

Von Hippel-Lindau Disease: Genetics and Role of Genetic Counseling in a Multiple Neoplasia Syndrome

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A B S T R A C T

Von Hippel-Lindau disease (VHL) is one of the most common inherited neoplasia syndromes and is characterized by highly vascular tumors of the eyes, brain, and spine, as well as benign and malignant tumors and/or cysts of the kidneys, adrenal medullae and sympathetic paraganglia, endolymphatic sac, epididymis, and broad ligament. Since the discovery of the *VHL* gene in 1993, more than 900 families with VHL have been identified and examined. Genetic testing for *VHL* is widely available and will detect a disease-causing mutation in rate 95% to 100% of individuals who have a clinical diagnosis of VHL, making it the standard of care for diagnosis of VHL. Furthermore, genetic testing for *VHL* is indicated in some individuals with seemingly sporadic VHL-related tumor types, as $\leq 10\%$ of pheochromocytoma or early-onset renal cell carcinoma and $\leq 40\%$ of CNS hemangioblastoma harbor germline *VHL* mutations without a family history or additional features of VHL disease. The majority of *VHL* mutations are private, but there are also well-characterized founder mutations. VHL is a complex, multiorgan disease that spans the breadth of oncology subspecialties, and, as such, providers in these subspecialties should be aware of when to consider a diagnosis of VHL, when to refer a patient to a genetics specialist for consideration of gene testing, and, perhaps most importantly, how to communicate this sensitive information in an age-appropriate manner to at-risk families. This review will provide state-of-the-art information regarding the genetics of VHL and will serve as a key reference for nongenetics professionals who encounter patients with VHL.

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INTRODUCTION

Von Hippel-Lindau disease (VHL) is an inherited multiple-neoplasia syndrome that is characterized by highly vascular tumors of the eyes, brain, and spine (retinal and CNS hemangioblastomas [HBs]), as well as benign and malignant tumors and/or cysts of the kidneys (clear cell renal cell carcinoma [RCC]), adrenal glands and sympathetic paraganglia (pheochromocytoma [PCC] and paraganglioma [PGL]), pancreas (cysts and cystadenomas or pancreatic neuroendocrine tumors), endolymphatic sac (endolymphatic sac tumors [ELSTs]), epididymis (epididymal cysts and cystadenomas), and broad ligament (broad ligament and mesosalpinx cystadenoma).¹⁻⁴ Since the first description of the disease in 1926⁵ and the discovery of the *VHL* gene > 60 years later,⁶ more than 900 families worldwide with VHL have been identified and examined.^{7,8}

A timely review of the genetics of VHL is warranted because genetics is becoming increasingly integrated into health care in the name of

personalized or precision medicine. As such, health care providers must now, more than ever, understand the sensitive and unique nature of communicating genetic information to patients. This is especially true in the field of oncology, for which both somatic and germline genetic testing is becoming a standard part of oncologic work-up and clinical care. In the context of VHL, it is important to consider the sensitive nature of presymptomatic testing of children as well as unexpected (incidental) VHL diagnoses as a result of incorporation of multigene next-generation sequencing panels into clinical practice for sporadic VHL-associated tumors, namely RCC and PCC and/or PGL. Other special considerations in VHL include preconception counseling, including pregnancy-related risks, and the burden of extensive clinical screening.

CLINICAL DIAGNOSIS AND *VHL* GENE

A VHL diagnosis is established in an individual with a family history of VHL when he or she

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presents with a single characteristic VHL-related tumor, for example, retinal or cerebellar HB, RCC, etc. In the absence of a family history of VHL, a diagnosis requires two or more retinal or cerebellar HB, or one HB and a visceral tumor, excluding epididymal and renal cysts which are common in the general population.^{1,9-11}

The VHL tumor suppressor gene (*VHL*) was mapped to 3p25-26 in 1993.⁶ Individuals with the hereditary form of these tumors inherit a single mutant *VHL* allele, and tumor development occurs when the second wild-type copy is spontaneously lost or inactivated. This second hit can occur through a variety of mechanisms, including point mutations, deletions, or promoter hypermethylation.¹² As with many predisposition genes that cause rare inherited cancer syndromes, somatic loss of function of *VHL* occurs in sporadic cancers.¹³⁻¹⁵ Indeed, inactivation of *VHL* is a critical driver of nearly all clear-cell RCC,^{16,17} approximately 40% of sporadic CNS HB, and 10% of sporadic PCC.¹⁸⁻²¹

MOLECULAR BIOLOGY OF VHL

More than two decades of research has implicated VHL protein (pVHL) in transcriptional regulation, apoptosis, extracellular matrix formation, and ubiquitinylation of specific targets.²¹ In particular, the role of pVHL in the adaptive cellular response to hypoxia has been robustly investigated; pVHL regulates hypoxia-inducible genes via the targeted ubiquitinylation and degradation of the α -subunits of hypoxia-inducible factor transcription factors (HIF-1 α , HIF-2 α , and HIF-3 α).

pVHL binds to elongin C, which forms a complex with elongin B, cullin-2, and Rbx1. This complex catalyzes the polyubiquitinylation of specific proteins and targets them for proteosomal degradation. Under normoxic conditions, HIF α subunits are hydroxylated by prolyl hydroxylases, which is a reaction that requires oxygen. pVHL protein then binds to hydroxylated HIF α , targeting it for degradation by its attached destruction complex. In the absence of oxygen or functional pVHL, HIF α subunits are stabilized, accumulate, and translocate to the nucleus where HIF α forms heterodimers with HIF β to activate the transcription of dozens of hypoxia-inducible genes, for example, *VEGF*, *EPO*, *TGF α* , *PDGF β* .²¹ *VHL* mutant cells experience pseudohypoxia and shift metabolism to glycolysis even in the presence of oxygen, a process referred to as the Warburg effect. In fact, our ability to better manage patients with nonfamilial, advanced RCC and the surgical management guidelines of small renal masses have been largely driven by a better understanding of VHL and the consequent biochemical alterations that underlie these tumors, in particular, first-line vascular endothelial growth factor (VEGF)-targeting agents.²²

Pathogenic variants in *VHL* either reduce expression, that is, deletions, frameshifts, nonsense variants, and splice site variants, or lead to the expression of an abnormal protein, that is, pathogenic missense variants. The type of VHL that results from a pathogenic missense variant depends on its effect on the three-dimensional structure of the protein.²³ Pathogenic variants in *VHL* cause misfolding and subsequent chaperonin-mediated breakdown.²⁴ Pathogenic missense variants that destabilize packing of the α -helical domains, decrease the stability of the α - β domain

interface, interfere with binding of elongin C and HIF α , or disrupt hydrophobic core residues result in loss of HIF regulation. Furthermore, mutant pVHL may predispose patients to pheochromocytoma by altering the molecular regulation of apoptosis of sympathoadrenal precursor cells during development.²⁵

HIF-independent pVHL functions have added greater breadth to the understanding of the pathophysiology of VHL. For example, cyst formation in patients with VHL has been linked microtubule-based organelles called primary cilia. pVHL directs microtubule orientation and subsequent stability.²⁶⁻²⁸ pVHL also regulates primary cilia via both HIF- and microtubule-independent functions.²⁹⁻³¹ Furthermore, genetic instability in tumors is driven by VHL loss.³²

pVHL has been shown to mediate transcriptional regulation of nuclear factor- κ B,³³ Rbp1 large subunit of RNA polymerase complex II,^{34,35} p53 tumor suppressor,³⁶ p400 chromatin remodeling factor,³⁷ and JunB transcription factor via protein kinase C^{25,38}; however, pVHL also plays an important transcription-independent role in the regulation of extracellular matrix (ECM) and the microtubule cytoskeleton. pVHL is involved in the correct formation and turnover of the ECM³⁹ by interacting with collagen IV⁴⁰ and fibronectin.⁴¹ *Caenorhabditis elegans vhl-1* knockout worms also displayed genetic evidence for defects in ECM formation.⁴² Furthermore, the activity of enzymes involved in the degradation and remodeling of ECM, matrix metalloproteinase (MMP)-2, and MMP-9⁴³ is increased in VHL-mutant cells, and HIF-2 α induces the expression of membrane type 1 MMP. As endothelial cells require pVHL for correct vascular patterning and maintenance of vascular integrity during development,⁴⁴ loss of pVHL function causes both HIF-independent and -dependent defects in ECM that may promote angiogenesis, invasion, and metastasis of tumor cells.³⁹

Development of malignant disease after biallelic inactivation of *VHL* has only been adequately addressed in the context of RCC. Several RCCs sequenced in two patients with VHL revealed clonally independent and distinct secondary events that all converge on the PI3K-AKT-mTOR signaling pathway and are not characterized by inactivating mutations in p53, similar to sporadic RCCs in the general public.⁴⁵ Overall, there was limited evidence of intratumor heterogeneity in patients with VHL, although the number was small and requires independent validation.

ROLE OF GENETIC TESTING, MUTATION FREQUENCY, AND SPECTRA

The role of genetic testing in VHL is to confirm or exclude a diagnosis in at-risk relatives from established families with VHL, individuals with suspected clinical diagnoses, or individuals with atypical presentation or moderate suspicion, keeping in mind that failure to find a disease-causing mutation does not rule out a clinical diagnosis in the second scenario.

Among the more than 900 families in whom VHL has been identified, approximately 200 distinct mutations have been found.^{7,8,46} The mutation spectrum includes missense (52% of patients), frameshift (13%), nonsense (11%), large and complete deletions (11%), in-frame deletions or insertions (6%), and splice site (7%).⁷ Almost 100% of individuals that meet classic VHL

criteria with multiorgan involvement carry identifiable germline *VHL* mutations, but mutation detection rate decreases to 24% in those who meet criteria with limited *VHL* manifestations, and to 3.3% in those with *VHL*-associated tumors who do not meet diagnostic criteria.⁴⁷ Unexpected germline *VHL* mutations can be found in patients who have seemingly sporadic *VHL*-type tumors. *VHL* germline mutations occur in 30% to 50% of patients with retinal HB, 4% to 40% of patients with CNS HB, 20% of patients with ELST, 3% to 11% of patients with PCC, and 1% to 2% of patients with RCC.^{1,48-55} These observations underlie guidelines that suggest genetics evaluation when certain tumors or clinical features are present. Referral to genetics professionals for consideration of testing (Table 1) has been suggested for individuals with simplex cases of retinal or CNS HB, PCC, or ELST, as well as clear-cell RCC with any of the following features: diagnosed at an age \leq 46 years, bilateral or multifocal tumors, or one or more close relatives with clear-cell RCC.⁵⁶ Whereas other groups have suggested that, in addition to the above, genetic evaluation is warranted for individuals with more than one of the following: pancreatic cystadenoma, pancreatic neuroendocrine tumor, and epididymal and adnexal cystadenoma.⁵⁷

VHL GENE TESTING

VHL genetic testing is available at multiple laboratories worldwide (Table 2). Sanger sequencing of the coding region, along with deletion/duplication analysis, is the gold standard for analyzing the *VHL* gene and it results in a 95% to 100% detection rate, though mosaicism may cause false-negative test results.^{59,60} Multiplex ligation-dependent probe amplification is used for detecting partial and complete gene deletions/duplications.^{47,61}

When there is a high prior probability of *VHL* mutation, single gene testing is appropriate; however, when the genetic differential diagnosis is large, next-generation sequencing multigene panels should be considered in the setting of genetic counseling. This technology is often used for testing seemingly sporadic PCC and/or PGL or familial and early-onset RCC to determine if there is an inherited component. Thus, referral for genetics evaluation should be considered for RCC diagnosed at an age \leq 46

| Organization | Web Site |
|--|--|
| VHL Family Alliance | www.vhl.org |
| GeneReviews-VHL | www.ncbi.nlm.nih.gov/books/NBK1463/PDQ_Summaries-VHL |
| PDQ Summaries-VHL | www.cancer.gov/types/kidney/hp/kidney-genetics-pdq |
| National Society of Genetic Counselors | www.nsgc.org |
| Genetic Testing Registry | www.ncbi.nlm.nih.gov/gtr/ |
| GeneTests | www.genetests.org/ |

Abbreviation: PDQ, physician data query; VHL, von Hippel-Lindau.

years,⁵⁸ although for clinical purposes, we often cast a wider net and consider referral for diagnoses at an age \leq 50 years, or with the presence of a family history or other syndromic features.⁶² More than 40% of PCC and/or PGL are associated with germline mutation in any of 12 genes, which supports multigene panel testing for all cases of PCC and/or PGL.⁵⁴

Many laboratories worldwide now offer multigene panels that target PCC and/or PGL and RCC. It is critical to include genetics professionals in the testing process as they have the skills to ensure that the appropriate testing method is selected on the basis of their astute analysis of personal and family history. If more than one syndrome is in the differential diagnosis, genetics professionals will review the implications of each syndrome so that the patient is providing true informed consent and that there are no surprise diagnoses. In addition, genetics teams have expertise in interpretation of genetic testing results, which is particularly crucial in the realm of next-generation sequencing as results are often not straightforward and misinterpretation can have devastating effects on patient and family. Whereas positive genetic test results seem relatively straightforward, there are many issues to consider once a diagnosis has been made. Genetics professionals can help individuals cope with a diagnosis and develop strategies to share this information with at-risk family members. A negative genetic test result must be interpreted in the context of the personal and family history of the individual—often it does not rule out a clinical or a hereditary cause for the cancer or disease in the family. In this instance, an individualized approach must be adopted for further surveillance recommendations, taking into account personal and family history and patient preferences. Lastly, variants of uncertain significance (VUS) that are identified via genetic testing need to be carefully considered. A VUS means a genetic change is identified but the significance of that change is unknown. The patient and the medical team must understand that these results do not immediately affect medical management recommendations, which are always based on personal and family history, until the VUS is reclassified—a process that could take several months or years.

CLINICAL AND GENETIC FEATURES

Incidence of *VHL* is approximately one in 36,000,⁶³ and it has a penetrance of $>$ 90% by age 65 years, with a mean age at tumor diagnosis of 26 years (range, 1 to 70 years).^{3,64} The breakdown of

Table 1. Indications For Consideration of Genetic Counseling and Testing for VHL

| Simplex Case Is Sufficient for Referral | Presence of $>$ 1 Tumor Is Suggested for Referral |
|---|---|
| Retinal/CNS HB | Pancreatic cystadenoma |
| PCC/PGL | PNET |
| ELST | Epididymal/adnexal cystadenoma* |
| Clear-cell RCC† | Clear-cell RCC‡ |

NOTE. See Hampel et al,⁵⁶ O'Brien et al,⁵⁷ and Shuch et al.⁵⁸ Abbreviations: ELST, endolymphatic sac tumor; HB, hemangioblastoma; PCC, pheochromocytoma; PGL, paraganglioma; PNET, pancreatic neuroendocrine tumor; RCC, renal cell carcinoma; VHL, von Hippel-Lindau.

*Bilateral papillary cystadenomas of adnexal/broad ligament are pathognomonic for VHL.

†If diagnosed at age $<$ 50 years or one or more close relatives have clear-cell RCC.

‡If diagnosed at age $>$ 50 years or no close relatives have clear-cell RCC.

frequency and mean age at diagnosis for specific VHL tumor types is outlined in Table 3. Long-term outcomes in individuals with VHL continue to improve as a result of improvements in surveillance and treatment of RCC and CNS HB, the leading causes of morbidity and mortality in patients with VHL.⁶⁴ Phenotypic heterogeneity, both inter- and intrafamilial, is a hallmark of VHL.^{65,66} Clinically, VHL is classified into type 1 or type 2 disease on the basis of the frequency of RCC and PCC (Table 4).⁷⁰⁻⁷² Although this classification facilitates genotype-phenotype studies, reviewed elsewhere,⁷ it has limited clinical use as families move between subtypes as additional tumors are discovered.^{6,23} In brief, families with truncating mutations or exon deletions infrequently manifest PCC and, thus, usually have type 1 disease characterized by increased incidence of RCC and retinal and CNS HBs but not PCC, whereas type 2 VHL is characterized by missense mutations that predispose to PCC, some with PCC alone (type 2C), and other families with additional manifestations.^{4,60-72} Because the relationship between genotype and phenotype is still evolving, it is recommended that all individuals with a diagnosis of VHL follow the same surveillance protocol, which screens for all possible manifestations of the disease.

As with most tumor suppressors, the majority of VHL mutations are private; however, recurrent founder mutations are well documented. The most well-characterized founder mutations are those originating from Germany: c.T292C (previously c.T505; p.Y98H) in families from the Black Forest region and c.T334C (previously c.T547C; p.Y112H) in families from east central Germany (Leipzig).^{70,74-78} These families have migrated across Europe and America, especially to Western Pennsylvania. Both mutations predispose to type 2A VHL, with a high risk of PCC, a moderate risk of retinal and CNS HB, and a low risk of RCC.^{67,77}

A mutation hot spot is at codon 167 as a result of the presence of CpG dinucleotide, with attendant risks of deamination.⁷² There have been > 82 families identified with mutations at this location, which represent approximately 43% of mutations in American and

Canadian families with VHL type 2.^{7,60,72} Individuals with mutations at this location have a high risk of developing PCC (approximately 62%) and RCC.⁷²

VHL genotype-phenotype correlation is further complicated by a unique congenital polycythemia syndrome that is caused by biallelic—homozygous/compound heterozygous—mutations of the VHL gene without any manifestations of VHL disease.⁴ The most frequent mutation in this syndrome is c.C598T (p.R200W).⁷⁹ Individuals who are homozygous for this mutation have polycythemia, pulmonary hypertension, varicose veins, elevated serum VEGF concentrations, and occasional vertebral hemangiomas.^{4,80}

VHL is inherited in an autosomal-dominant manner, with the majority of cases (80%) inherited from an affected parent and ≤ 20% de novo.^{81,82} Once a VHL mutation is identified in a family, it is recommended that genetic testing be offered to the parents of the individual, if they are available, even with a seemingly absent family history, as family history may seem to be negative as a result of reduced penetrance or later age of onset, variable expressivity among family members, or death of an affected parent before the onset of symptoms.⁸³ Mosaicism occurs when a new mutation arises in some but not all tissues, which can result in negative genetic testing if an unaffected cell or tissue type is sampled.⁸² There are data that suggest that mosaicism is an under-recognized phenomenon in VHL, which could result in an overestimation of true cases of de novo mutations in probands. Generally, patients with mosaicism tend to be more mildly affected or asymptomatic,⁸³ although this is not always the case, and mosaicism has been confirmed in individuals with classic VHL disease as well.^{84,85} It is now recommended that additional testing methods be used to rule out mosaicism in the parents of a patient with proband with a seemingly de novo mutation and in cases moderately or highly suspicious of VHL in whom standard testing methods have failed to detect a disease-causing mutation.⁸²⁻⁸⁵ Various techniques have been successful in identifying mosaic mutations,^{82,84} and as an alternative, different tissue types can be sampled, including skin fibroblasts and oral epithelial cells.^{83,86} Detection of mosaicism is critical in terms of confirming a diagnosis and estimating the risk to siblings and offspring.^{84,85} As next-generation sequencing replaces Sanger sequencing, mosaic cases may be more easily detected, which could provide the data needed to elucidate the true frequency of mosaicism in VHL.

GENETIC COUNSELING AND SURVEILLANCE CONSIDERATIONS

Genotype-phenotype issues are only of scientific value at this point and play no role in clinical or counseling care for patients with VHL. Given the complexity of disease, a multidisciplinary approach with coordination of care among multiple medical specialists, including genetics professionals, is essential for individuals with VHL. Although preventative treatment cannot yet be offered for VHL, it is generally accepted that comprehensive surveillance programs improve outcomes by preventing avoidable morbidity and mortality.^{4,87,88} Therefore, genetics professionals may take a more directive approach to their counseling because of the importance of initiating or continuing screening for gene carriers and discontinuing it for noncarriers.⁸⁸ At-risk family members who received genetic counseling were more likely to

Table 3. Frequency and Age of Onset of VHL-Associated Tumors

| Tumor | Mean (range) Age of Onset, Years | Frequency in Patients, % |
|----------------------------|----------------------------------|--------------------------|
| CNS | | |
| Retinal HB | 25 (1-68) | 25-60 |
| ELST | 22 (12-50) | 10-15 |
| Craniospinal HB overall | 30 (9-70) | 60-80 |
| Cerebellum | 33 (9-78) | 44-72 |
| Brainstem | 32 (12-46) | 10-25 |
| Spinal cord | 33 (11-66) | 13-50 |
| Visceral | | |
| RCC or cysts | 39 (13-70) | 25-75 |
| PCC | 27 (5-58) | 10-25 |
| PNET or cyst | 36 (5-70) | 35-75* |
| Epididymal cystadenoma | Unknown | 25-60 |
| Broad ligament cystadenoma | Unknown (16-46) | Unknown |

NOTE. Adapted from Lonser et al³ and Maher and Kaelin.⁵⁹ See also Maher et al⁴ and Richard et al.⁴⁶

Abbreviations: ELST, endolymphatic sac tumor; HB, hemangioblastoma; PCC, pheochromocytoma; PNET, pancreatic neuroendocrine tumor; RCC, renal cell carcinoma.

*Frequency of PNET is 11% to 17%, whereas that of pancreatic cysts is ≤ 75%.⁴⁶

Table 4. VHL Subtypes

| VHL Subtype | VHL Mutation Type | High Risk | Low Risk |
|-------------|---|--------------------------|---|
| Type 1 | Deletions, insertions, truncations, missense | CNS/retinal HB, RCC | PCC |
| Type 1B | Contiguous gene deletions encompassing <i>VHL</i> | CNS/retinal HB | PCC, RCC (risk may increase if <i>C3</i> or <i>f10</i> remains increased) |
| Type 2A | Missense (eg, p.Y98H, p.Y112H, p.V116F) | CNS/retinal HB, PCC | RCC |
| Type 2B | Missense (eg, p.R167Q, p.R167W) | CNS/retinal HB, RCC, PCC | |
| Type 2C | Missense (eg, p.V84L p.L188V) | PCC | CNS/retinal HB, RCC absent |

NOTE. See Chen et al,⁶⁷ Maher et al,⁶⁸ and Hes et al.⁶⁹
Abbreviations: HB, hemangioblastoma; PCC, pheochromocytoma; RCC, renal cell carcinoma; VHL, von Hippel-Lindau.

pursue *VHL* testing compared with those who were only informed of the possibility of testing through a relative or written material.⁸⁹ Genetics professionals can aid families in the risk communication process and help identify and work through barriers to genetic testing and follow-up.

Presymptomatic Testing of Children

Because children of patients with VHL have a 50% chance of being affected, the topic of genetic testing for VHL in children is one that arises often in clinical care. For healthy children, many professional statements and guidelines support the recommendation that genetic testing be pursued only if the condition is associated with childhood onset and if a positive result leads to effective and safe screening and/or interventional options, thereby reducing morbidity and mortality.^{90,91} Although the average age of onset of VHL tumors is in the third decade of life, some patients develop tumors at age younger than 10 years and as early as infancy; therefore, presymptomatic genetic testing for VHL is justified,⁹² and also may identify those children who did not inherit the familial *VHL* mutation, thus sparing them from a lifetime of clinical screening.

Many factors should be considered before presymptomatic genetic testing is pursued. Genetic testing may be offered to a family with a child who is too young to give their informed assent, which can lead to a potential loss of autonomy for that child who may grow up with genetic information that they were not able to elect to know themselves.⁹³ Testing can also be associated with many complex emotions, including anxiety, denial, and guilt on the part of the parent who is affected with VHL.^{89,91} Many families may have lived through the experience of loved ones who developed tumors or other VHL-related complications at young ages that may impact coping when children are found to carry the VHL mutation.^{89,93} In addition, at-risk or affected children may be treated differently than their noncarrier siblings.^{89,93-95} Surveillance fatigue and/or burnout should also be considered in families who are considering testing their children for VHL as the surveillance is initiated in childhood for mutation-positive children and is lifelong.⁹⁶ This topic is discussed more extensively in subsequent section, Psychosocial Impact of VHL, Including the Burden of Lifelong Surveillance. It is strongly recommended that genetic counseling for presymptomatic genetic testing be conducted by a genetics professional in a comfortable environment and with the option of having multiple genetic counseling sessions as necessary.^{89,91,93,97}

Genetic Communication Needs of Children With VHL

A major question that arises from parents and health professionals is how and when to inform children of their genetic status. Research specific to communication among families with VHL is limited, but studies on the communication needs of children with other genetic conditions have found that the majority of patients would have preferred receiving information before age 12 years and ideally between the ages of 6 and 10 years. The majority parents with VHL want their children tested either at birth or at least before the age of 10 years.^{98,99} Adolescents preferred that the focus of a genetic counseling session be on understanding and managing their health condition rather than on their reproductive risks. They also identified their parents as their primary source of genetic information—with doctors or other health professionals coming second to this—and many wanted to be seen by their health care provider with their parents present.¹⁰⁰

Parents are often unsure of the best way to discuss information regarding a genetic diagnosis with their children, and common concerns include how the information may impact the self-esteem, coping, and anxiety level of their child.¹⁰¹ Parents may feel overwhelmed by the information, not knowing how, when, or what information to provide.⁹⁵ In addition, they may feel insecure in their own understanding of that information.¹⁰⁰ Studies show that parents feel that guidance and support from health care professionals on how to deliver this information is important, although often not available.⁹⁵ An important part of the genetic counseling process is to discuss with families how they plan to present the information to their children throughout different stages of their lives.¹⁰²

Children report their preference of learning about their genetic condition gradually through open and continuous communication during childhood.⁹⁴ In this way, children are provided with developmentally appropriate information of which they can ask questions and understand at their own pace, which helps them come to terms with their genetic risk in a natural and self-driven way.^{95,102} This genetic information then becomes part of the family narrative or culture; talking about those in the family who are also affected helps normalize the information by making it part of a shared family identity.^{94,95,102}

In contrast, not acknowledging the genetic condition in the family dissuades children from asking questions, as they do not want to upset their parents.^{94,95,101,102} Genetics professionals can help facilitate the communication process, elicit any perceived barriers to communication, and provide a safe place for

parents to practice these discussions. Resources that provide parents with techniques, diagrams, and appropriate language to use when communicating with their children can be developed, and support groups or additional professional psychosocial support should be encouraged.^{95,102} One such example available to the VHL community is the VHL Alliance Handbook Kids' Edition.¹⁰³

Preconception Counseling, Including Pregnancy-Related Risks

Availability of genetic testing for VHL introduces options for couples who are at risk of having a child with VHL, including prenatal diagnosis and preimplantation genetic diagnosis (PGD). Although perceptions may vary across countries, the French VHL study group interviewed 18 women and 13 men with VHL and found that a significant proportion of them (11 women and 11 men; approximately 70%) intended to use prenatal diagnosis in the case of a pregnancy, although one half of the group would not terminate an affected pregnancy or were undecided because they hoped for better outcomes and treatments in the future for their children compared with their own experience of VHL.⁹⁸ PGD uses in vitro fertilization techniques to identify genetic mutations within embryos before implantation.¹⁰⁴ This is a technology that patients with VHL are interested in exploring: 71% of Australian patients (10 of 14 respondents) viewed it as a favorable option to avoid having a child with VHL compared with 33% (26 of 79 respondents) in the Dutch population.^{89,105} At least 11 children have already been born using this method from the French VHL study group, which now comprises 802 individuals living with VHL, 28 of whom have attempted to have children using PGD (unpublished data). It is important that patients understand the practical limitations of PGD, namely, the cost, as many insurance companies currently will not cover the service. In addition, there are limitations to the technology that must be communicated, including the germline mutation in the family must be known; there are no data about the effect of in vitro fertilization–related hormone treatment of egg harvest on tumor development; and the process often takes > 1 year, and if a tumor develops in that period, application of PGD may be delayed or abandoned.

Another factor that complicates reproductive decision making in patients with VHL is the pregnancy-related risk that is associated with the disease. Whereas pregnancy is not typically considered a contraindication in patients with VHL, certain precautions must be considered. Available studies on the subject show conflicting results regarding development or progression of tumors and disease-related complications.¹⁰⁶⁻¹⁰⁸ It is critical to evaluate for potentially life-threatening complications, namely, PCC or hydrocephalus as a result of cerebellar HB, before attempting to become pregnant.¹⁰⁶ Many groups also advocate for additional screening and monitoring during pregnancy, including routine evaluation of retinal angiomas, noncontrast magnetic resonance imaging during the fourth month for CNS lesions, plasma metanaphrine testing during early, mid, and late pregnancy, and consideration of delivery via caesarian section to lower the chance of increased intracranial pressure.^{106,109} As long as patients are closely observed by a multidisciplinary team, pregnancy is typically a safe option for

women with VHL but other options, such as surrogacy and adoption, can also be explored.

Psychosocial Impact of VHL, Including the Burden of Lifelong Surveillance

There are few data on the psychosocial impact of complex tumor predisposition syndromes with limited prevention options; however, the data that do exist suggest that a significant proportion of those affected by VHL and those who care for them experience clinically important levels of distress.¹¹⁰ Those who experience the death of a close relative as a result of VHL during adolescence are particularly vulnerable. Approximately one third of participants had received professional psychosocial support, and the rest seemed amenable to it.¹¹⁰ Many patients struggle with the complex medical, social, and psychologic aspects of VHL, for example, uncertainty about future tumor development, frustration regarding lifelong screening, strained relationships with family and partners, difficulty communicating with others about VHL, and complex decisions regarding childbearing.^{89,111}

A highly sensitive concern for patients with VHL is the burden of lifelong surveillance. Suggested surveillance guidelines are summarized in Table 5. Whereas surveillance can pick up early-stage lesions that are amenable to treatment, that is, retinal angiomas, it also identifies lesions for which there is no immediate clinical benefit, that is, pancreatic cysts, and even findings unrelated to VHL that require further follow-up.⁸⁸ For these reasons, most individuals with VHL view surveillance regimens as a necessary yet anxiety-provoking burden that incite a variety of responses, including denial, anger, fear, sadness, and anxiety.⁸⁹

Table 5. Suggested VHL Surveillance Guidelines

| Age, Years | Screening | Frequency |
|------------|--|---|
| 0-4 | Eye/retinal exam with indirect ophthalmoscope | Annually |
| | Physical exam with blood pressure check and neurologic assessment | Annually |
| 5-15 | All the above, plus: Test for plasma-free metanephrines or urinary metanephrines using 24-hour urine test | Annually |
| | Abdominal ultrasound from age ≤ 8 years if indicated; abdominal MRI or functional imaging scan only if biochemical abnormalities found | Annually |
| | Audiology assessment; in the case of repeated ear infections, MRI with contrast of the internal auditory canal | 2-3 years (1 year if tinnitus, hearing loss, or vertigo) |
| ≥ 16 | All the above, plus: Quality ultrasound of abdomen MRI of abdomen with and without contrast MRI of brain and cervical spine | Annually Every 2 years Every 1-2 years |

NOTE. See VHL Family Alliance,¹⁰⁹ Binderup et al,¹¹² and Poulsen et al.¹¹³ Abbreviations: MRI, magnetic resonance imaging; VHL, von Hippel-Lindau.

Although the uptake of genetic testing is generally high in families with VHL, as many as 60% of identified mutation carriers will be lost to follow-up 5 years after testing, which suggests that patient concerns regarding surveillance are not being appropriately addressed.⁹² As current VHL surveillance guidelines are largely based on expert medical opinion and limited evidence, health care providers also struggle with determining optimal surveillance recommendations while also minimizing patient psychologic distress (“scanxiety”) and expenses to the health care system.¹¹²

Recently, nationwide efforts by VHL care teams in Denmark and the Netherlands have sought to address these issues by providing additional evidence regarding the optimal initiation and frequency of surveillance regimes.¹¹²⁻¹¹⁶ Kruizinga et al¹¹⁵ calculated the organ-specific age at which to initiate surveillance as well as surveillance intervals. These were age 0 years/at birth for the adrenal glands and a 4-year interval between screenings, age 7 years for the retina with a 2-year interval, age 14 years for the cerebellum with a 1-year interval, age 15 years for the spinal cord with a 1-year interval, age 16 years for the pancreas with a 2-year interval, and age 18 years for the kidneys with a 1-year interval. These findings represent significant deviation from current surveillance guidelines, in particular, in terms of adrenal and retinal surveillance, with a later initiation of retinal surveillance (by 6 years), with a 1-year longer interval follow-up, and an earlier initiation of adrenal surveillance (by 5 years) with a 3-year longer interval follow-up.¹¹⁵ They were also able to calculate the age at which the probability of developing a first manifestation of VHL is < 5% (age 34 years), which represents a reasonable age at which to stop surveillance, for instance, in at-risk family members of a proband whose disease-causing mutation cannot be identified.¹¹⁵

Other groups have suggested possible modifications in the current guidelines for other organs. For example, Poulson et al¹¹³ found that biennial CNS examinations led to a relatively high rate (7.2%) of interval lesions with clinical consequences, whereas annual screening reduced the risk to an acceptable rate of 2.7%. Binderup et al¹¹² pointed out that these and other studies have assumed the risk of new tumor development is constant throughout the lifetime of a patient with VHL; however, risk can vary significantly with age and genotype and depends on the organ involved. They found that tumor development was highest at age 30 to 34 years, and when broken down by the most common organs affected in their cohort, the risk of retinal tumors was highest during teenage years (age 15 to 19 years) and the risk of cerebellar tumors was highest during age 30 to 39 years. Therefore, adherence to surveillance of these organs during those ages should be particularly encouraged. In addition, Binderup et al¹¹² stratified by genotype and found that carriers of truncating mutations had significantly higher rates of manifestations compared with missense mutation carriers, with the exception of retinal tumors, which were significantly less frequent in carriers of truncating mutations. Whereas some argue that surveillance recommendations should not be influenced by specific mutations, as the second hit that results in tumor development is random, the goal in any hereditary cancer predisposition syndrome is to be able to tailor management guidelines on the basis of individual factors, such as genotype, environmental stimuli, or other genetic alterations.

As all of the previously mentioned studies represent significant deviations from current surveillance guidelines, the results need to be confirmed by larger prospective studies in other geographic populations before incorporation into clinical practice.

In terms of practical strategies for increasing adherence to surveillance protocols, it is crucial for health care providers to set expectations before screening with regard to benefits, limitations, and logistical matters, including how and when results will be relayed. It is important to engage the whole family in this discussion, if possible, as studies have shown that family members tend to take the same stance toward long-term surveillance.⁹² Families must also understand that the absence of symptoms is not a reason to delay screening; the variable nature of disease within families can create the misconception that only members who are most symptomatic require close observation.^{92,116} It is important that health care providers adhere to national guidelines for surveillance because patients who are given variable advice at different institutions tend not to fully adhere to the advice.¹¹⁶ If feasible, a case manager—a specially trained nurse practitioner or genetic counselor—for families with VHL is advised to serve as a primary contact and to help coordinate multidisciplinary care, including medical follow-up and psychosocial needs.¹¹⁶

The role of patient associations is crucial in disseminating up-to-date information about rare diseases to patients and physicians. The VHL Alliance, established in 1994, has a worldwide presence, actively contributes to supporting VHL research, and works with experts in the field to establish current surveillance recommendations. There are now National VHL networks and/or specialized clinical care centers in > 30 countries that offer specialized medical and psychosocial support as well as the opportunity to connect with patients with VHL from around the world.^{46,109} Table 4 provides a list of VHL and genetics resources for patients, caregivers, and managing physicians.

In summary, VHL is a complex and intriguing disease from a genetic, clinical, and psychosocial standpoint. It is a disease that spans a breadth of pediatric and adult oncologic subspecialties, and, as such, providers should be aware of when to consider a diagnosis and the special considerations involved in genetic work-up and familial testing. There have been many advances in the understanding of VHL over the years, and continued discoveries will lend insight into the treatment of a variety of hereditary and sporadic cancers as well as to help optimize all aspects of care for patients with VHL and their families. Strategies may need to adjust as new therapies are expected to become available, likely on an organ-by-organ basis. For example, in the treatment of ccRCC, both patients with VHL and sporadic patients have enormously benefited from VHL-driven molecular biology, in particular, VEGF pathway inhibitors such as sunitinib and pazopanib, which currently form the only two first-line therapies recommended for treatment of metastasized RCC. However, recent US Food and Drug Administration approval of immuno-oncological agents, such as nivolumab, for second-line treatment of advanced RCC¹¹⁷ should be carefully followed in patients with VHL, as presumably a single patient with VHL may have hundreds or more subclinical lesions throughout his or her body. Exciting developments in gene therapy offer promise for patients with

VHL,¹¹⁸ but, for now, surveillance remains the best approach for disease management.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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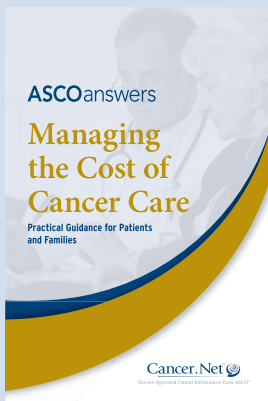
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Von Hippel-Lindau Disease: Genetics and Role of Genetic Counseling in a Multiple Neoplasia Syndrome

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