POLICY STATEMENT
Consensus Recommendations for Ocular Surveillance of von Hippel-Lindau Disease

Introduction:
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*. identified the *VHL* tumor suppressor gene, located on chromosome 3 (3p25-26).[4] 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.[5,6]

RH 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.[7] Extrapapillary RHs, denoting those that arise >1.5 mm from the optic disc, initially appear as a red or grayish pinpoint lesion with diameter <500 μm, similar in appearance to a microaneurysm or small intraretinal hemorrhage. Larger tumors are associated with dilated and tortuous feeding arterioles and draining venules and become variably associated with exudation and fibrovascular proliferation. Juxtapapillary RHs arising ≤1.5 mm from the optic disc have a distinct appearance, often exhibiting a variably pink-grey localized fullness of the neural rim or retina that typically becomes more distinct and nodular with growth, absent visible feeding and draining vessels. Less common features of ocular VHL disease include epiretinal membrane, retinal exudation, retinal vascular proliferation and retrobulbar optic nerve hemangioblastoma.[8,9]

Genetic testing for VHL disease became available in the 1990s,[10] providing a ready method to identify those with the condition prior to the clinical development of disease features. This allowed for testing of extended kindreds 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 two decades,[2,11-14] and the resulting progress in systematic screening, in combination with more effective treatments for some of the life-threatening manifestations such as renal cell carcinoma,[15,16] has been credited with improved survival of individuals with VHL disease.[17]

The recommendations for screening and early treatment of RHs presented herein represent part of a coordinated effort by the International VHL Surveillance Guidelines Consortium (**Figure 1**) to develop a comprehensive set of evidence-based surveillance guidelines for patients with VHL disease, with the goal of promoting universal and standardized multi-disciplinary 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 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/wp-content/uploads/2020/10/Active-Surveillance-Guidelines-2020.pdf.

Methods:

A panel discussion at the 2018 International VHL Medical / 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 (**Figure 1**). An ophthalmology sub-committee 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).

Members of the ophthalmology sub-committee reviewed existing guidelines and formulated a list of subjects for consideration and review. For each question / 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 employed, and the literature results from each query can all be found in the **Supplemental Table**.

For each question posed, two committee members each conducted an independent review of the literature and presented findings to the group. The entire committee then assigned three different types of grades for each topic / corresponding recommendation (**Figure 2**).

First, the quality of evidence was graded based on its best available source according to the system proposed by Shekelle *et al.*[18]:
> *Ia: Meta-analysis of randomized controlled trials*
> *Ib: At least one randomized controlled trial*
> *IIa: At least one controlled study without randomization*
> *IIb: At least one other type of quasi-experimental study*
> *III: Non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies*
> *IV: Expert committee reports or opinions; or clinical experience of respected authorities, or both*

Second, the relevance of the evidence to the guideline under consideration was graded based on the following criteria proposed by Shekelle *et al.*[18]:
> *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 category I or II evidence*
> *D: Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence*

Third, the committee assessed the strength of the consensus guideline for each topic, taking into account 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 (NCCN) system[19]:
> *1: Based upon high-level evidence, there is uniform consensus that the intervention is appropriate.*
> *2A: Based upon lower-level evidence, there is uniform consensus that the intervention is appropriate.*
> *2B: Based upon lower-level evidence, there is consensus that the intervention is appropriate.*
> *3: Based upon any level of evidence, there is major disagreement that the intervention is appropriate.*

Results and Discussion:
Recommendations and the corresponding grades assigned by the committee are listed below and summarized in **Table 1**. Following each recommendation, we have included discussion of the main 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.

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.[2,7,11-14,20] No controlled trials testing the efficacy of ocular screening have been performed, and such trials are likely 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,[21-27] documenting the high frequency of RHs in individuals with VHL disease (present in 335 (38%) of 890 patients from 220 unrelated pedigrees, with mean age of 37 years, in the largest cohort described to date);[24] the capacity for appearance of new tumors over a lifetime (with a cumulative probability of developing a RH rising with each decade of life, reaching nearly 80% in patients over the age of 80 years);[28] the typically asymptomatic nature of small RHs early in their development (97 (85%) of 116 RHs were asymptomatic in a cohort of 37 patients in Denmark for whom ocular screening was initiated before age 18);[27] and vision loss 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).[24]

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 were not diagnosed 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.* indicate that approximately 60% of cases were diagnosed in adulthood.[27] Confining analysis to 37 patients diagnosed prior to age 18 years on the basis of a family history of VHL disease, positivity 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 (95%) of 98 disease manifestations were found at an asymptomatic stage when considering time periods of active surveillance. Although Launbjerg *et al.* did not provide details about RH diagnosis or about management outcomes, Kreusel *et al.* reported such information in their cohort of 57 patients (mean age at presentation, 23 years; mean follow-up, 7.3 years), in which 36 (63%) presented with symptoms (including 25 with exudative and/or tractional retinal detachment) and 21 (37%) presented without symptoms.[23] 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 #4 below), in which almost all new RHs were detected when small (diameter ≤ 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. While 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 offered in timely fashion for new lesions detected in the context of periodic surveillance by a group with expertise in ocular VHL disease (see #7 below).

Smaller sized tumors have better response rate than larger tumors and small tumors (1/2 DD or 0.75 mm. Two large retrospective case series have reported near-universal success using one or more sessions of laser photocoagulation for small RHs with diameter ≤1.5 mm with a reassuring safety profile.[54,55] Singh *et al.* achieved favorable outcomes with laser photocoagulation in 18 of 18 (100%) tumors with diameter of ≤ 1.5 mm, compared with 8 of 17 (47%) larger RH.[54] Krivosic *et al.* described a similar reporting successful destruction in 271 of 271 (100%) RH with diameter ≤ 1.5 mm, over an average of 1.3 laser sessions, compared with 24 (73%) of 33 larger RH, over a mean of 3.5 sessions.[55] These results suggests a window of opportunity for detection and treatment of extrapapillary / extramacular lesions while they are small (see #8 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 only discovered 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 in the sections below.

2. Patients at risk for VHL disease, including first degree relatives of patients with known VHL disease, or any patient with single or multifocal RHs, should have 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 and neuro-endocrine tumors, and clear cell renal carcinoma.[3,29] Relevant to findings on ophthalmic evaluation, diagnosis of one or more RHs in the setting of a family history of VHL disease, or two or more RH even in 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 cases where a solitary RH is discovered in the absence of a family history; where a RH exists alongside additional lesions that are missed on eye evaluation or difficult to differentiate because of size or appearance; or where an at-risk individual with a family history of VHL disease does not manifest RHs but has not had 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 manuscript, and is addressed in separate guidelines for renal cell carcinoma,[30] central nervous system hemangioblastoma,[31] pheochromocytoma, endolymphthatic sac tumors,[32] and pancreatic neuroendocrine tumors.[33] 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 cases ascertained from subspecialty clinics in Great Britain prior to 1990, Maher *et al.* reported a median actuarial survival of 49 years calculated using life-table analysis.[21] More recently, using data available through 2016, Binderup *et al.* analyzed a cohort of all known Danish families with a pathogenic *VHL* gene mutation, including 143 cases with genetically-proven VHL disease and 137 siblings without a

causative mutation.[17] Although sequelae of VHL disease were the cause of death in 53 (79%) of 67 individuals 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% to 4.21%, p<0.001) with each later birth year. The estimated mean life expectancies for males and females with VHL disease born in 2000 were 67 and 60 years, respectively.

Considering 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 sub-committees[30-33]), we were in universal agreement that those at risk for VHL disease should receive appropriate medical evaluation and genetic testing / counseling. Children at-risk should undergo genetic testing early in life, to maximize the benefit of surveillance for early manifestations in those positive for gene mutation, and to spare those who test negative the need for unnecessary surveillance. While a solitary RH in the absence of any family or medical history suggestive of VHL disease may occur sporadically, and while the chance of sporadic disease is higher with increasing age at presentation,[34] 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 / counseling irrespective 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; in contrast, patients with multiple RHs already meet the clinical criteria for VHL even in the absence of finding a *VHL* gene mutation. In these patients, genetic testing primarily serves to identify the specific mutation by which to screen and exclude other family members. For the patient him/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 6-12 months until age 30 years, and then at least yearly after age 30 years. 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
There is little information 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.* report a 2-year-old as the youngest case in a series of 31 patients with VHL disease),[34] and we can reasonably presume that RHs were present for some time before detection in most children described in retrospective series.[21-27,34] 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.[2,7,11-14,20] 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 for VHL disease be genetically tested young in life, so that those negative for *VHL* gene mutation can be spared

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unnecessary procedures and examinations (see #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. While there was a difference of opinions as to whether to begin screening at birth, there was unanimous consensus 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 – 12 months through age 30 years is based on several considerations. First, natural history studies suggest high incidence of RHs during adolescence and young adulthood. Maher *et al*. reported 89 patients with RHs, with mean age at diagnosis of ocular findings of 25 years (± 11.3 years), but in this group, 54 (61%) were symptomatic, representing relatively advanced cases of ocular VHL disease that ideally would have been detected at the pre-symptomatic stage had they been screened at a younger age.[21] Singh *et al.* reported a mean age of RH diagnosis of 17 years (range, 2 – 46 years) in 31 patients representing referrals to subspecialty clinics,[34] similar to the Maher cohort. Feletti *et al.* found a mean age of 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.[25] Kreusel *et al.* 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 years (± 10.4 years; range, 5 – 62 years) in a cohort where 36 (63%) patients were symptomatic at presentation, and in which 95% of cases were identified by 37 years of age.[23] 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 – 12 months before the next ocular evaluation. In the cohort described by Kreusel *et al.*, 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.[23] Third, a range of potentially appropriate follow up intervals seems appropriate in children and young adults to accommodate circumstances and 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 are often likewise 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.*, new RHs with diameter > 0.5 disc diameters were identified after follow up intervals from 6 to 24 months.[23] 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 cases, more frequent follow up is warranted.

A recommended frequency of eye evaluation annually after age 30 years 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 present with new tumors in later adulthood, particularly over 50 years of age. The best longitudinal data comes from the cohort mentioned above reported by Kreusel *et al*. In this study, many patients over 50 years old did not manifest new RHs from one year to the next, a small number did so, even between 60 and 70 years of age.[23] Screening recommendations in older adults call for a comprehensive eye evaluation every 1-3 years for those ages 55 to 64 years, and every 1-2 years for those ages 65 and older, even in the absence of any risk factors.[35] 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 prior to a planned pregnancy, and every 6-12 months during pregnancy.
    Evidence (type): **IV**
    Evidence (strength): **D**
    Recommendation (strength): **2A**
There is very little data about the effects of pregnancy on ocular VHL disease, and no information about the utility of closer surveillance during a pregnancy. Frantzen *et al.* performed a retrospective analysis of 48 pregnancies in 29 patients evaluating the reciprocal effects of VHL disease and pregnancy.[36] Among these 29 patients, one underwent laser treatment of an RH during pregnancy, and three others manifested ablatio retinae (retinal detachment) evolving from RHs that were known to pre-date the pregnancy in 2 of 3 cases.

There is more information in the literature about VHL-associated central nervous system hemangioblastomas and pregnancy, and given the pathologic similarities with retinal hemangioblastomas, the former may be instructive for RH lesions. The only prospective study is a small case-control analysis by Ye *et al.* that compared new hemangioblastoma development and growth of existing hemangioblastomas in 9 patients during pregnancy with the development and growth during non-pregnant intervals in the same patients and in 27 women with VHL disease who did not become pregnant.[37] 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.*,[38] but other work suggesting potential for progression during pregnancy, including published cases describing fulminant presentations that can include hydrocephalus and cerebellar tonsillar herniation, often from expansion of a cystic component of a hemangioblastoma.[36,39] While 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. A rapid progression during pregnancy seems uncommon for both tumor types, yet may be serious with increased exudation / transudation. We were in universal agreement that a dilated eye examination prior to a planned conception is helpful to stratify and minimize risk from ocular VHL disease during pregnancy. We did not find compelling evidence to recommend deviation from normal surveillance intervals during pregnancy, tailored to circumstances. There was general agreement 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.[40] Fluorescein sodium for use in angiography is designated as category C,[41] and we would only suggest use of fluorescein angiography for pregnant individuals with VHL disease when testing is necessary and 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 modalities can serve as adjuncts to, but cannot replace, a detailed dilated funduscopic examination.
    Evidence (type): **IV**
    Evidence (strength): **D**
    Recommendation (strength): **2A**
    VHL-associated RHs and foci of vascular proliferation are generally visible on dilated ophthalmoscopy at an early stage.[7] 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 utility 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 on dilated fundus examination for our patients with VHL disease. Committee members felt 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.* evaluated the utility of ultra-widefield fluorescein angiography for detection of VHL-associated lesions in a small retrospective study.[42] In 12 eyes with discrete lesions identified (after exclusion of eyes with images that were ungradable because of proliferative vitreoretinopathy and/or presence of silicone oil) and with an adequate, available, dilated clinical exam, 46 lesions were identified on ultra-widefield fluorescein images, compared with only 15 lesions in exam notes. For 5 eyes that were evaluated with gaze-steered images, 18% of lesions could only be seen on images with gaze steering. One of 20 eyes had a lesion that was seen on examination but missed on ultra-widefield fluorescein angiographic imaging. While it is not the experience of members of our 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, there was general agreement 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 there are no obscuring features such as pre-retinal fibrosis or hemorrhage. However, there was general agreement that the limitations above, the small risks of intravenous fluorescein administration for angiography, and the variable access to these modalities 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 #7 below).

7. Patients should be managed, whenever possible, by those with subspecialty training and/or with experience with VHL disease / RHs, and ideally within the context of a multidisciplinary center capable of providing multi-organ 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. There is at least limited evidence from retrospective studies on large longitudinal cohorts that good ocular outcomes can be achieved with regular surveillance at centers with experience in VHL disease.[23]

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 multi-system surveillance. There is evidence that optimal surveillance as defined by previous guidelines has been difficult to achieve, even in places where genetic testing and subspecialty care are available.[43,44] The multidisciplinary team approach has been widely adopted in management of cancer and has also been implemented for some rare multisystem diseases. Effects of care coordination on survival of patients with cancer have been difficult to isolate from other factors. Reports of 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 positively affected, suggesting mechanisms to improve fundamental outcomes.[45,46] For rare multi-system diseases that pose more significant challenges because of their complexity and unfamiliarity, the potential benefits of care coordination are even greater.[47-49]

Considering these factors, we were in general agreement that care of individuals with VHL disease optimally involves ophthalmologists with specific experience/expertise managing the condition who also work in coordination with established multidisciplinary teams.

8. Extramacular / extrapapillary retinal hemangioblastomas should be treated promptly. Even for small (diameter ≤ 500 µm) extramacular / 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 (less than 1 year).
> *Evidence (type):* **III**
> *Evidence (strength):* **C**
> *Recommendation (strength):* **2A**

The purview of screening guidelines would not typically extend to disease management beyond considerations of timely detection of lesions. However, there was concern in our working group that "surveillance" might be construed to include observation of small, asymptomatic extrapapillary / extramacular RHs, or even larger such lesions, with institution of treatment only for more advanced disease or only if tumors became 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.[21-27,50-53] We were in universal agreement that the benefits of ocular surveillance are best realized when paired with a strategy of early intervention for extrapapillary / extramacular RHs, considering the limitations of current treatment paradigms.

No prospective study evaluating the efficacy of intervention, which generally consists of ablation of extrapapillary / extramacular RHs, has been conducted. Kreusel *et al.* reported on a cohort of 57 consecutive cases of ocular VHL disease referred to a specialty clinic in Germany followed for an average of 7.3 years, during which 254 new RHs were detected (exclusive of those present at presentation).[23] Almost all of these 254 tumors were small and effectively treated with laser photocoagulation. Eyes treated prior to symptoms maintained good vision.

Similarly, two large retrospective case series have reported near-universal success using one or more sessions of laser photocoagulation for small RHs with diameter ≤1.5 mm with a reassuring safety profile.[54,55] Singh *et al.* reported using ablation with one or more sessions of laser photocoagulation in the management of 174 RH in 86 eyes (68 patients) and achieved favorable outcomes in 18 of 18 (100%) tumors with diameter of ≤ 1.5 mm, compared with 8 of 17 (47%) larger RH.[54] Krivosic *et al.* described a similar experience with 304 RH in 100 eyes (74 patients) treated with laser photocoagulation, reporting successful destruction in 271 of 271 (100%) RH with diameter ≤ 1.5 mm, over an average of 1.3 laser sessions, compared with 24 (73%) of 33 larger RH, over a mean of 3.5 sessions.[55] These results are in alignment with the collective experience of our working group and suggests a window of opportunity for detection and treatment of extrapapillary / extramacular lesions while they are small.

There are no good data regarding how many small (diameter ≤ 500 µm) RHs undergo spontaneous involution or never grow. Close observation has been employed in the past as an approach for such tumors. Our experience is that spontaneous regression is uncommon, and the majority of 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.[50-53,55] Given the minimal risks of treatment for small extrapapillary / extramacular RHs, we were in universal agreement that prompt treatment is preferred following 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, are beyond the scope of these guidelines and are reviewed elsewhere.[7] However, one emerging therapy with implications for RH surveillance and management bears mentioning. The recent FDA approval[56] of an oral small molecule HIF2-alpha inhibitor, belzutifan, for treatment of VHL-related renal cell carcinoma, pancreatic neuro-endocrine tumors, and central nervous system hemangioblastomas on the basis of a phase 2 clinical trial[57] 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-alpha inhibition may have efficacy for RHs, and we anticipate that this may affect both aspects of surveillance and treatment of ocular VHL disease. Since this systemic treatment avoids the direct damage of local ablation, systemic HIF2alpha inhibitors might 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 are currently lacking. Similarly, it might also 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 VHL patients on chronic HIF2alpha 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. Creation of a tumor registry to collect data in a standardized format is needed to generate evidence based recommendations. However, the availability of genetic testing has created a significant opportunity, offering identification of those with VHL disease prior to 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 a chance for safe and effective ablation of small extrapapillary / extramacular RHs as demonstrated by retrospective series.[54,55] Consideration of the morbidity caused by larger RHs and the limited current treatment options for advanced ocular VHL disease complete the rationale for a program of early identification and prompt treatment of extramacular / extrapapillary RHs as a means of preserving vision in those with VHL disease. New systemic pharmaceutical agents targeting HIF2alpha could assist in control of RHs and might allow particularly early treatment for all RHs, especially those in the macula and juxtapapillary region.

Figure 1
Overall Structure of International VHL Surveillance Guideline Consortium and the Ophthalmology Subcommittee

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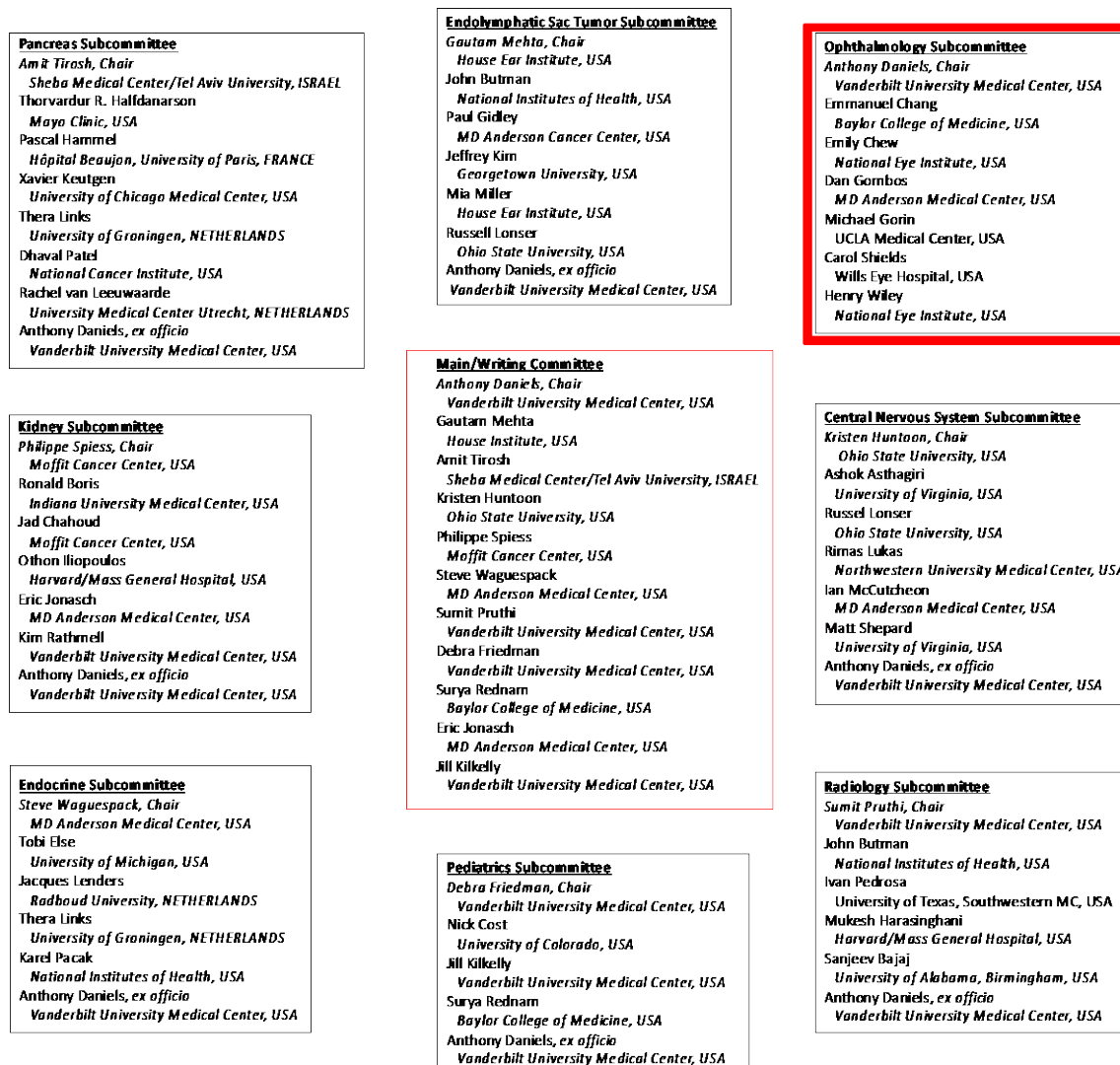 *Vanderbilt University Medical Center, USA*

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Figure 2
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 the Supplementary Table.
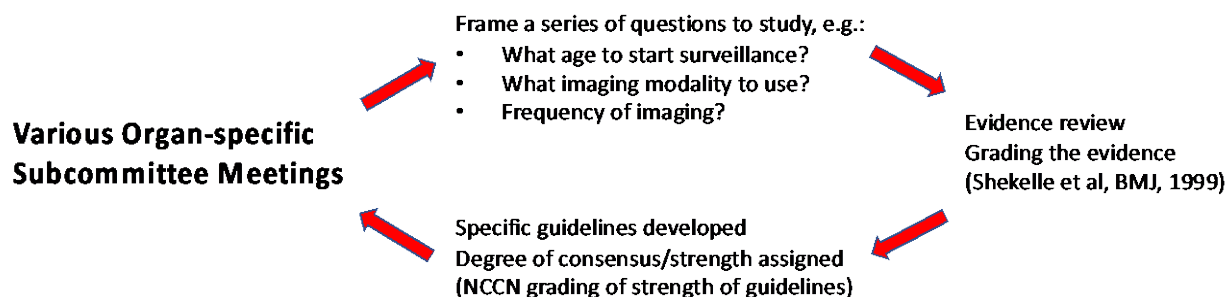
Table 1. Consensus Guidelines for Surveillance for Ocular VHL Disease

	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 for VHL disease, including first degree relatives of patients with known VHL disease, or any patient with single or multifocal RHs, should have 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 age 30 years, and then at least yearly after age 30 years. 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 prior to 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 modalities 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 and/or with experience with VHL disease / RHs, and ideally within the context of a multidisciplinary center capable of providing multi-organ surveillance and access to genetic testing.*	IV	D	2A
8	*Extramacular / extrapapillary retinal hemangioblastomas should be treated promptly. Even for small (diameter ≤ 500 µm) extramacular / 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 (less than 1 year).*	III	C	2A

* Level/strength of evidence, based on the method of Shekelle, *et al*.[18]
** Strength of recommendation, based on the National Comprehensive Cancer Network.

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