuesta, A.M., Botella, L.M., Jimenez-Escribano, R.M., 2019. Evaluation of the safety and effectiveness of oral propranolol in patients with von Hippel-Lindau disease and retinal hemangioblastomas: phase III clinical trial. BMJ Open Ophthalmol. 4 (1), e000203.
Gossage, L., Eisen, T., Maher, E.R., 2015. VHL, the story of a tumour suppressor gene. Nat. Rev. Cancer 15 (1), 55–64.
Guyatt, G.H., Oxman, A.D., Vist, G.E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., Schunemann, H.J., 2008. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336 (7650), 924–926.
Hammel, P.R., Vilgrain, V., Terris, B., Penfornis, A., Sauvanet, A., Correas, J.M., Chauveau, D., Balian, A., Beigelman, C., O'Toole, D., Bernades, P., Ruszniewski, P., Richard, S., 2000. Pancreatic involvement in von Hippel-Lindau disease. The Groupe Francophone d'Etude de la Maladie de von Hippel-Lindau. Gastroenterology 119 (4), 1087–1095.
Hes, F.J., Hoppener, J.W., Luijt, R.B., Lips, C.J., 2005. Von hippel-lindau disease. Hered. Cancer Clin. Pract. 3 (4), 171–178.
Hes, F.J., van der Luijt, R.B., Janssen, A.L., Zewald, R.A., de Jong, G.J., Lenders, J.W., Links, T.P., Luyten, G.P., Sijmons, R.H., Eussen, H.J., Halley, D.J., Lips, C.J., Pearson, P.L., van den Ouweland, A.M., Majoor-Krakauer, D.F., 2007. Frequency of Von Hippel-Lindau germline mutations in classic and non-classic Von Hippel-Lindau disease identified by DNA sequencing, Southern blot analysis and multiplex ligation-dependent probe amplification. Clin. Genet. 72 (2), 122–129.
Hes, F.J., van der Luijt, R.B., Lips, C.J., 2001. Clinical management of von hippel-lindau (VHL) disease. Neth. J. Med. 59 (5), 225–234.
Huntoon, K., Shepard, M.J., Lukas, R.V., McCutcheon, I.E., Daniels, A.B., Asthagiri, A.R., 2021. Hemangioblastoma diagnosis and surveillance in von Hippel-Lindau disease: a consensus statement. J. Neurosurg. 1–6.
Jasim, S., Jimenez, C., 2020. Metastatic pheochromocytoma and paraganglioma: management of endocrine manifestations, surgery and ablative procedures, and systemic therapies. Best Pract. Res. Clin. Endocrinol. Metabol. 34 (2), 101354.
Jonasch, E., Donskov, F., Iliopoulos, O., Rathmell, W.K., Narayan, V.K., Maughan, B.L., Oudard, S., Else, T., Maranchie, J.K., Welsh, S.J., Thamake, S., Park, E.K., Perini, R. F., Linehan, W.M., Srinivasan, R., 2021. Belzutifan for renal cell carcinoma in von Hippel-lindau disease. N. Engl. J. Med. 385 (22), 2036–2046.
Kasparian, N.A., Rutstein, A., Sansom-Daly, U.M., Mireskandari, S., Tyler, J., Duffy, J., Tucker, K.M., 2015. Through the looking glass: an exploratory study of the lived experiences and unmet needs of families affected by Von Hippel-Lindau disease. Eur. J. Hum. Genet. 23 (1), 34–40.
Kruizinga, R.C., Sluiter, W.J., de Vries, E.G., Zonnenberg, B.A., Lips, C.J., van der Horst-Schrivers, A.N., Walenkamp, A.M., Links, T.P., 2014. Calculating optimal surveillance for detection of von Hippel-Lindau-related manifestations. Endocr. Relat. Cancer 21 (1), 63–71.
Laks, S., van, L.R., Patel, D., Keutgen, X.M., Hammel, P., Nilubol, N., Links, T.P., Halfdanarson, T.R., Daniels, A.B., Tirosh, A., 2021. Management recommendations for pancreatic manifestations of von Hippel-Lindau disease. Cancer.
Lammens, C.R., Aaronson, N.K., Hes, F.J., Links, T.P., Zonnenberg, B.A., Lenders, J.W., Majoor-Krakauer, D., Van Os, T.A., Gomez-Garcia, E.B., de, H.W., van der Luijt, R.B., van den Ouweland, A.M., Van Hest, L.P., Verhoef, S., Bleiker, E.M., 2011. Compliance with periodic surveillance for Von-Hippel-Lindau disease. Genet. Med. 13 (6), 519–527.
Launbjerg, K., Bache, I., Galanakis, M., Bisgaard, M.L., Binderup, M.L.M., 2017. von Hippel-Lindau development in children and adolescents. Am. J. Med. Genet. 173 (9), 2381–2394.
Lenders, J.W., Duh, Q.Y., Eisenhofer, G., Gimenez-Roqueplo, A.P., Grebe, S.K., Murad, M. H., Naruse, M., Pacak, K., Young Jr., W.F., 2014. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. 99 (6), 1915–1942.
Lonser, R.R., Butman, J.A., Huntoon, K., Asthagiri, A.R., Wu, T., Bakhtian, K.D., Chew, E. Y., Zhuang, Z., Linehan, W.M., Oldfield, E.H., 2014. Prospective natural history study of central nervous system hemangioblastomas in von Hippel-Lindau disease. J. Neurosurg. 120 (5), 1055–1062.
Lonser, R.R., Glenn, G.M., Walther, M., Chew, E.Y., Libutti, S.K., Linehan, W.M., Oldfield, E.H., 2003. von Hippel-Lindau disease. Lancet 361 (9374), 2059–2067.
Maddock, I.R., Moran, A., Maher, E.R., Teare, M.D., Norman, A., Payne, S.J., Whitehouse, R., Dodd, C., Lavin, M., Hartley, N., Super, M., Evans, D.G., 1996. A genetic register for von Hippel-Lindau disease. J. Med. Genet. 33 (2), 120–127.
Maher, E.R., Iselius, L., Yates, J.R., Littler, M., Benjamin, C., Harris, R., Sampson, J., Williams, A., Ferguson-Smith, M.A., Morton, N., 1991. Von Hippel-Lindau disease: a genetic study. J. Med. Genet. 28 (7), 443–447.
Maher, E.R., Neumann, H.P., Richard, S., 2011. von Hippel-Lindau disease: a clinical and scientific review. Eur. J. Hum. Genet. 19 (6), 617–623.
Maranchie, J.K., Afonso, A., Albert, P.S., Kalyandrug, S., Phillips, J.L., Zhou, S., Peterson, J., Ghadimi, B.M., Hurley, K., Riss, J., Vasselli, J.R., Ried, T., Zbar, B., Choyke, P., Walther, M.M., Klausner, R.D., Linehan, W.M., 2004. Solid renal tumor severity in von Hippel Lindau disease is related to germline deletion length and location. Hum. Mutat. 23 (1), 40–46.
McNeill, A., Rattenberry, E., Barber, R., Killick, P., MacDonald, F., Maher, E.R., 2009. Genotype-phenotype correlations in VHL exon deletions. Am. J. Med. Genet. 149A (10), 2147–2151.
Melmon, K.L., ROSEN, S.W., 1964. LINDAU'S disease. Review of the literature and study of a large kindred. Am. J. Med. 36, 595–617.
Mehta, G.U., Kim, H.J., Gidley, P.W., Daniels, A.B., Miller, M.E., Lekovic, G.P., Butman, J.A., Russel, R.L., 2021. Endolymphatic sac tumor screening and diagnosis in von Hippel-lindau disease: a consensus statement. J Neurol Surg B.
Moller, H.U., 1930. Familiær Angiomatosis retinae et cerebelli -Lindau's Sygdom. Ugeskr Laeger 92 (16), 379–384.
Moller, P.M., 1952. Another family with von Hippel-Lindau's disease. Acta Ophthalmol. 30 (2).
Neumann, H.P., Wiestler, O.D., 1991. Clustering of features of von Hippel-Lindau syndrome: evidence for a complex genetic locus. Lancet 337 (8749), 1052–1054.
Nordstrom-O'Brien, M., van der Luijt, R.B., van, R.E., van den Ouweland, A.M., Majoor-Krakauer, D.F., Lolkema, M.P., van, B.A., Voest, E.E., Giles, R.H., 2010. Genetic analysis of von Hippel-Lindau disease. Hum. Mutat. 31 (5), 521–537.
Pavel, M., O'Toole, D., Costa, F., Capdevila, J., Gross, D., Kianmanesh, R., Krenning, E., Knigge, U., Salazar, R., Pape, U.F., Oberg, K., 2016. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. Neuroendocrinology 103 (2), 172–185.
Poulsen, M.L., Budtz-Jorgensen, E., Bisgaard, M.L., 2010. Surveillance in von Hippel-Lindau disease (vHL). Clin. Genet. 77 (1), 49–59.
Poulsen, M.L., Gimsing, S., Kosteljanetz, M., Moller, H.U., Brandt, C.A., Thomsen, C., Bisgaard, M.L., 2011. von Hippel-Lindau disease: surveillance strategy for endolymphatic sac tumors. Genet. Med. 13 (12), 1032–1041.
Rasmussen, A., Alonso, E., Ochoa, A., De, B., I Familiar, I., Yescas, P., Sosa, A.L., Rodriguez, Y., Chavez, M., Lopez-Lopez, M., Bidichandani, S.I., 2010. Uptake of genetic testing and long-term tumor surveillance in von Hippel-Lindau disease. BMC Med. Genet. 11, 4.
Rednam, S.P., Erez, A., Druker, H., Janeway, K.A., Kamihara, J., Kohlmann, W.K., Nathanson, K.L., States, L.J., Tomlinson, G.E., Villani, A., Voss, S.D., Schiffman, J.D., Wasserman, J.D., 2017. Von hippel-lindau and hereditary pheochromocytoma/paraganglioma syndromes: clinical features, genetics, and surveillance recommendations in childhood. Clin. Cancer Res. 23 (12), e68–e75.
Richards, C.S., Bale, S., Bellissimo, D.B., Das, S., Grody, W.W., Hegde, M.R., Lyon, E., Ward, B.E., 2008. ACMG recommendations for standards for interpretation and reporting of sequence variations: revisions 2007. Genet. Med. 10 (4), 294–300.
Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W.W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., Rehm, H.L., 2015. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of medical genetics and genomics and the association for molecular Pathology. Genet. Med. 17 (5), 405–424.
Salama, Y., Albanyan, S., Szybowska, M., Bullivant, G., Gallinger, B., Giles, R.H., Asa, S., Badduke, C., Chiorean, A., Druker, H., Ezzat, S., Hannah-Shmouni, F., Hernandez, K. G., Inglese, C., Jani, P., Kaur, Y., Krema, H., Krimus, L., Laperriere, N., Lichner, Z., Mete, O., Sit, M., Zadeh, G., Jewett, M.A.S., Malkin, D., Stockley, T., Wasserman, J. D., Xu, W., Schachter, N.F., Kim, R.H., 2019. Comprehensive characterization of a Canadian cohort of von Hippel-lindau disease patients. Clin. Genet.
Sgambati, M.T., Stolle, C., Choyke, P.L., Walther, M.M., Zbar, B., Linehan, W.M., Glenn, G.M., 2000. Mosaicism in von Hippel-Lindau disease: lessons from kindreds with germline mutations identified in offspring with mosaic parents. Am. J. Hum. Genet. 66 (1), 84–91.
Singh, A.D., Nouri, M., Shields, C.L., Shields, J.A., Smith, A.F., 2001. Retinal capillary hemangioma: a comparison of sporadic cases and cases associated with von Hippel-Lindau disease. Ophthalmology 108 (10), 1907–1911.
The VHL Alliance, 2015. The VHL Handbook 5. Edition.
Wang, J.Y., Peng, S.H., Li, T., Ning, X.H., Liu, S.J., Hong, B.A., Liu, J.Y., Wu, P.J., Zhou, B.W., Zhou, J.C., Qi, N.N., Peng, X., Zhang, J.F., Ma, K.F., Cai, L., Gong, K., 2018. Risk factors for survival in patients with von Hippel-Lindau disease. J. Med. Genet. 55 (5), 322–328.

Wang, J.Y., Peng, S.H., Ning, X.H., Li, T., Liu, S.J., Liu, J.Y., Hong, B.A., Qi, N.N., Peng, X., Zhou, B.W., Zhang, J.F., Cai, L., Gong, K., 2017. Shorter telomere length increases age-related tumor risks in von Hippel-Lindau disease patients. Cancer Med. 6 (9), 2131–2141.

Wiley, H.E., Krivosic, V., Gaudric, A., Gorin, M.B., Shields, C., Shields, J., Aronow, M.E., Chew, E.Y., 2019. Management of retinal hemangioblastoma IN VON hippel-lindau disease. Retina 39 (12), 2254–2263.

Wind, J.J., Lonser, R.R., 2011. Management of von Hippel-Lindau disease-associated CNS lesions. Expert Rev. Neurother. 11 (10), 1433–1441.

Ye, D.Y., Bakhtian, K.D., Asthagiri, A.R., Lonser, R.R., 2012. Effect of pregnancy on hemangioblastoma development and progression in von Hippel-Lindau disease. J. Neurosurg. 117 (5), 818–824.

Yoon, S.J., Kwon, W.K., Hong, G., Jang, J.H., Jeong, B.C., Kim, J.H., Kim, J.W., 2022. Genetic counseling and long-term surveillance using a multidisciplinary approach in von Hippel-lindau disease. Ann. Lab. Med. 42 (3), 352–357.

Yu, Y., Yu, Q., Zhang, X., 2019. Allosteric inhibition of HIF-2alpha as a novel therapy for clear cell renal cell carcinoma. Drug Discov. Today 24 (12), 2332–2340.

Zhang, K., Qiu, J., Yang, W., Ma, K., Li, L., Xie, H., Xu, Y., Gong, Y., Zhou, J., Cai, L., Gong, K., 2021. Clinical characteristics and risk factors for survival in affected offspring of von Hippel-Lindau disease patients. J. Med. Genet.