AMERICAN ACADEMY OF OPHTHALMOLOGY®

Consensus Guidelines for Ocular Surveillance of von Hippel-Lindau Disease

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Purpose: To develop guidelines for ocular surveillance and early intervention for individuals with von Hippel-Lindau (VHL) disease.

Design: Systematic review of the literature.

Participants: Expert panel of retina specialists and ocular oncologists.

Methods: A consortium of experts on clinical management of all-organ aspects of VHL disease was convened. Working groups with expertise in organ-specific features of VHL disease were tasked with development of evidence-based guidelines for each organ system. The ophthalmology subcommittee formulated questions for consideration and performed a systematic literature review. Evidence was graded for topic quality and relevance and the strength of each recommendation, and guideline recommendations were developed.

Results: The quality of evidence was limited, and no controlled clinical trial data were available. Consensus guidelines included: (1) individuals with known or suspected VHL disease should undergo periodic ocular screening (evidence type, III; evidence strength, C; degree of consensus, 2A); (2) patients at risk of VHL disease, including first-degree relatives of patients with known VHL disease, or any patient with single or multifocal retinal hemangioblastomas (RHs), should undergo genetic testing for pathologic VHL disease gene variants as part of an appropriate medical evaluation (III/C/2A); (3) ocular screening should begin within 12 months after birth and continue throughout life (III/C/2A); (4) ocular screening should occur approximately every 6 to 12 months until 30 years of age and then at least yearly thereafter (III/C-D/2A); (5) ocular screening should be performed before a planned pregnancy and every 6 to 12 months during pregnancy (IV/D/2A); (6) ultra-widefield color fundus photography may be helpful in certain circumstances to monitor RHs, and ultra-widefield fluorescein angiography may be helpful in certain circumstances to detect small RHs (IV/D/2A); (7) patients should be managed, whenever possible, by those with subspecialty training, with experience with VHL disease or RHs, or with both and ideally within the context of a multidisciplinary center capable of providing multiorgan surveillance and access to genetic testing (IV/D/2A); (8) extramacular or extrapapillary RHs should be treated promptly (III/C/2A).

Conclusions: Based on available evidence from observational studies, broad agreement was reached for a strategy of lifelong surveillance and early treatment for ocular VHL disease. These guidelines were endorsed by the VHL Alliance and the International Society of Ocular Oncology and were approved by the American Academy of Ophthalmology Board of Trustees.

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Von Hippel-Lindau (VHL) disease is a rare autosomal dominantly inherited multisystem neoplastic condition caused by mutation in the *VHL* gene.[1] Cardinal manifestations include retinal hemangioblastoma (RH), central nervous system hemangioblastoma, renal cell carcinoma, pheochromocytoma, endolymphatic sac tumor, broad ligament and epididymal cystadenomas, pancreatic neuroendocrine tumors, and renal and pancreatic cysts.[2,3] In 1993, Latif et al[4] identified the VHL tumor suppressor gene, located on chromosome 3 (3p25−26). The product of the gene, the VHL protein, plays a critical role in cellular oxygen sensing. In the absence of normal VHL protein, hypoxia-inducible factors inappropriately induce expression of a wide array of target genes that normally coordinate a cell's response to hypoxia.[5-7]

Retinal hemangioblastoma is a benign, highly vascular neoplasm of the neurosensory retina that can occur in sporadic solitary form or as a common manifestation of VHL disease. Typically asymptomatic at early stages, RHs can cause vision loss secondary to tumor-associated exudation, fibrosis, hemorrhage, or retinal detachment as they grow.[8] Extrapapillary RHs, defined as those that arise more than 1.5 mm from the optic disc, initially appear as a red or grayish pinpoint lesion with diameter of less than 500 μm, similar in appearance to a microaneurysm or small intraretinal hemorrhage. Larger tumors are

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associated with dilated and tortuous feeding arterioles and draining venules and become associated variably with exudation and fibrovascular proliferation. Juxtapapillary RHs arising 1.5 mm or less from the optic disc have a distinct appearance. They often exhibit a variably pink-grey localized fullness of the neural rim or retina that typically becomes more distinct and nodular with growth, and visible feeding and draining vessels generally are absent. Less common features of ocular VHL disease include epiretinal membrane, retinal exudation, retinal vascular proliferation, and retrobulbar optic nerve hemangioblastoma.[9,10]

Genetic testing for VHL disease became available in the 1990s,[11] providing a ready method to identify those with the condition before the clinical development of disease features. This allowed for testing of extended kindred with a positive family history to identify those with VHL disease and, importantly, offered the opportunity to institute surveillance measures at an early age for those harboring *VHL* gene mutations. Various guidelines for surveillance have been developed over the past 2 decades.[2,12–15] The resulting progress in systematic screening, in combination with more effective treatments for some of the life-threatening manifestations such as renal cell carcinoma,[16,17] has been credited with improved survival of individuals with VHL disease.[18]

The recommendations for screening and early treatment of RHs presented herein represent part of a coordinated effort by the International VHL Surveillance Guidelines Consortium (Fig 1) to develop a comprehensive set of evidence-based surveillance guidelines for patients with VHL disease, with the goal of promoting universal and standardized multidisciplinary care. The organ-specific ophthalmology subcommittee met alongside other organ-specific subcommittees for the central nervous system, endolymphatic sac tumors, kidney, pancreas, endocrine system, radiology, and pediatrics, along with representatives from anesthesia and individuals with expertise in guidelines development. Each subcommittee was tasked with the development of a coordinated set of recommendations based on a standardized evidence grading system. Summary guidelines for all organ systems are available via the VHL Alliance at https://www.vhl.org/storage/2023/08/VHL-Active-Surveillance-Guidelines-VHL-Alliance.pdf (last accessed December 5, 2023), and have been published.[19]

Methods

A panel discussion at the 2018 International VHL Medical and Research Symposium (Houston, TX) identified a need for a comprehensive and cohesive set of evidence-based guidelines for surveillance of VHL disease to be developed by working groups with expertise in prototypical features of the condition and coordinated by a steering committee. This became the International VHL Surveillance Guidelines Consortium (Fig 1), which functioned independently from the VHL Alliance, but with the VHL Alliance agreeing to provide logistical and administrative support. An ophthalmology subcommittee was convened, with infrastructural support from the patient advocacy organization the VHL Alliance (Boston, MA) and literature search assistance by the medical librarian (Andre Ambrus, MLIS) for the American Academy of Ophthalmology (San Francisco, CA). This is a retrospective study using de-identified subject details. Individual patient-level consent was not required.

Members of the ophthalmology subcommittee met between late 2019 and early 2022 via a series of teleconferences attended by all members to review existing guidelines and to formulate a list of subjects for consideration and review. For each question or subject area, a search of the English and foreign language literature using appropriate terms was performed. Details on the specific questions addressed, the search strategies used, and the literature results from each query can all be found in Table S1 (available at www.aaojournal.org).

For each question posed, 2 committee members each conducted an independent review of the literature and presented findings to the group. The entire committee then met via an additional series of teleconferences and assigned 3 different types of grades for each topic or corresponding recommendation (Fig 2).

First, the type of evidence was graded based on its best available source according to the system proposed by Shekelle et al[20]:

- Ia. Meta-analysis of randomized controlled trials,
- Ib. At least 1 randomized controlled trial,
- IIa. At least 1 controlled study without randomization,
- IIb. At least one other type of quasiexperimental study,
- III. Nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies,
- IV. Expert committee reports or opinions, clinical experience of respected authorities, or both.

Second, the strength of the evidence applicable to the guideline under consideration was graded based on the following criteria proposed by Shekelle et al[20]:

- A. Directly based on category I evidence,
- B. Directly based on category II evidence or extrapolated recommendation from category I evidence,
- C. Directly based on category III evidence or extrapolated recommendation from categories I or II evidence,
- D. Directly based on category IV evidence or extrapolated recommendation from categories I, II, or III evidence.

Third, the committee assessed the strength of the consensus guideline for each topic, considering the quality and consistency of evidence, the extent of extrapolation from existing evidence, availability of resources and practical considerations, balance of potential benefits and harms, and degree of consensus among committee members, assigning a summary grade using the National Comprehensive Cancer Network system[21]:

1. Based on high-level evidence, uniform consensus exists that the intervention is appropriate,
2A. Based on lower-level evidence, uniform consensus exists that the intervention is appropriate,
2B. Based on lower-level evidence, consensus exists that the intervention is appropriate,
3. Based on any level of evidence, major disagreement exists that intervention is appropriate.

Results and Discussion

Recommendations and the corresponding grades assigned by the committee are listed and summarized in Table 2. Following each recommendation, we include discussion of the main

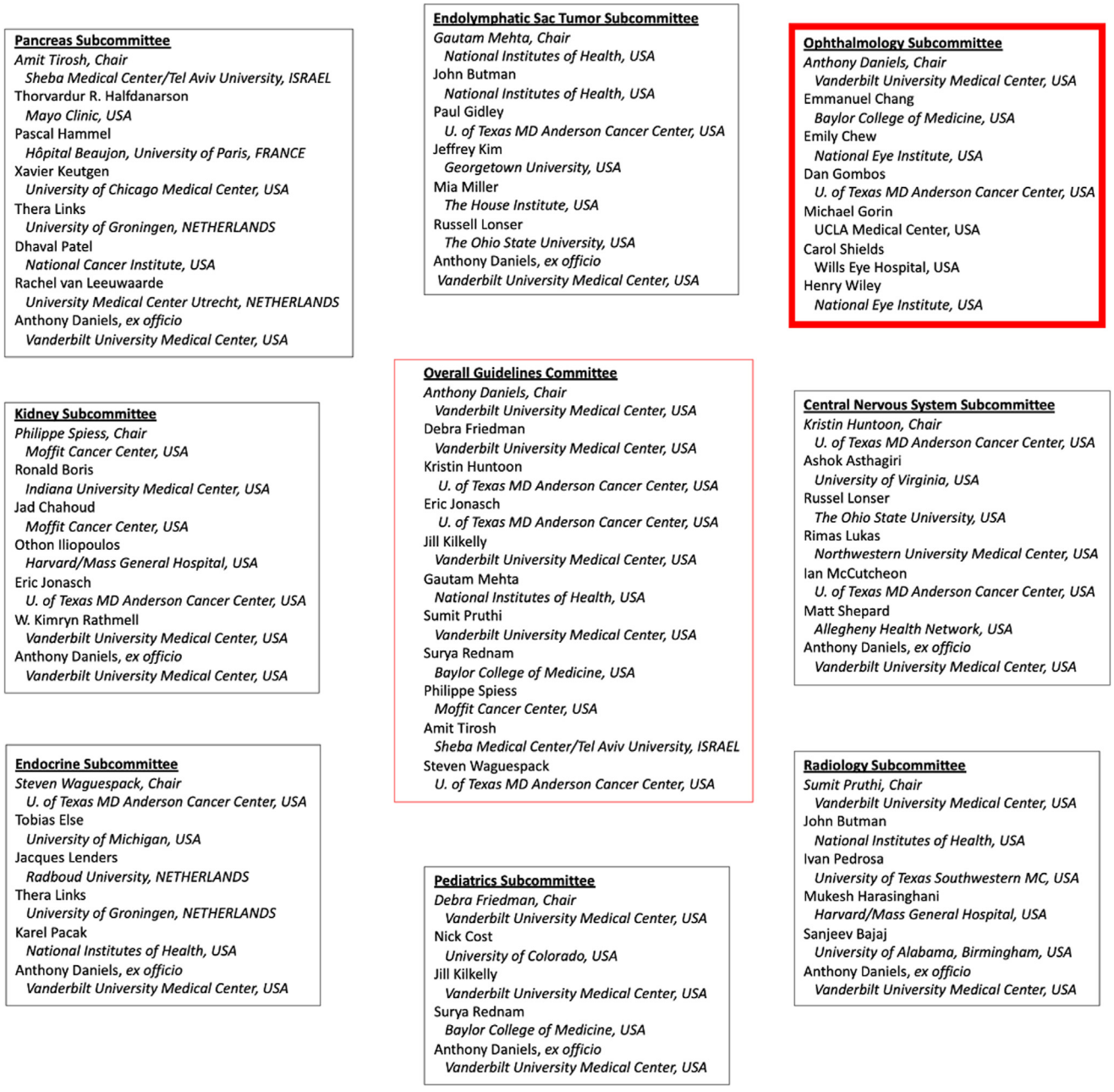

Figure 1. Diagram showing the overall structure of the International VHL Surveillance Guidelines Consortium and the ophthalmology subcommittee. VHL = von Hippel-Lindau disease.

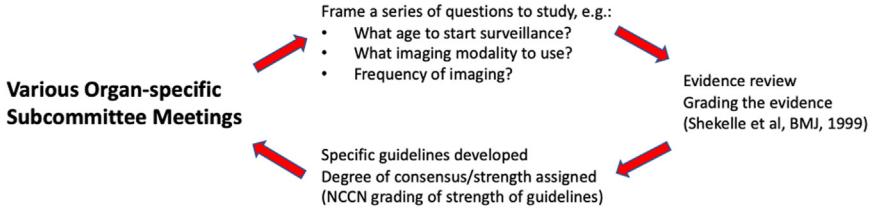

Figure 2. Diagram showing the methodology for asking and answering the various questions, grading the evidence, and developing the guidelines. Specific questions that were generated by the ophthalmology subcommittee and results of the search terms and literature review are included in Table S1 (available at www.aaojournal.org). NCCN = National Comprehensive Cancer Network.

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sources of evidence considered by the committee, key points of discussion (including acknowledgment of ancillary considerations and uncertainties), and further information about the degree of group consensus.

The newly proposed guidelines are more thorough regarding various clinical circumstances, and they include more detail on the type of examination and ancillary testing that ideally should be performed. Also, the current recommendations examine the strength of available data that has informed each recommendation.

1. Individuals with known or suspected VHL disease should undergo periodic ocular screening with dilated ophthalmoscopy.

Evidence (type): III
Evidence (strength): C
Recommendation (strength): 2A

The value of periodic ocular screening for those with known or suspected VHL disease has been asserted in guidelines and consensus reviews published by multiple groups over the last few decades.[2,8,12–15,22] No controlled trials testing the efficacy of ocular screening have been performed, and such trials likely are not feasible for ethical reasons. Prior recommendations for ocular surveillance are based on (1) recognition of the risks to vision suggested by cross-sectional natural history and longitudinal cohort studies; (2) the relative efficacy and safety of early intervention for small, typically asymptomatic RHs arising outside the posterior pole documented in large retrospective case series; and (3) the limited benefit and complications of various interventions for more advanced RHs in small prospective and retrospective series.

The natural history of ocular VHL disease has been characterized in large cross-sectional and longitudinal studies.[23–29] These studies document: (1) the high frequency of RHs in individuals with VHL disease (present in 335 of 890 patients [38%] from 220 unrelated pedigrees, with mean age of 37 years, in the largest cohort described to date),[26] (2) the capacity for appearance of new tumors over a lifetime (with a cumulative probability of an RH developing rising with each decade of life, reaching nearly 80% in patients older than 80 years),[30] (3) the typically asymptomatic nature of small RHs early in their development (97 of 116 RHs [85%] were asymptomatic in a cohort of 37 patients in Denmark for whom ocular screening was initiated before 18 years of age),[29] and (4) vision loss resulting from exudation, fibrovascular proliferation, and hemorrhage of large RHs (some degree of at least unilateral vision impairment present in approximately 20% of 335 patients with ocular VHL disease, with 6% having visual acuity of $< 20/200$ in both eyes).[26]

Even recently published cohorts can be difficult to evaluate for outcomes relevant to early diagnosis and a program of periodic ocular surveillance, because many patients in such series did not receive a diagnosis until adulthood, with severe ocular symptoms at initial presentation. In a published Danish cohort, including all individuals identified through a Denmark national registry and consenting to participation, with year of diagnosis ranging from 1969 to 2015, Launbjerg et al[29] indicated that approximately 60% of patients received a diagnosis in adulthood. Confining analysis to 37 patients who received a diagnosis before 18 years of age on the basis of a family history of VHL disease, positive results for *VHL* gene mutation, or clinical diagnosis of VHL disease, they found that RHs were the most frequent manifestation in this group (34% of all manifestations) and that 93 of 98 disease manifestations [95%] were found at an asymptomatic stage when considering periods of active surveillance. Although Launbjerg et al did not provide details about RH diagnosis or about management outcomes, Kreusel et al[25] reported such information in a cohort of 57 patients (mean age at presentation, 23 years; mean follow-up, 7.3 years) in which 36 patients (63%) demonstrated symptoms (including 25 patients with exudative or tractional retinal detachment, or both) and 21 patients (37%) did not demonstrate symptoms. Average visual acuity at presentation was 20/87 in symptomatic eyes and 20/22 in asymptomatic eyes. Under a scheme of periodic eye examination mentioned above for this series (see guideline no. 4 below), in which almost all new RHs were detected when small (diameter, $\leq$ 0.5 disc diameters), eyes asymptomatic at presentation maintained similar good visual acuity (average, 20/24) at the end of follow-up in the setting of laser treatment for ablation of RHs when detected. Although the asymptomatic eyes represent a subgroup with less severe disease, limiting generalizability about management of ocular VHL disease at large, this study suggests that good vision frequently can be maintained when treatment for RHs is instituted before symptom onset and is offered in a timely fashion for new lesions detected in the context of periodic surveillance by a group with expertise in ocular VHL disease (see guideline no. 7 below).

Taken together, these studies suggest a role for ocular surveillance as a means to enable early and effective treatment and highlight the limitations of initiating treatment when RHs are discovered only at a larger, symptomatic stage. Acknowledging the availability and minimal risk of an eye examination, we were in universal agreement on a recommendation for periodic ocular evaluation that includes dilated ophthalmoscopy. Further considerations of such screening are discussed below. We acknowledge that resource unavailability throughout many parts of the world may necessitate modification of screening approaches to meet local conditions.

2. Patients at risk of VHL disease, including first-degree relatives of patients with known VHL disease, or any patient with single or multifocal RHs, should undergo genetic testing of the *VHL* gene as part of an appropriate medical evaluation. At-risk children should be tested early in life.

Evidence (type): III
Evidence (strength): C
Recommendation (strength): 2A

The clinical diagnosis of VHL disease is made using criteria based on family history and cardinal manifestations such as RH, central nervous system hemangioblastoma, pheochromocytoma, neuroendocrine tumors, and clear cell renal carcinoma.[3,31] Relevant to findings on ophthalmic evaluation, diagnosis of 1 or more RHs in the setting of a family history of VHL disease, or 2 or more RHs even in

Table 2. Consensus Guidelines for Surveillance for Ocular von Hippel-Lindau Disease

Specific Recommendation	Evidence Type	Evidence Strength*	Recommendation†
1. Individuals with known or suspected VHL disease should undergo periodic ocular screening with dilated ophthalmoscopy.	III	C	2A
2. Patients at risk of VHL disease, including first-degree relatives of patients with known VHL disease, or any patient with single or multifocal RHs should undergo genetic testing of the VHL gene as part of an appropriate medical evaluation. At-risk children should be tested early in life.	III	C	2A
3. Ocular screening should begin within 12 months after birth and continue throughout life.	III	C	2A
4. Ocular screening should occur approximately every 6–12 months until 30 years of age and then at least yearly thereafter. The frequency may be influenced by the quality of the previous examination obtained in young children, and examination under anesthesia may be considered in children in whom a detailed office examination is not possible.	III	C/D	2A
5. Ocular screening should be performed before a planned pregnancy and every 6–12 months during pregnancy.	IV	D	2A
6. Ultra-widefield photography may be helpful in certain circumstances to monitor RHs, and ultra-widefield fluorescein angiography may be helpful in certain circumstances to detect small RHs. These imaging methods can serve as adjuncts to, but cannot replace, a detailed dilated funduscopic examination.	IV	D	2A
7. Patients should be managed, whenever possible, by those with subspecialty training, by those with experience with VHL disease or RHs, or by those with both, and ideally within the context of a multidisciplinary center capable of providing multiorgan surveillance and access to genetic testing.	IV	D	2A
8. Extramacular or extrapapillary RHs should be treated promptly. Even for small (diameter $\leq$ 500 μm) extramacular or extrapapillary RHs, favor early treatment over observation. This is especially true for patients in whom poor compliance with follow-up or poor reporting of symptoms (such as children) is a concern. If close observation is selected, consider early follow-up (< 1 year).	III	C	2A

RH = retinal hemangioblastoma; VHL = von Hippel-Lindau.
*Level or strength of evidence based on the method of Shekelle et al.[20]
†Strength of recommendation based on the National Comprehensive Cancer Network.

the absence of a family history of VHL disease, is sufficient for the clinical diagnosis of the condition. However, ophthalmologists often face diagnostic uncertainty, as in (1) patients in whom a solitary RH is discovered in the absence of a family history, (2) when a RH exists alongside additional lesions that are missed on eye evaluation or are difficult to differentiate because of size or appearance, or (3) when an at-risk individual with a family history of VHL disease does not demonstrate RHs, but has not undergone a full evaluation for extraocular manifestations or genetic testing.

The value of medical and genetic testing for at-risk individuals is tied to evidence for the benefits of early diagnosis, surveillance, and timely intervention, particularly for life-threatening complications of the disease. A detailed review of this evidence is beyond the scope of this article and is addressed in separate guidelines for renal cell carcinoma,[32] central nervous system hemangioblastoma,[33] pheochromocytoma, endolymphatic sac tumors,[34] and pancreatic neuroendocrine tumors.[35] However, it is worth mentioning that the latest large cohort study suggests an increase in the life expectancy of individuals with VHL disease in recent decades, presumably secondary to some combination of improvements in early diagnosis of the condition, more effective surveillance, and better treatment. In an older cohort comprising 152 patients ascertained from subspecialty clinics in the United Kingdom before 1990, Maher et al[23] reported a median actuarial survival of 49 years calculated using lifetable analysis. More recently, using data available through 2016, Binderup et al[18] analyzed a cohort of all known Danish families with a pathogenic *VHL* gene mutation, including 143 patients with genetically proven VHL disease and 137 siblings without a causative mutation. Although sequelae of VHL disease were the cause of death in 53 of 67 individuals (79%) with VHL disease, and although this reflected poorer survival than seen in matched siblings, the excess mortality of those with VHL disease was calculated to be decreased by 2.93% (95% CI, 1.64%–4.21%; $P < 0.001$) with each later birth year. The estimated mean life expectancies for male and female individuals with VHL disease born in 2000 were 67 and 60 years, respectively.

We considered several factors, including the life-threatening nature of some VHL disease tumors, the heterogeneity and latency of clinical manifestations, the implications for other family members in an autosomal dominant condition with high penetrance, and the value of early intervention for various manifestations of VHL disease (discussed below for ocular VHL disease and addressed separately for extraocular features by other

subcommittees[32–35]). Based on these considerations, we were in universal agreement that those at risk of VHL disease should receive appropriate medical evaluation and genetic testing and counseling. Children at risk should undergo genetic testing early in life to maximize the benefit of surveillance for early manifestations in those with positive results for gene mutation and to spare those with negative results the need for unnecessary surveillance. We acknowledge that a solitary RH in the absence of any family or medical history suggestive of VHL disease may occur sporadically, and the chance of sporadic disease is higher with increasing age at presentation.[36] However, we were in general agreement that the presence of even a solitary RH (exhibiting prototypical features differentiating it from a vasoproliferative tumor of the ocular fundus and other lesions) should prompt appropriate medical evaluation and genetic testing and counseling regardless of patient age, given the ready availability of testing and the potential cost of a missed diagnosis of VHL disease. In fact, it is specifically in those patients with a single RH in whom genetic testing can be helpful in confirming the diagnosis of VHL disease; in contrast, patients with multiple RHs already meet the clinical criteria for VHL disease, even in the absence of finding a *VHL* gene mutation. In these patients, genetic testing primarily identifies the specific mutation by which to screen and to exclude other family members. For the patient himself or herself, knowledge of the specific mutation is important as well, because certain (nonocular) manifestations may exhibit genotype–phenotype correlations, and thus may predict the likelihood of specific tumors forming.

3. Ocular screening should begin within 12 months after birth and continue throughout life.

Evidence (type): III
Evidence (strength): C (regarding RH development at any age)
Recommendation (strength): 2A

4. Ocular screening should occur approximately every 6 to 12 months until 30 years of age and then at least yearly thereafter. The frequency may be influenced by the quality of the previous examination obtained in young children, and examination under anesthesia may be considered in children in whom a detailed office examination is not possible.

Evidence (type): III
Evidence (strength): C (regarding peak incidence in adolescence and early adulthood); D (regarding the specific screening intervals at different ages)
Recommendation (strength): 2A

The literature concerning the age at which to start screening (guideline no. 3) and the frequency of surveillance in childhood and adulthood (guideline no. 4) have significant overlap, and therefore are discussed together below.

Little information is available in the literature about the frequency of RHs in children with VHL disease. Natural history studies document occasional cases occurring in very young children (for example, Singh et al[36] report a 2-year-old as the youngest case in a series of 31 patients with VHL disease), and we can presume reasonably that RHs were present for some time before detection in most children described in retrospective series.[23–29,36] Given the potential for development of RHs very early in life, various other guidelines have recommended starting ages for ocular surveillance as early as birth and as late as age 7 years.[2,8,12–15,22] The potential benefits of early detection of RH in a young child must be weighed against the greater discomforts and risks of dilated eye evaluation at these ages, particularly in cases where an examination under anesthesia is required for adequate evaluation in the setting of uncertainty about the incidence of tumors at very young ages. These risks and discomforts figure into our prior recommendation that children at risk of VHL disease be genetically tested when young, so that those with negative results for *VHL* gene mutation can be spared unnecessary procedures and examinations (see guideline no. 1 above). We were in universal agreement about the value of initiating ocular screening in young children, with the decision about office examination versus examination under anesthesia left to the discretion of the ophthalmologist. We did not find sufficient data on the prevalence of RHs in young children to recommend an initial screening age, a problem faced by others in the past as reflected in the variability in previous guidelines. Although a difference of opinions occurred regarding whether to begin screening at birth, unanimous consensus was reached about starting within the first year of life. We judged that the benefits of early identification of RHs in a small number of infants outweigh the small risks and discomforts of examination for all of those with VHL disease, acknowledging that examination under anesthesia may be necessary in some children, but would not be required in many others.

A recommended frequency of eye evaluation every 6 to 12 months through 30 years of age is based on several considerations. First, natural history studies suggest high incidence of RHs during adolescence and young adulthood. Maher et al[23] reported 89 patients with RHs, with mean age at diagnosis of ocular findings of 25 ± 11.3 years, but in this group, 54 patients (61%) were symptomatic, representing relatively advanced cases of ocular VHL disease that ideally would have been detected at the presymptomatic stage had they been screened at a younger age. Singh et al[36] reported a mean age at RH diagnosis of 17 years (range, 2–46 years) in 31 patients representing referrals to subspecialty clinics, similar to the Maher et al cohort. Feletti et al[27] found a mean age at RH diagnosis of 29 years (median, 25 years) in a cohort of 128 patients at the national referral center for VHL disease in Italy, with average follow-up of 3.8 years. Kreusel et al[25] reported on 57 consecutive cases of ocular VHL disease referred to a specialty clinic in Germany with average follow-up of 7.3 years, finding a mean age at first detection of 20 ± 10.4 years (range, 5–62 years) in a cohort in which 36 patients (63%) were symptomatic at presentation and in which 95% of patients were identified by 37 years of age. Second, RHs begin as tiny lesions first visible when they reach the size of

a large microaneurysm (approximately 200 μm) and exhibit variable but generally slow growth, such that a new lesion first detectable shortly after a prior examination is unlikely to grow to a threatening or difficult-to-treat size within 6 to 12 months before the next ocular evaluation. In the cohort described by Kreusel et al,[25] 254 new RHs were detected during follow-up, and almost all were designated as small (diameter, ≤ 0.5 disc diameter; approximately 0.75 mm) in the context of a mean interval between examinations of 1 year. Third, a range of potentially appropriate follow-up intervals seems appropriate in children and young adults to accommodate circumstances and to allow for reasonable discretion, especially in young children, for whom the burdens and discomforts of eye evaluation are greater (favoring less frequent examination), but for whom the challenges of an adequate examination often likewise are greater and self-report of symptoms is lower (favoring more frequent examination). Fourth, the recommended follow-up interval should be tailored to circumstances and may require evaluation more often than every 6 months. For example, when an eye is being treated for viable RHs or a particular patient manifests new tumors with greater-than-typical frequency, treatment should be tailored. In 7 eyes of 5 patients in the cohort reported by Kreusel et al,[25] new RHs with diameter of more than 0.5 disc diameters were identified after follow-up intervals from 6 to 24 months. In all of these eyes, ocular VHL disease was severe, with a mean of 15 RHs per eye and retinal detachment in 6 of 7 eyes, and in such patients, more frequent follow-up is warranted.

A recommended frequency of eye evaluation annually after 30 years of age is based on similar considerations and data relevant to this age group taken from the studies above. Putting aside a small fraction of patients who manifest the frequent appearance of additional RHs over the course of many years, most cohorts contain only small numbers of patients who demonstrate new tumors in later adulthood, particularly after 50 years of age. The best longitudinal data come from the cohort mentioned above reported by Kreusel et al. In this study, many patients older than 50 years did not manifest new RHs from one year to the next; a small number did so, even between 60 and 70 years of age.[25] Screening recommendations in older adults call for a comprehensive eye evaluation every 1 to 3 years for those 55 to 64 years of age and every 1 to 2 years for those 65 years of age and older, even in the absence of any risk factors.[37] In this context, an annual eye examination for individuals with VHL disease, who are at above average risk for eye disease, seems appropriate despite the likely decreased incidence of RHs with more advanced age. Once again, such follow-up should be tailored to circumstances, with more frequent examination for more severely afflicted eyes. We were in universal agreement about the need for lifelong surveillance and in general agreement about appropriate intervals for screening at different ages based on extrapolation from the evidence above.

5. Ocular screening should be performed before a planned pregnancy and every 6 to 12 months during pregnancy.

   Evidence (type): IV
   Evidence (strength): D
   Recommendation (strength): 2A

Very few data about the effects of pregnancy on ocular VHL disease are available, and no information is available about the usefulness of closer surveillance during a pregnancy. Frantzen et al[38] performed a retrospective analysis of 48 pregnancies in 29 patients evaluating the reciprocal effects of VHL disease and pregnancy. Among these 29 patients, 1 underwent laser treatment of an RH during pregnancy and 3 others manifested ablatio retinae (retinal detachment) evolving from RHs that were known to predate the pregnancy in 2 of 3 patients.

More information is available in the literature about VHL disease-associated central nervous system hemangioblastomas and pregnancy, and given the pathologic similarities with RHs, the former may be instructive for RH lesions. The only prospective study is a small case-control analysis by Ye et al[39] that compared new hemangioblastoma development and growth of existing hemangioblastomas in 9 patients during pregnancy with the development and growth during nonpregnant intervals in the same patients and in 27 women with VHL disease who did not become pregnant. This study found no significant difference in the development or growth of central nervous system hemangioblastoma. Evidence from case reports and retrospective case series is conflicting, with some supporting the findings of Ye et al,[40] but other work suggesting potential for progression during pregnancy, including published case reports describing fulminant presentations that can include hydrocephalus and cerebellar tonsillar herniation, often resulting from expansion of a cystic component of a hemangioblastoma.[38,41] Although caution is warranted in making any extrapolations about the behavior of RHs based on central nervous system hemangioblastoma data, the existing literature suggests a potential analogy. Rapid progression during pregnancy seems uncommon for both tumor types, yet may be serious with increased exudation or transudation. We were in universal agreement that a dilated eye examination before a planned conception is helpful to stratify and minimize risk resulting from ocular VHL disease during pregnancy. We did not find compelling evidence to recommend deviation from normal surveillance intervals during pregnancy, tailored to circumstances. General agreement was reached about the importance of continuation of ocular surveillance for individuals with VHL disease during pregnancy, and we agree with existing guidance about the relative safety of dilated eye examination in this setting.[42] Fluorescein sodium for use in angiography is designated as category C,[43] and we suggest the use of fluorescein angiography for pregnant individuals with VHL disease *only* when testing is necessary and is likely to influence management.

6. Ultra-widefield fundus photography may be helpful in certain circumstances to monitor RHs, and ultra-widefield fluorescein angiography may be helpful in certain circumstances to detect small RHs. These imaging methods can serve as adjuncts to, but

cannot replace, a detailed dilated funduscopic examination.

Evidence (type): IV
Evidence (strength): D
Recommendation (strength): 2A

von Hippel-Lindau disease-associated RHs and foci of vascular proliferation generally are visible on dilated ophthalmoscopy at an early stage.[8] However, lesions that are very small (diameter, < 300 μm), very peripheral, or poorly differentiated from the peripapillary nerve fiber layer (in the case of juxtapapillary tumors) can be missed, particularly in cases where a patient has difficulty with extended ophthalmoscopy. Traditional fundus photography and fluorescein angiography can be useful for documenting disease status, but are of variable usefulness for lesion detection because of limitations to the field of view. Ultra-widefield imaging is used for an expanding array of indications for the management of retinal disease, and some of us in the working group routinely use ultra-widefield pseudocolor images to corroborate and supplement findings from dilated fundus examination for our patients with VHL disease. Committee members believed that it was important to emphasize that such images do not replace extended ophthalmoscopy because lesions can be missed secondary to limitations of resolution or field of view. Chen et al[44] evaluated the usefulness of ultra-widefield fluorescein angiography for detection of VHL disease-associated lesions in a small retrospective study. In 12 eyes with discrete lesions identified (after exclusion of eyes with images that were ungradable because of proliferative vitreoretinopathy, presence of silicone oil, or both) and with an adequate, available, dilated clinical examination, 46 lesions were identified on ultra-widefield fluorescein images, compared with only 15 lesions in examination notes. For 5 eyes that were evaluated with gaze-steered images, 18% of lesions could be seen only on images with gaze steering. One of 20 eyes had a lesion that was seen on examination, but was missed on ultra-widefield fluorescein angiographic imaging. Although it is not the experience of members of the working group that many RHs visible on ultra-widefield fluorescein angiography are missed on extended ophthalmoscopy by an examiner with experience in ocular VHL disease, general agreement was reached that photography can be valuable to monitor lesions. Similarly, the sensitivity of ultra-widefield fluorescein angiography for detection of RHs can be excellent in cases where the images are clear, coverage of the retina is maximal, and no obscuring features such as preretinal fibrosis or hemorrhage are present. However, general agreement was reached that the limitations above, the small risks of intravenous fluorescein administration for angiography, and the variable access to these methods among retina clinics mean that retinal imaging is best considered discretionary and ancillary to a dilated ophthalmoscopic examination by an ophthalmologist proficient in management of ocular VHL disease (see guideline no. 7 below).

7. Patients should be managed, whenever possible, by those with subspecialty training, by those with experience with VHL disease or RHs, or by those with both, and ideally within the context of a multidisciplinary center capable of providing multiorgan surveillance and access to genetic testing.

Evidence (type): IV
Evidence (strength): D
Recommendation (strength): 2A

We did not find published data with a direct comparison of screening outcomes among distinct models for management of VHL disease. At least limited evidence from retrospective studies on large longitudinal cohorts indicates that good ocular outcomes can be achieved with regular surveillance at centers with experience in VHL disease.[25]

The relative rarity of VHL disease poses a challenge for ophthalmologists and other specialists trying to gain and maintain experience in its management. The heterogeneous manifestations complicate early diagnosis and coordination of multisystem surveillance. Evidence suggests that optimal surveillance, as defined by previous guidelines, has been difficult to achieve, even in places where genetic testing and subspecialty care are available.[45,46] The multidisciplinary team approach has been adopted widely in management of cancer and also has been implemented for some rare multisystem diseases, including for VHL.[47] Effects of care coordination on survival of patients with cancer have been difficult to isolate from other factors. Reports on the efficacy of multidisciplinary care have been mixed. Current evidence supports that certain facets of management, such as screening compliance, time to intervention, and treatment adherence, are affected positively, suggesting mechanisms to improve fundamental outcomes.[48,49] For rare multisystem diseases that pose more significant challenges because of their complexity and unfamiliarity, the potential benefits of care coordination are even greater.[50–52]

Considering these factors, we were in general agreement that care of individuals with VHL disease optimally involves ophthalmologists with specific experience or expertise managing the condition working in coordination with established multidisciplinary teams whenever possible, but all ophthalmologists should be familiar with the guidelines.

8. Extramacular or extrapapillary retinal hemangioblastomas should be treated promptly. Even for small (diameter ≤ 500 μm) extramacular or extrapapillary RHs, early treatment is favored over observation. This is especially true for patients in whom poor compliance with follow-up or poor reporting of symptoms (such as children) is a concern. If close observation is selected, consider early follow-up (less than 1 year).

Evidence (type): III
Evidence (strength): C
Recommendation (strength): 2A

The purview of screening guidelines typically would not extend to disease management beyond considerations of timely detection of lesions. However, our working group was concerned that "surveillance" might be construed to include observation of small, asymptomatic extrapapillary

or extramacular RHs, or even larger such lesions, with institution of treatment only for more advanced disease or only if tumors become symptomatic. Data from some of the retrospective cohort studies and case series mentioned previously point to the morbidity of advanced disease and the limitations of current treatments for restoring vision, or even for eye salvage, in severely afflicted eyes.[23–29,53–56] We were in universal agreement that the benefits of ocular surveillance are realized best when paired with a strategy of early intervention for extrapapillary or extramacular RHs, considering the limitations of current treatment paradigms.

No prospective study evaluating the efficacy of intervention, which generally consists of ablation of extrapapillary or extramacular RHs, has been conducted. Kreusel et al[25] reported on a cohort of 57 consecutive patients with ocular VHL disease referred to a specialty clinic in Germany followed up for an average of 7.3 years, during which 254 new RHs were detected (exclusive of those present at presentation). Almost all of these 254 tumors were small and were treated effectively with laser photocoagulation. Eyes treated before symptoms emerged maintained good vision.

Similarly, 2 large retrospective case series reported near-universal success using 1 or more sessions of laser photocoagulation for small RHs with diameter of 1.5 mm or less with a reassuring safety profile.[57,58] Singh et al[57] reported using ablation with 1 or more sessions of laser photocoagulation in the management of 174 RHs in 86 eyes (68 patients) and achieved favorable outcomes in 18 of 18 tumors (100%) with diameter of 1.5 mm or less, compared with 8 of 17 larger RHs (47%). Krivosic et al[58] described a similar experience with 304 RHs in 100 eyes (74 patients) treated with laser photocoagulation, reporting successful destruction in 271 of 271 RHs (100%) with diameter of 1.5 mm or less over an average of 1.3 laser sessions, compared with 24 of 33 larger RHs (73%) over an average of 3.5 sessions. These results are in alignment with the collective experience of our working group and suggest a window of opportunity for detection and treatment of extrapapillary or extramacular lesions while they are small.

No good data are available regarding how many small (diameter $\leq$ 500 μm) RHs undergo spontaneous involution or never grow. Close observation has been used in the past as an approach for such tumors. Our experience is that spontaneous regression is uncommon, and most lesions do grow and evolve at rates that are variable and unpredictable. Retrospective case series demonstrate the difficulties of controlling large RHs and higher risks associated with options such as surgery, external beam radiation, and brachytherapy.[53–56,58] Given the minimal risks of treatment for small extrapapillary or extramacular RHs, we were in universal agreement that prompt treatment is preferred after detection.

Further discussion of treatment, differentiation of RHs from foci of retinal vascular proliferation (an uncommon but prototypical manifestation of ocular VHL disease), management of large RHs, and the occasional role for non-ablative treatments, is beyond the scope of these guidelines, and these are reviewed elsewhere.[8] However, one emerging therapy with implications for RH surveillance and management bears mentioning. The recent Food and Drug Administration approval[59] of an oral small-molecule HIF2-α inhibitor, belzutifan, for treatment of VHL disease-related renal cell carcinoma, pancreatic neuroendocrine tumors, and central nervous system hemangioblastomas on the basis of a phase 2 clinical trial[60] represents an advancement that seems likely to change management for many patients with VHL disease. Preliminary findings regarding ocular VHL disease from that trial suggest that HIF2-α inhibition may have efficacy for RHs, and we anticipate that this may affect both aspects of surveillance and treatment of ocular VHL disease. Because this systemic treatment avoids the direct damage of local ablation, systemic HIF2-α inhibitors may provide a safer option for the management of juxtapapillary tumors ($\leq$ 1.5 mm from disc edge) and macular tumors ($\leq$ 3.0 mm from foveal center [foveola]), or for large tumors for which safe and effective treatment options currently are lacking. Similarly, it also might allow other (extrapapillary) tumors to be treated earlier without ablative therapies and might even play a role in suppression of RH formation. How ocular screening of patients with VHL disease receiving chronic HIF2-α inhibition might differ from the current guidelines presented here still remains to be determined as clinical experience expands with these inhibitors.

Summary

The relative rarity and clinical heterogeneity of VHL disease have hampered the development of prospective studies and clinical trials to date, and the evidence base for the recommendations we have presented is generally limited. However, the availability of genetic testing has created a significant opportunity, offering identification of those with VHL disease before any clinical manifestations. Diagnosis of the disease shortly after birth enables targeted and timely surveillance of individuals at very high risk of RH development. Periodic dilated eye examination allows identification of RHs at an early stage, enabling an opportunity for ablation of small extrapapillary or extramacular RHs, as demonstrated by retrospective series.[57,58] Consideration of the morbidity caused by larger RHs and the limited current treatment options for advanced ocular VHL disease[61] complete the rationale for a program of early identification and prompt treatment of extramacular or extrapapillary RHs as a means of preserving vision in those with VHL disease. New systemic pharmaceutical agents targeting HIF2-α could assist in control of RHs and might allow particularly early treatment for all RHs, especially those in the macula and juxtapapillary region. Further studies of these new pharmaceutical agents will provide potential new treatment strategies for the treatment of all RHs.

Footnotes and Disclosures

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Conception and design: Daniels

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RH = retinal hemangioblastoma; **VHL** = von Hippel-Lindau.

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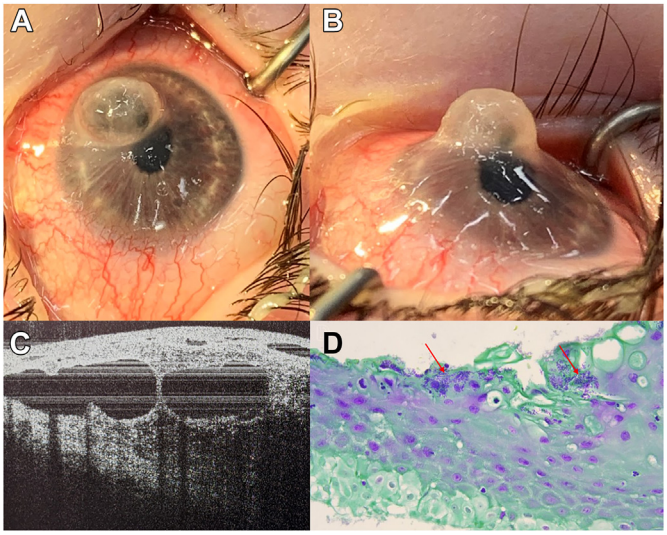
References

1. Kaelin Jr WG. Molecular basis of the VHL hereditary cancer syndrome. *Nat Rev Cancer*. 2002;2(9):673–682.
2. Lonser RR, Glenn GM, Walther M, et al. von Hippel-Lindau disease. *Lancet*. 2003;361(9374):2059–2067.
3. Schmid S, Gillessen S, Binet I, et al. Management of von Hippel-Lindau disease: an interdisciplinary review. *Oncol Res Treat*. 2014;37(12):761–771.
4. Latif F, Tory K, Gnarra J, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science*. 1993;260(5112):1317–1320.
5. Maxwell PH, Wiesener MS, Chang GW, et al. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature*. 1999;399(6733):271–275.
6. Gossage L, Eisen T, Maher ER. VHL, the story of a tumour suppressor gene. *Nat Rev Cancer*. 2015;15(1):55–64.
7. Arreola A, Payne LB, Julian MH, et al. Von Hippel-Lindau mutations disrupt vascular patterning and maturation via Notch. *JCI Insight*. 2018;3(4):e92193.
8. Wiley HE, Krivosic V, Gaudric A, et al. Management of retinal hemangioblastoma in von Hippel-Lindau disease. *Retina*. 2019;39(12):2254–2263.
9. Wong WT, Yeh S, Chan CC, et al. Retinal vascular proliferation as an ocular manifestation of von Hippel-Lindau disease. *Arch Ophthalmol*. 2008;126(5):637–643.
10. Meyerle CB, Dahr SS, Wetjen NM, et al. Clinical course of retrobulbar hemangioblastomas in von Hippel-Lindau disease. *Ophthalmology*. 2008;115(8):1382–1389.
11. Stolle C, Glenn G, Zbar B, et al. Improved detection of germline mutations in the von Hippel-Lindau disease tumor suppressor gene. *Hum Mutat*. 1998;12(6):417–423.
12. Hes FJ, van der Luijt RB, Lips CJ. Clinical management of von Hippel-Lindau (VHL) disease. *Neth J Med*. 2001;59(5):225–234.
13. Binderup ML, Bisgaard ML, Harbud V, et al. von Hippel-Lindau disease (vHL). National clinical guideline for diagnosis and surveillance in Denmark. 3rd edition. *Dan Med J*. 2013;60(12):B4763:1–9.
14. Kruizinga RC, Sluiter WJ, de Vries EG, et al. Calculating optimal surveillance for detection of von Hippel-Lindau-related manifestations. *Endocr Relat Cancer*. 2014;21(1):63–71.
15. Rednam SP, Erez A, Druker H, et al. von Hippel-Lindau and hereditary pheochromocytoma/paraganglioma syndromes: clinical features, genetics, and surveillance

recommendations in childhood. *Clin Cancer Res*. 2017;23(12):e68–e75.
16. Grubb 3rd RL, Choyke PL, Pinto PA, et al. Management of von Hippel-Lindau-associated kidney cancer. *Nat Clin Pract Urol*. 2005;2(5):248–255.
17. Stukalin I, Alimohamed N, Heng DY. Contemporary treatment of metastatic renal cell carcinoma. *Oncol Rev*. 2016;10(1):295.
18. Binderup ML, Jensen AM, Budtz-Jorgensen E, Bisgaard ML. Survival and causes of death in patients with von Hippel-Lindau disease. *J Med Genet*. 2017;54(1):11–18.
19. Daniels AB, Tirosh A, Huntoon K, et al; International VHL Surveillance Guidelines Consortium. Guidelines for surveillance of patients with von Hippel-Lindau disease: Consensus statement of the International VHL Surveillance Guidelines Consortium and VHL Alliance. *Cancer*. 2023;129(19):2927–2940.
20. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *BMJ*. 1999;318(7183):593–596.
21. National Comprehensive Cancer Network. NCCN Categories of Evidence and Consensus. Available online at: nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines. Accessed February 15, 2024.
22. Moore AT, Maher ER, Rosen P, et al. Ophthalmological screening for von Hippel-Lindau disease. *Eye (Lond)*. 1991;5(Pt 6):723–728.
23. Maher ER, Yates JR, Harries R, et al. Clinical features and natural history of von Hippel-Lindau disease. *Q J Med*. 1990;77(283):1151–1163.
24. Dollfus H, Massin P, Taupin P, et al. Retinal hemangioblastoma in von Hippel-Lindau disease: a clinical and molecular study. *Invest Ophthalmol Vis Sci*. 2002;43(9):3067–3074.
25. Kreusel KM, Bechrakis NE, Krause L, et al. Retinal angiomatosis in von Hippel-Lindau disease: a longitudinal ophthalmologic study. *Ophthalmology*. 2006;113(8):1418–1424.
26. Wong WT, Agron E, Coleman HR, et al. Clinical characterization of retinal capillary hemangioblastomas in a large population of patients with von Hippel-Lindau disease. *Ophthalmology*. 2008;115(1):181–188.
27. Feletti A, Anglani M, Scarpa B, et al. von Hippel-Lindau disease: an evaluation of natural history and functional disability. *Neuro Oncol*. 2016;18(7):1011–1020.
28. Binderup MLM, Stendell AS, Galanakis M, et al. Retinal hemangioblastoma: prevalence, incidence and frequency of underlying von Hippel-Lindau disease. *Br J Ophthalmol*. 2018;102(7):942–947.
29. Launbjerg K, Bache I, Galanakis M, et al. von Hippel-Lindau development in children and adolescents. *Am J Med Genet A*. 2017;173(9):2381–2394.
30. Milam Jr R, Daniels A. Retinal hemangioblastomas. In: Patel D, Tirosh A, eds. *von Hippel-Lindau Disease—A Comprehensive Guide to Diagnosis, Treatment, and Management*. London: Springer-Nature; 2024 [In Press].
31. Melmon KL, Rosen SW. Lindau's disease. Review of the literature and study of a large kindred. *Am J Med*. 1964;36:595–617.
32. Chahoud J, McGettigan M, Parikh N, et al. Evaluation, diagnosis and surveillance of renal masses in the setting of VHL disease. *World J Urol*. 2021;39(7):2409–2415.
33. Huntoon K, Shepard MJ, Lukas RV, et al. Hemangioblastoma diagnosis and surveillance in von Hippel-Lindau disease: a consensus statement. *J Neurosurg*. 2021;136(6):1511–1516.
34. Mehta GU, Kim HJ, Gidley PW, et al. Endolymphatic sac tumor screening and diagnosis in von Hippel-Lindau disease: a consensus statement. *J Neurol Surg B Skull Base*. 2021;83(Suppl 2):e225–e231.
35. Laks S, van Leeuwaarde R, Patel D, et al. Management recommendations for pancreatic manifestations of von Hippel-Lindau disease. *Cancer*. 2022;128(3):435–446.
36. Singh AD, Nouri M, Shields CL, et al. Retinal capillary hemangioma: a comparison of sporadic cases and cases associated with von Hippel-Lindau disease. *Ophthalmology*. 2001;108(10):1907–1911.
37. AAO Hoskins Center for Quality Eye Care. Frequency of ocular examination—2015. American Academy of Ophthalmology. Available at: https://www.aao.org/clinical-statement/frequency-of-ocular-examinations; 2015. Accessed August 30, 2021.
38. Frantzen C, Kruizinga RC, van Asselt SJ, et al. Pregnancy-related hemangioblastoma progression and complications in von Hippel-Lindau disease. *Neurology*. 2012;79(8):793–796.
39. Ye DY, Bakhtian KD, Asthagiri AR, Lonser RR. Effect of pregnancy on hemangioblastoma development and progression in von Hippel-Lindau disease. *J Neurosurg*. 2012;117(5):818–824.
40. Binderup ML, Budtz-Jorgensen E, Bisgaard ML. New von Hippel-Lindau manifestations develop at the same or decreased rates in pregnancy. *Neurology*. 2015;85(17):1500–1503.
41. Othmane IS, Shields C, Singh A, et al. Postpartum cerebellar herniation in von Hippel-Lindau syndrome. *Am J Ophthalmol*. 1999;128(3):387–389.
42. American Academy of Ophthalmology. Diagnostic agents. Available at: https://www.aao.org/focalpointssnippetdetail.aspx?id=9c240b2e-6134-4926-a91d-6c69b1ee4a3d. Accessed August 30, 2021.
43. AK-FLUOR (fluorescein sodium) injection for intravenous use [Package Insert]. HF Acquisition Co LLC, DBA HealthFirst. Revision Date: 8/2019.
44. Chen X, Sanfilippo CJ, Nagiel A, et al. Early detection of retinal hemangioblastomas in von Hippel-Lindau disease using ultra-widefield fluorescein angiography. *Retina*. 2018;38(4):748–754.
45. Rasmussen A, Alonso E, Ochoa A, et al. Uptake of genetic testing and long-term tumor surveillance in von Hippel-Lindau disease. *BMC Med Genet*. 2010;11:4.
46. Lammens CR, Aaronson NK, Hes FJ, et al. Compliance with periodic surveillance for von-Hippel-Lindau disease. *Genet Med*. 2011;13(6):519–527.
47. Wolters WPG, Dreijerink KMA, Giles RH, et al. Multidisciplinary integrated care pathway for von Hippel-Lindau disease. *Cancer*. 2022;128(15):2871–2879.
48. Taylor C, Munro AJ, Glynne-Jones R, et al. Multidisciplinary team working in cancer: what is the evidence? *BMJ*. 2010;340:c951.
49. Taplin SH, Weaver S, Salas E, et al. Reviewing cancer care team effectiveness. *J Oncol Pract*. 2015;11(3):239–246.
50. Van Groenendael S, Giacovazzi L, Davison F, et al. High quality, patient centred and coordinated care for Alstrom syndrome: a model of care for an ultra-rare disease. *Orphanet J Rare Dis*. 2015;10:149.
51. von Kodolitsch Y, Rybczynski M, Vogler M, et al. The role of the multidisciplinary health care team in the management of patients with Marfan syndrome. *J Multidiscip Healthc*. 2016;9:587–614.
52. Auvin S, Bissler JJ, Cottin V, et al. A step-wise approach for establishing a multidisciplinary team for the management of tuberous sclerosis complex: a Delphi consensus report. *Orphanet J Rare Dis*. 2019;14(1):91.
53. Gaudric A, Krivosic V, Duguid G, et al. Vitreoretinal surgery for severe retinal capillary hemangiomas in von Hippel-Lindau disease. *Ophthalmology*. 2011;118(1):142–149.

54. Krzystolik K, Stopa M, Kuprjanowicz L, et al. Pars plana vitrectomy in advanced cases of von Hippel-Lindau eye disease. *Retina*. 2016;36(2):325−334.
55. Kreusel KM, Bornfeld N, Lommatzsch A, et al. Ruthenium-106 brachytherapy for peripheral retinal capillary hemangioma. *Ophthalmology*. 1998;105(8):1386−1392.
56. Raja D, Benz MS, Murray TG, et al. Salvage external beam radiotherapy of retinal capillary hemangiomas secondary to von Hippel-Lindau disease: visual and anatomic outcomes. *Ophthalmology*. 2004;111(1):150−153.
57. Singh AD, Nouri M, Shields CL, et al. Treatment of retinal capillary hemangioma. *Ophthalmology*. 2002;109(10):1799−1806.
58. Krivosic V, Kamami-Levy C, Jacob J, et al. Laser photocoagulation for peripheral retinal capillary hemangioblastoma in von Hippel-Lindau disease. *Ophthalmol Retina*. 2017;1(1):59−67.
59. FDA OK's HIF2α inhibitor belzutifan. *Cancer Discov*. 2021;11(10):2360−2361.
60. Jonasch E, Donskov F, Iliopoulos O, et al. Belzutifan for renal cell carcinoma in von Hippel-Lindau disease. *N Engl J Med*. 2021;385(22):2036−2046.
61. Aronow ME, Wiley HE, Gaudric A, et al. von Hippel-Lindau Disease: update on pathogenesis and systemic aspects. *Retina*. 2019;39(12):2243−2253.

Pictures & Perspectives



print & web 4C/FPO

Cystic Focal Ectasia Due to Moraxella Keratitis Identified in Formalin-Fixed Tissue

A 21-month-old with Moebius syndrome presented with parental concern of increased right eye rubbing. The eyes had symmetric moderate conjunctival injection, with 6-8 mm lagophthalmos bilaterally. Examination under anesthesia revealed a soft eye with shallow anterior chamber, and a 5 × 4 mm, minimally opaque cystic protuberance in the right nasal cornea that was subtlety Seidel-positive (**A**, **B**). Intraoperative OCT demonstrated large cystic fluid cavities throughout the effected corneal stroma, with communication to the anterior chamber (**C**). A therapeutic penetrating keratoplasty was performed, and Gram stain of the corneal button revealed Gram-negative diplococci (**D**). 16s ribosomal RNA sequencing identified *Moraxella nonliquifaciens* within the formalin-fixed tissue. (Magnified version of Figure **A**-**D** is available online at www.aaojournal.org).

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Footnotes and Disclosures

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