What You Need to Know About VHL

A reference handbook for
people with von Hippel-Lindau,
their families, and their medical teams

Written by the VHL Alliance

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If you are interested in a translation of this handbook, please contact the VHL Alliance (info@vhl.org) for more information.

Disclaimer

This book is intended to add to, not replace conversations between a patient and their healthcare team. The specific details and the patient's total health situation need to be considered in making the final decision about treatment. The content of this book should not be taken or relied upon as medical advice on how to treat your specific manifestation or medical condition. Rather, by providing context and understanding, this book empowers patients to better partner with their care team and facilitate constructive conversation.

VHL Alliance

The VHL Alliance (VHLA) is a 501c3 non-profit organization founded in 1993 by three families with VHL to share experiences, learn from one another, support one another, and help the doctors understand and treat VHL, and improve life for patients. Today, the VHL Alliance is the preeminent resource and clearinghouse of patients, caregivers, researchers, and the medical community.

Our Vision:

Curing Cancer through VHL

Our Mission:

The VHL Alliance (VHLA) is dedicated to research, education, and support to improve awareness, diagnosis, treatment, and quality of life for those affected by VHL.

Copies of this handbook, as well as information on VHL-related resources and events can be found on the VHL Alliance website: vhl.org.

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Preface

This handbook has been developed as a tool to help individuals with VHL, their caregivers and families, and other interested people learn more about VHL. The information presented here is intended to add to conversations with physicians and other health care providers, and is not meant to replace working with qualified medical professionals.

One of the primary goals of this handbook is to provide affected individuals and their families greater confidence in the future. With early detection and appropriate treatment, there is more hope today for families with von Hippel-Lindau disease than ever before. Research on VHL and related diseases has led to better methods of diagnosis and treatment. Knowledge is increasing rapidly by the open sharing of information throughout the world among families, health professionals and the research community.

The VHL Alliance wants to thank the following physicians and medical professionals for their expert review of this handbook:

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Dr. Rachel van Leeuwaarde, University Medical Center, Utrecht (Pancreas)
Dr. Steven Waguespack, MD Anderson Cancer Center (Adrenal)

Revision 6, 2020, provides updates on surveillance guidelines, best practices, research, information about manifestations, and VHLA resources. It is clear that the best way to manage VHL is to identify issues early, monitor and treat them

appropriately with minimal invasion and damage, and focus on long-term health. The VHL Alliance looks forward to working with you and your medical team.

Print and digital versions of the handbook are available at: vhl.org/handbook. Please submit any suggestions and comments on ways to make future editions of this handbook even more useful to: info@vhl.org.

Please note that the VHL Handbook Kids' Edition, specifically geared toward children and their families, is also available in multiple languages in print, e-book, or pdf.

Throughout this handbook, words that may be new to readers are printed for the first time in each section in italics. Definitions of these and other medical terms related to VHL appear in the glossary section of this handbook.

Suggestions and comments to make future editions of this handbook even more useful are always welcome. Please write to info@vhl.org.

COVID-19

A Message for the VHL Alliance's Clinical Advisory Council

The COVID-19 pandemic has yielded significant changes with regard to healthcare. Hospitals around the world have developed strategies to treat coronavirus patients, while making sure that the care of existing patients is minimally disrupted and safe.

While there is no question that surveillance is one of the most important tools for managing VHL, in light of the situation, each person must weigh the risks and benefits of attending an in-person office appointment versus temporarily delaying a scan. This is something that only you, in conjunction with your medical team, can decide. Therefore, if you are scheduled for routine follow up or surveillance examinations or scans, please contact your VHL provider to decide if the timing should be changed. Telemedicine is a great option, when possible and appropriate. In the event of an emergency or the development of new VHL-related symptoms, do not hesitate to seek advanced medical care.

Please note that there is currently no evidence to suggest that VHL patients are at greater risk of contracting COVID-19 compared to the general public. If you have any concerns regarding your specific situation, please contact your VHL provider.

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SECTION 1

WHAT IS VHL?

Von Hippel-Lindau disease, or VHL disease, is one of more than 7,000 known inherited rare disorders. It is a disease caused by a mutation in the *VHL* gene, which normally prevents tumor growth. The mutation to this gene prevents it from working properly, resulting in both benign tumors and malignant tumors. The latter can spread and become metastatic.

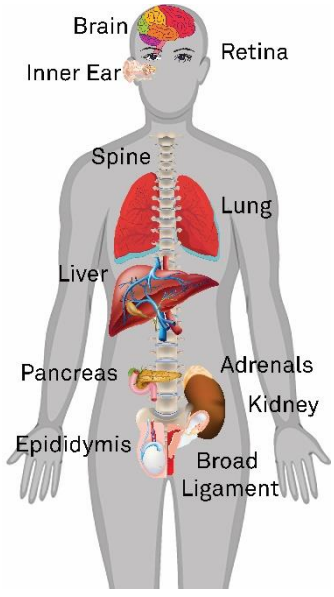


Figure 1. Manifestations of VHL. Lesions can appear in up to ten different parts of the body.

In people with VHL, tumors may develop in up to ten different parts of the body. All of these tumors involve the abnormal growth of blood vessels. Most of these tumors are benign, meaning that they will not spread to nearby organs. However, VHL tumors in the kidneys, adrenals, and pancreas can grow to a stage where they become "malignant," where the cancer can spread to other parts of the body. The VHL Active Surveillance Guidelines (vhl.org/surveillance-guidelines) were developed as a way for patients and doctors to actively work together to prevent most of the worst effects of VHL.

VHL is different in every patient. Even in the same family, people may show different manifestations of VHL. Since it is impossible to predict exactly which VHL manifestations each person will have, and at what age, it is important to continue to check for all the possibilities throughout a person's lifetime.

VHL is different from other conditions in a few ways: it has no single primary symptom, it does not manifest exclusively in one organ, and onset does not always begin in a particular age group. Approximately 87% of all people with a *VHL* mutation express at least one manifestation by the age of 60. Appearance and severity are so variable that some people may have only relatively mild issues, while others may have much more serious ones. Due to its complex nature, VHL may not be recognized for many years. However, with careful monitoring, early detection, and appropriate treatment, the most harmful consequences of VHL can be greatly reduced, or in some cases even prevented entirely.

Discovery of VHL

VHL is named after the two physicians who first described the symptoms that they observed in their patients. Dr. Eugen von Hippel, a German ophthalmologist, described hemangioblastomas in the eye in 1893–1911. His name was originally used only in association with VHL in the retina. Dr. Arvid Lindau, a Swedish pathologist, first described hemangioblastomas of the brain and spine in 1926. Dr. Lindau's description included a systematic compilation of all other published patients, including those of von Hippel, and described changes in different abdominal organs. It is now understood that both of these physicians were describing different aspects of the same disease.

While about 80% of people with VHL inherited it from a parent, approximately 20% of people with VHL are a result of a random genetic mutation before birth. It is not yet understood why this happens, but it underscores the importance of the need for careful differential diagnosis in all people, not just those in families known to be at risk for VHL.

WHAT IS CANCER?

Cancer can be a frightening word. It is not one disease, but rather a group of more than 100 different diseases. While each type of cancer differs from each other, they all are a disease of the body's cells. It is important to realize that not all VHL tumors have the potential for spreading to other parts of the body, or forming metastases. Therefore, a personalized approach must be taken when deciding on treatment options.

Normally, healthy cells that make up the body's tissues grow, divide, and replace themselves in an orderly way. This process keeps the body in good repair. Sometimes, however, normal cells lose their ability to limit and direct their growth. They divide too rapidly and grow without any order. Too much tissue is produced, causing tumors to begin to form.

> "Cancer is an abnormal growth of cells. Cancer cells rapidly reproduce despite restriction of space, nutrients shared by other cells, or signals sent from the body to stop reproduction... Tumors, abnormal growth of tissue, are clusters of cells that are capable of growing and dividing uncontrollably; their growth is not regulated."
>
> —Stanford Health Care: stanfordhealthcare.org/medical-conditions/cancer/cancer.html;

Tumors can be benign or malignant

Benign tumors do not spread. VHL-related tumors of the brain, spinal cord, and retina are benign.

Malignant tumors can invade and destroy nearby healthy tissues and organs. Malignant cancer cells can also spread, or metastasize, to other parts of the body and form new tumors. VHL tumors in the kidney and pancreas may become malignant.

The objective is to find tumors early, watch for signs that a tumor is becoming aggressive in its behavior, and to remove, or disable, the tumor before it invades other tissues. Benign tumors may also need treatment, or removal, if their growth will impact other areas by causing loss of function or pain. Since these tumors are inside the body, medical imaging techniques are needed to find and watch them.

Not all VHL-related tumors require surgery when they are found. Research is ongoing to better predict when a tumor requires action. Patients can help researchers learn more about how long we can safely watch tumors by sharing their family's own experiences through the MyVHL: Patient Natural History Study at: vhl.org/MyVHL.

COMMONLY OCCURRING MANIFESTATIONS

If you have been diagnosed with VHL, you were born with it. However, age of onset can vary considerably from family to family and from individual to individual. The values provided in Table 1 include age at presymptomatic diagnosis and symptomatic diagnosis. The age difference between presymptomatic and symptomatic diagnosis is a reflection of a patient's compliance with VHL

surveillance. With better diagnostic techniques, presymptomatic diagnoses are being made earlier and earlier. This does not mean that action needs to be taken when early tumors are found, but care must be taken to watch their progression in order to act at the appropriate moment.

	Most Common Presymptomatic Diagnosis Age	Most Common Symptomatic Diagnosis Age	Frequency in Patients
Central Nervous System			
Retinal hemangioblastomas	12–25 yrs	0–68 yrs	25–60%
Endolymphatic sac tumor	24–35 yrs	12–46 yrs	10–25%
Cerebellar hemangioblastomas	18–25 yrs	9–78 yrs	44–72%
Brain stem hemangioblastomas	24–35 yrs	12–36 yrs	10–25%
Spinal cord hemangioblastomas	24–35 yrs	12–66 yrs	13–50%
Viscera			
Renal cell carcinoma or cysts	25–50 yrs	16–67 yrs	25–60%
Pheochromocytomas*	12–25 yrs	4–58 yrs	10–20%**
Pancreatic tumor or cyst	24–35 yrs	5–70 yrs	35–70%
Epididymal cystadenomas	14–40 yrs	17–43 yrs	25–60% of males
APMO or broad ligament cystadenomas	16–46 yrs	16–64 yrs	est. 10% of females

* Includes the 20% of these tumors that occur outside the adrenal gland, also called paragangliomas.
** Frequency of pheochromocytoma varies widely depending on genotype. Refer to Table 2.

Table 1. Occurrence and age of onset in VHL: Compiled from a survey of papers from 1976 through 2004, and including data from the VHL Alliance.

Pheochromocytomas are very common in some families, while renal cell carcinoma is more common in others. Individuals in the same family may differ as to which of the family tumor types they express.

Pancreatic neuroendocrine tumors (pNETs) may be more aggressive in people with an alteration in exon 3 of the gene.

Other manifestations include cerebral (upper brain) hemangioblastomas, retinal hemangioblastomas, adrenal tumors, endolymphatic sac (inner ear) tumors, and rare occurrences of broad ligament and epididymal cystadenomas. Rare hemangioblastomas in the liver, the skin, and the lungs can also be detected. It is important to note that hemangioblastomas are different tumors from "hemangiomas" of the liver or vertebral bodies; the latter are common in the general population and unrelated to VHL disease.

HOW DO PEOPLE GET VHL?

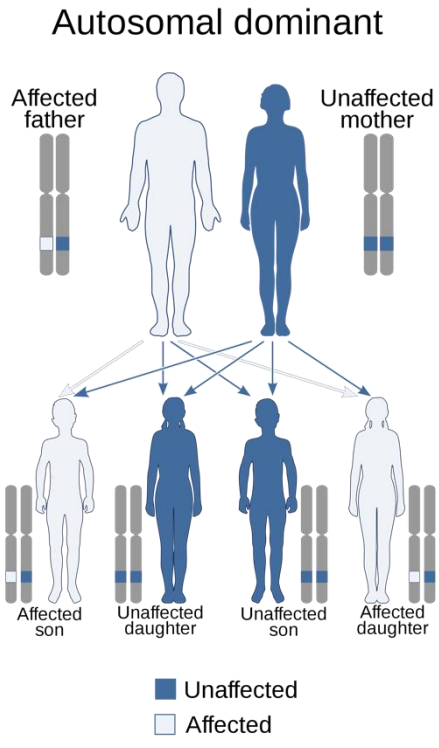


Figure 2. Illustration of autosomal dominant pattern of inheritance.

Normally, every cell has two working copies of each gene: one inherited from the mother and one inherited from the father. VHL is caused by an autosomal dominant mutation, which means that only one altered copy of the

gene is necessary to cause the condition. Manifestations related to VHL can vary quite a bit. The occurrence and severity of VHL is not related to gender. Each child of a person with VHL is at 50% risk of inheriting the altered copy of the gene. There is nothing anyone can do, or not do, to control which gene is passed on; it is completely up to chance. Although some people with VHL have few tumors and virtually no symptoms, VHL does not skip generations. Unless there is a *de novo* mutation, every person with VHL must have a parent with VHL (see Figure 2).

It is important to note that genetic mutations are very common. Every single human being has genetic mutations, however, most mutations are benign, which means that they do not cause disease or health problems.

In most cases, the alteration in the *VHL* gene occurred a very long time ago; the original mutation has been passed down through several generations in a family. VHL has been documented back to the early 1600's in the Black Forest family in Germany and Pennsylvania. About 20% of people with VHL are the first in their family to have an alteration in the *VHL* gene. Neither parent is affected. They are considered "*de novo*," or "first-in-family". This new mutation occurs during the copying of the gene in one of the early stages of cell division, soon after the sperm fertilizes the egg. This new alteration in the *VHL* gene can be passed onto future children of this affected person and necessitates medical surveillance of these children.

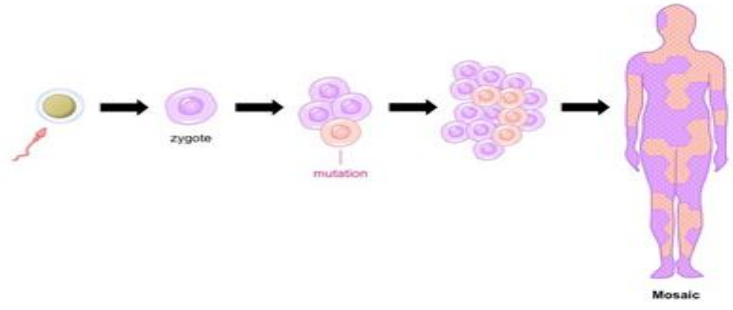


Figure 3. Illustration of a *de novo* mosaic mutation: A mutation occurs in a later stage of cell division and is only present in some of the cells. A person with a mosaic genetic condition has two different populations of cells.

In *de novo* cases of VHL, depending on exactly when the mutation occurred, mosaicism is possible. A person with mosaic VHL has two different populations of cells that make up their body (see Figure 3). One cell population contains two working copies of the *VHL* gene (these cells are normal) and a second cell population contains one working and one non-working *VHL* gene copy (these cells have a mutation). It is difficult to know which and how many cells of the body of a mosaic individual are affected. Therefore, it is not possible to predict the risk to

develop manifestations or to pass an altered gene copy onto future children. If the mutation is present in the cells of the sperm (father) or the oocyte (mother) the parents have a 50% chance to pass the mutation to the children. This is the reason that some children have a positive blood test while their parent's blood test is negative. In other words, if the parent has no detectable mutation in the blood test it is possible that the child has a truly *de novo* mutation or that the mutant *VHL* gene is inherited from a "mosaic" parent.

GENETIC TESTING

Anyone with a first-degree (parents, children, sisters, and brothers) or second-degree (aunts, uncles, grandparents, and grandchildren) relative with VHL is "at risk" for VHL. Each child of a person with VHL is at 50% risk for VHL. The only way to determine for sure that someone has an altered *VHL* gene is through DNA or genetic testing. In any given family, it is most informative to begin DNA testing of a person with VHL manifestations. This is a blood test that must be processed at a clinical testing laboratory (lab) that has the necessary capabilities to test for VHL, and has been certified as compliant with the Clinical Laboratory Improvement Amendments (CLIA or College of American Pathologists (CAP) in the United States, or has achieved equivalent quality ratings in other countries.

If DNA testing finds the alteration in the *VHL* gene, the results are POSITIVE: this person has VHL. If the DNA testing finds two unaltered copies of the *VHL* gene, the test is NEGATIVE, which means that this person is very unlikely to have VHL. While there is always some margin for error, a negative test result in a person with manifestations of VHL is very rare. However, this may occur if the person is mosaic or because current genetic testing methods cannot detect every possible alteration that can disrupt the *VHL* gene. In a CLIA or CAP-certified lab, the possibility of error is under 1–2%, which is considered as certain as it can be in nature. Anyone at risk for VHL who has not received a negative DNA test result should continue to follow a surveillance program to ensure early diagnosis of any VHL problems.

To have DNA testing done for a family, it is important to work with a geneticist or genetic counselor. First, the person in the family with a clinical diagnosis of VHL should submit a blood sample for testing. The lab will check to see if they can determine the alteration in this person by performing a complete screening of the *VHL* gene. Properly done, this test is greater than 99% successful in finding mutations in patients with a germline mutation in the *VHL* gene. Once a mutation has been found, the exact change in this person's *VHL* gene will be the same mutation that is passed within their family. With this information, another person in the family, who does not have a clinical diagnosis of VHL, can submit a blood sample and the lab can check for the same mutation in this second person's DNA.

For people who are the first in their families to be tested for VHL, or for adoptees or others who do not have known blood relatives to assist in the testing, it can take a little longer and cost a little more to get results from a complete screen. However, once the first test in the family is completed, it becomes a road map for subsequent tests in other family members, which can be done faster and often cost less. This is called a single site genetic testing because it is asking whether the gene is mutated at the spot that characterizes the family mutation.

People who were tested prior to the year 2000 using a method called "linkage analysis" may wish to be re-tested using DNA sequencing or more modern methods that are significantly more reliable. There have been situations where the results of linkage analysis have proven to be incorrect.

To find a geneticist or genetic counselor, contact a VHL Clinical Care Center (vhl.org/ccc) or check nsgc.org. Large medical centers will usually have a genetics department. This is the best place to assess your risk for VHL. The genetics department at these large medical centers may be located within pediatrics, but genetics clinics typically see both children and adults. It is also important to check with your health insurance company regarding coverage for DNA testing. If your health plan tells you that it will not cover the test, you can work with your doctor or genetic counselor to appeal this decision. Note that in recent years, DNA testing has become much more affordable.

If a pregnant woman is having any genetic testing done, she may request a VHL test be part of those tests, especially if there is any VHL in the family or any history of VHL-related tumors in other family members.

If your DNA diagnosis is unclear, please contact the VHL Alliance (info@vhl.org or 617.277.5667 x4) to discuss it further.

VHL SUBTYPES

Researchers have identified four categories of VHL that may be useful in predicting the relative risk in a family for certain manifestations of VHL. Please note that these categories are not absolute, so it is important that all VHL patients undergo surveillance for all the features of VHL, regardless of subtype. (See Table 2.)

VHL Subtype	VHL Mutation Type	High Risk Manifestations	Low Risk Manifestations
Type 1	Deletions, insertions, truncations, missense	Central Nervous System hemangioblastomas Retinal hemangioblastomas Renal cell carcinoma	Pheochromocytoma
Type 1B	Contiguous gene deletions encompassing *VHL*	Central Nervous System hemangioblastomas Retinal hemangioblastomas	Pheochromocytoma Renal Cell Carcinoma (risk may increase if *C3 or f10 remains increased*)
Type 2A	Missense; e.g. p.Y98H, p.Y112H, p.V116F	Central Nervous System hemangioblastomas Retinal hemangioblastomas Pheochromocytoma	High probability for Renal Cell Carcinoma
Type 2B	Missense; e.g. p.R167Q, p.R167W	Central Nervous System hemangioblastomas, Retinal hemangioblastomas Renal cell carcinoma	
Type 2C	Missense; e.g. p.V84L, p.L188V	Pheochromocytoma only	

Table 2. Genotype-phenotype classifications in families with von Hippel-Lindau disease. Note: Endolymphatic sac tumors and cystadenomas of the epididymis and broad ligament have not been assigned to specific VHL subtypes.

EARLY DETECTION

Because VHL varies so widely, there is no consistent set of symptoms. Each possible feature of the disease is detected in a different way.

If there is a family history of VHL, it is important to inform your doctor(s), or your child's pediatrician, and begin surveillance early before any symptoms occur. Most VHL lesions are easier to treat when they are small. Using the information provided in VHL Suggested Active Surveillance Guidelines (vhl.org/surveillance-guidelines), speak with your doctor about the best time to begin surveillance and the right schedule for return visits. The VHL Alliance recommends informing the pediatrician of the family's history of VHL and beginning eye examinations with an ophthalmologist for children at risk by age 1.

Nearly everyone at one time or another has wondered if it is better not to know—perhaps if we just don't go through the testing, everything will be okay. For a while, that may seem to be true. But a number of possible complications of VHL are "silent"—symptoms may not even be present until the problem has developed to a critical level. It is a little like not taking care of one's house or car. They may get away with it for a while, but then it all catches up and costs a great deal all at once. However, unlike a house or car, it may not be possible to reverse symptoms that have occurred and go back to normal. There is clear, documented evidence that people with VHL will stay healthier, for longer, if they follow the recommended surveillance guidelines.

SURVEILLANCE

> "My family has become convinced that one should never go alone to a doctor's appointment. If the news is difficult to hear, the brain shuts off at a certain point and just won't accept any more information. It helps if there are two people there, preferably with the unaffected person taking notes. If you have to go alone, record the conversation. You'll be amazed when you listen to the recording the next day."
>
> -Darlene Y., Massachusetts

Even if there is no family history of VHL, when any one of the features of VHL is found, a diagnosis of VHL should be considered and a full diagnostic evaluation of other areas of the body should be carried out. Twenty percent (20%) of VHL patients are the first in their family to have VHL. It is also estimated that no DNA mutation or deletion can be found in approximately 10% of people clinically diagnosed with VHL. These people have VHL, but current DNA testing has not been able to find the specific alteration.

Depending on the outcome of the surveillance, the doctor will describe what particular signs need to be closely followed. In general, vision or hearing problems, vomiting, headaches, dizziness/balance problems, progressive weakness in arms or legs, flushing, a racing heart, or persistent pain that stays in one place and lasts more than 1–2 days, should be checked by your doctor.

Once VHL has been diagnosed, it is important to undergo surveillance for possible evidence of the disease in all parts of the body as well. Even if manifestations have only been in one organ in the past, there is still a risk of involvement in other organs as well. A plan for future ongoing surveillance should be discussed with the doctor.

General Recommendations for Surveillance

Your medical team will work with you to develop the right surveillance and monitoring program for you and your family. The purpose of active surveillance is to monitor known issues to make sure that they are treated at the best time, and to ensure long-term health. Surveillance involves testing before symptoms appear to make sure that any issues are found early. See the VHL Active Surveillance Guidelines below (and vhl.org/surveillance-guidelines).

It is important to begin surveilling children who are at risk as early as possible. Fifty percent (50%) of children of a parent with VHL will inherit the gene. Using genetic testing, it is possible to identify which children have VHL and need surveillance and which children do not carry the VHL mutation and, therefore, do not need ongoing surveillance.

The VHL Alliance and its Clinical Advisory Council recommend that you begin surveillance of children as early as before age one. Make sure that the pediatrician knows that the child is at risk for VHL. Complete eye examinations, including a dilated retinal examination, at this young age are specifically recommended.

Surveillance methods are age dependent and can be done using noninvasive techniques that are not painful. The VHL Alliance and its Clinical Advisory Council recommend the "5-11-15 rule":

- An annual thorough medical eye examination by a retina specialist and a complete physical examination, including blood pressure and neurological examination
- An annual 24-hour urine collection or blood test beginning at age 5
- A hearing test by an audiologist, and imaging of the brain and spine, every two years, beginning at age 11
- A MRI of the abdomen, every two years, beginning around age 15

VHL Suggested Active Surveillance Guidelines

The guidelines are current at the time of publication (Fall 2020), but please see the VHL Alliance website for the latest guidelines: vhl.org/surveillance-guidelines.

Modifications of surveillance schedules may sometimes be done by physicians familiar with individual patients and their family history. Once a person has a known manifestation of VHL or develops a symptom, the follow-up plan should be tailored to the patient's specific findings and circumstances with their medical team. More frequent testing may be needed to track the growth of lesions that have already started to grow.

People who have had a DNA test and do not carry the altered *VHL* gene, and have not been clinically diagnosed with VHL, do not require ongoing surveillance.

The surveillance guidelines recommend using MRI scans, instead of CT scans, in order to reduce total lifetime exposure to radiation for people with VHL. To monitor the most critical areas of the brain and spinal cord in the most efficient and cost-effective manner, CNS MRIs should include the brain, cervical, thoracic, and lumbar spine. Scans should be ordered as no less than a 1.5T MRI with and without contrast, with thin cuts through the posterior fossa, to rule out hemangioblastomas of the neuroaxis.

Type of Surveillance (Tumors being screened)	**AGE[1]**						**Pregnancy[11]**
	Until age 5 years	**Starting at age 5 years**	**Starting at age 11 years**	**Starting at age 15 years**	**Starting at age 30 years**	**Starting at age 65 years[1]**	
History and Physical Examination[2]	Yearly from age 1 year	Yearly	Yearly	Yearly	Yearly	Yearly	Prior to conception[11]
Blood Pressure and Pulse (Pheochromocytomas/ paragangliomas)	Yearly from age 2 years	Yearly	Yearly	Yearly	Yearly	Yearly	Prior to conception[11]
Dilated Eye Examination[3] (Retinal Hemangioblastomas)	Every 6-12 months, starting before age 1 year	Every 6-12 months	Every 6-12 months	Every 6-12 months	Yearly	Yearly	Prior to conception and then every 6-12 months[11]
Metanephrines[4] (Pheochromocytomas/ paragangliomas)		Yearly	Yearly	Yearly	Yearly	Stop routine[1]	Prior to conception[11]
MRI Brain and Spine w/wo Contrast[5,6,7] (CNS Hemangioblastomas)			Every 2 years[8]	Every 2 years[8]	Every 2 years[8]	Stop routine[1]	Prior to conception[11]
Audiogram (Endolymphatic sac tumors)			Every 2 years	Every 2 years	Every 2 years	Stop routine[1]	

Type of Surveillance (Tumors being screened)	AGE[1]						Pregnancy[11]
	Until age 5 years	Starting at age 5 years	Starting at age 11 years	Starting at age 15 years	Starting at age 30 years	Starting at age 65 years[1]	
MRI Abdomen w/wo Contrast[5,6,7] (Renal cell carcinomas, Pheochromocytomas/ paragangliomas, Pancreatic neuroendocrine tumors/cysts)				Every 2 years[9]	Every 2 years[9]	Stop routine[1]	Prior to conception[11]
MRI Internal Auditory Canal[10] (Endolymphatic sac tumors)				Once			

glad. VHL Suggested Active Surveillance Guidelines (2020)

Notes:

Your clinician may suggest more frequent surveillance based on existing lesions. In such a circumstance, it is important to be seen by a VHL specialist.

1. Beginning at age 65, routine laboratory and radiologic screening for patients who have never had specific VHL manifestations may cease. With the exception of routine physical examination and ophthalmologic assessment, this applies to all other routine screening/surveillance tests in asymptomatic patients. However, patients presenting with signs/symptoms should be evaluated with appropriate testing/imaging regardless of age.
2. Age-appropriate history and physical examination to include: Neurologic examination, auditory and vestibuloneural questions and testing, visual symptoms, catecholamine excess symptom assessment (headaches, palpitations, diaphoresis, hyperactivity, anxiety, polyuria, abdominal pain).
3. Dilated, in-person eye examination including ophthalmoscopy to occur every 6-12 months based on quality of examination obtained (especially in a child) and perceived adherence to follow-up. Consider examination under anesthesia in young children in whom a detailed eye examination cannot be adequately obtained in the clinic. Consider including ultrawidefield photography and ultrawidefield fluorescein angiography, but these should not replace a dilated eye examination with a specialist with experience in retinal manifestations of VHL.
4. Plasma free metanephrines (preferred, due to its higher sensitivity) or fractionated 24-hour urinary free metanephrines.
5. Use macrocyclic/class II gadolinium-based contrast agents. MRI of the neuroaxis may be obtained at the same time as MRI abdomen, and may be performed under a single long anesthesia event, especially in children. However, both the neuroaxis protocol and the abdominal protocols should be obtained consecutively. It is NOT recommended to evaluate the spine solely using an abdominal protocol MRI, nor is it recommended to evaluate the abdominal

organs solely using a neuroaxis protocol. See footnote #6 and #7 for how to combine these protocols.

6. Based on contraindications (metallic implants, renal failure, etc.), the following order of imaging priority applies: MRI (with and without contrast) > MRI (without contrast) > CT (with contrast) > CT (without contrast) > US (kidneys, adrenals and pancreas only) > Endoscopic US (pancreas only). See also footnote #5 and #7.
7. Timing of contrast administration when imaging multiple organ systems together should be as follows: Obtain non-contrasted images of CNS and abdomen first, then give contrast using a power injector and perform multi-phase contrast-enhanced imaging of the abdomen including pancreas and kidneys during the late arterial phase and delayed venous phases. Then late post-contrast imaging of neuroaxis. See also footnote #5 and #6.
8. **If no CNS hemangioblastomas, continue routine surveillance every 2 years. If hemangioblastomas are present and there is an increase in hemangioblastoma size, or if the patient has associated symptoms, scans should be yearly (or more frequently), as appropriate (or referred to neurosurgery).**
9. **If no renal lesions present on initial scan, continue routine surveillance every 2years. If small tumors (< 3 cm) found, reimage initially with MRI every 3-6 months to determine stability. Once stability has been determined over 3 consecutive scans, consider extending to every 2 years. If renal mass is > 3 cm, consider a referral to a urologist (preferably familiar with the care of VHL)**
10. High-resolution (1mm slice thickness) magnetic resonance imaging of the internal auditory canal. This baseline MRI of the internal auditory canal should be obtained after age 15 years (once the temporal bones have matured), and it should be added onto the MRI of the neuroaxis conducted between ages 15-20 years.
11. "Prior" indicates that this surveillance testing should ideally be performed prior to any planned conception, if possible. MRIs performed during pregnancy should be without contrast.

Diagnostic Imaging in VHL

In addition to physical examination by your doctor, evaluation of suspicious areas will probably involve some combination of magnetic resonance imaging (MRI), computed tomography (CT) scanning, Positron Emission Tomography (PET) scanning, ultrasound scanning, and angiography. The objective is to provide diagnostic pictures of both the blood vessels and soft tissues of your body. This may involve injecting contrast materials, or dyes, into the bloodstream to help the doctors see the blood vessels more clearly in the pictures. Various techniques are also used to determine the density of the tissues being examined, which helps the medical team determine whether it is normal tissue, a cyst, or a tumor.

Magnetic Resonance Image (MRI) uses magnetic fields, not ionizing radiation. This means that MRIs do not add to your lifetime radiation exposure. There are two primary drawbacks of MRIs: patient claustrophobia in the closed units, and incompatible implanted devices (cochlear implants, aneurysm clips, pacemakers, etc.). Certain patients, especially those with decreased kidney function, must use specific contrast agents (macrocyclic agents, not linear agents). Recent data has shown accumulation of gadolinium, a contrast agent used in MRIs, in neural tissue of patients undergoing repeated contrast-enhanced MRI scans, however the clinical significance, if any, is unclear at this time.

Computed Tomography Scan (CT) scans were used in the past for abdominal imaging. The problem is radiation exposure. Use of contrast agents has resulted in reduced radiation, while maintaining image quality. Iodine-based contrast agents can cause reduced renal function; therefore, it is important to drink liquid before a scan. Pre-contrast scans can be derived from a dual energy CT scanner that only needs to take one scan. Newer CTs also require the use of less contrast agent. Due to the unknown, but possible, risks of long-term low exposure, CT scans should be avoided for all pre-symptomatic people and should be reserved for occasions when it is truly needed to answer a diagnostic question. The value of CT scans in diagnosing small size hemangioblastomas is limited.

Other options and considerations include the ultrasound. Ultrasounds are safe and non-invasive, but it are very operator dependent. Ultrasounds can be used to detect paraganglioma (PGL) in the neck, which are uncommon in VHL. A whole body MRI is also an option for VHL patients.

TREATMENT

Your medical team will advise you on the best surveillance follow-up tests to use and the best course of treatment for the VHL involvement identified through your surveillance. There are no universal treatment recommendations; treatment options can only be determined by careful evaluation of the individual patient's total situation—symptoms, test results, imaging studies, and general physical condition.

Treatments usually involve some kind of surgery to remove potentially malignant tumors before they become harmful to other tissues. Surgery always has some level of risk, but keeping the hemangioblastoma, or tumor, also has risks. It is important to examine the relative benefits and risks of a proposed surgery in consultation with your medical team. Advances are providing surgical alternatives that are less invasive, but newer is not necessarily better. It is always a good idea to discuss the relative immediate and long-term risks.

Below are general guidelines for possible treatment therapies.f

Brain and Spinal Hemangioblastomas

Symptoms related to hemangioblastomas in the brain and spinal cord depend on tumor location, size, and the presence of associated swelling or cysts. Cysts can often cause more symptoms than the tumor itself. The cyst will often collapse once the lesion has been removed. If any portion of the tumor is left in place, the cyst may refill. Neurosurgeons usually remove the cyst along with the tumor. Small hemangioblastomas (under 3 cubic cm, or 1.7 cm measured diagonally), which are not symptomatic, are not associated with a cyst, and located in selected areas have

sometimes been treated with stereotactic radiosurgery. This is more a short-term fix and long-term results seem to show only limited benefit.

Pancreatic Neuroendocrine Tumors

Careful analysis is required to differentiate between serous cystadenomas and pancreatic neuroendocrine tumors (pNETs). Cysts and cystadenomas generally do not require treatment. pNETs should be rated on size and tumors greater than 3 cm should be resected. However, additional parameters may be used when considering the timing of surgical intervention. These may include the type of VHL mutation, the location of the tumor and other patient-related parameters.

Renal Cell Carcinoma

With improved imaging techniques, kidney tumors are often found at very small sizes and at very early stages of development. The strategy for ensuring that an individual will have a sufficient functioning kidney throughout their lifetime begins with careful monitoring and choosing to operate only when tumor size or rapid growth rate suggests that the tumor may gain metastatic potential (approximately 3 cm). This is particularly important for VHL patients who may need multiple interventions over their lifetime. There are several widely used techniques for kidney-sparing treatments in this instance. Radio Frequency Ablation (RFA) and cryotherapy may be considered, especially for smaller tumors at earlier stages or in patients at higher risk for surgery due to other coexisting diseases. They can be performed percutaneously (through the skin) using CT guidance without having to undergo major surgery. However, only surgically removing the primary tumor, as well as all of the remaining kidney tumors, effectively "resets the clock" on that kidney. Care must be taken not to injure nearby organs and tissues (for example, the adrenals are adjacent to the kidney) and to limit scarring that may complicate subsequent surgeries, as with each surgery, the next one becomes much more difficult. Robotic laparoscopic surgery can be used to limit scarring and blood loss. Additionally, the use of anti-scarring material (such as Seprafilm®) can limit development of scar tissue after traditional open and robotic surgery.

Retinal Hemangioblastomas

Research shows that small retinal hemangioblastomas can usually be treated with minimal vision loss or risk of treatment. In the peripheral retina, consider treatment of small lesions with laser therapy and larger lesions with cryotherapy or photodynamic therapy. As there are few treatment options for hemangioblastomas on the optic disc, the risks and benefits of treatment need to be weighed. Often, if these are not causing vision loss, they can just be monitored. In the case of a detached retina or vitreous hemorrhage, vitrectomy or scleral

buckling might be effective treatment options. Systemic anti-VEGF (vascular endothelial growth factor) drug treatments may have some effect in reducing exudation from tumors. While they have failed to demonstrate effectiveness in shrinking tumors, these drug treatments may improve visual acuity for a certain time due to reduction of the optic nerve swelling caused by the hemangioblastoma.

Pheochromocytoma (Pheos)

Surgery after adequate blocking with medication. Laparoscopic partial adrenalectomy is preferred. Carefully monitor vital signs for at least a week following surgery while the body readjusts to its "new normal." Special caution is warranted during surgical procedures of any type and during pregnancy and childbirth. Even pheos that do not appear to be active or causing symptoms should be removed.

Endolymphatic Sac Tumors (ELSTs)

Patients who have a tumor or hemorrhage visible on MRI, but who can still hear will require surgery to prevent a worsening of their condition. Deaf patients with evidence on imaging of a tumor should undergo surgery if other neurological symptoms are present, in order to prevent worsening of balance problems. Not all ELSTs are visible with imaging; some are only found during surgery.

PREVENTING COMPLICATIONS AFTER SURGERY

In order to benefit fully from any surgical procedure, not only VHL-related surgeries, it is important to follow all of the post-op instructions from your doctor. It is also important to note that the better your general health is going into a surgery, the better your prognosis will be after surgery. Perhaps most important is taking the recommended steps to prevent a blood clot in one of the veins deep inside your body. A clot in one of these veins, often a leg vein, is called a deep vein thrombosis (DVT). You may have been cautioned about the danger of DVTs when flying. That is because prolonged immobility of the legs can cause a blood clot to form, detach, and lodge in another organ. If the blood clot lodges in the lung, it causes a pulmonary embolism.

There are a number of things your doctor may prescribe to reduce the risk of DVT. In the hospital, you will be connected to mechanical compression devices on your legs to help pump blood back up to your heart. In some circumstances, blood thinners may also be prescribed. You will also be asked to get out of bed and begin walking as soon as possible.

Once you are home, you may be asked to wear compression stockings, continue to walk as much as possible, and drink fluids. If you notice any symptoms

of a possible DVT (discomfort, pain, heaviness, aching, throbbing, itching, or warmth in your legs, skin changes and/or swelling of legs, ankles, or feet), contact your doctor immediately. You want to prevent any possible DVT from progressing to a pulmonary embolism, which could be fatal.

Symptoms of a pulmonary embolism include sudden shortness of breath, chest pain which is worse when coughing or taking a deep breath, rapid or irregular heart rate, coughing up blood, or feeling lightheaded. Any symptoms of a pulmonary embolism are an emergency. It is important not to wait and see if they get better, but to go to the hospital immediately.

It is important to note that anyone can get a DVT under the right circumstances—even elite athletes. As a VHL warrior, you do not want to be sidelined by a DVT.

SECTION 2

POSSIBLE VHL MANIFESTATIONS

VHL IN THE BRAIN AND SPINAL CORD

In VHL, blood vessel rich tumors form in the brain and spinal cord, called hemangioblastomas. The most common locations of these tumors in the brain are the cerebellum and brainstem. In the spine, it occurs most commonly in the neck, in the cervical spine, particularly on the dorsal surface (back side) of the spinal cord. They may also involve the cauda equina, which is the collection of nerve roots arising from the bottom of the spinal cord. When hemangioblastomas occur, they are generally not treated until symptoms begin to develop, or if they are growing rapidly and loss of function is expected. By following the VHL Surveillance Guidelines (vhl.org/surveillance-guidelines), early signs may be found. Symptoms may include headaches, nausea, numbness in the arms, legs, or body, dizziness, bowel/bladder incontinence, increased reflexes, incoordination and/or weakness or pain in the arms and legs.

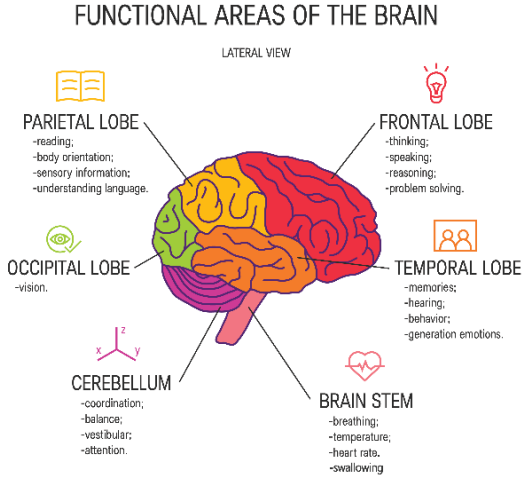


Figure 4. Regions of the brain and associated functions. The image shows the regions of the brain and lists possible symptoms for lesions in these locations. There is overlap of function among some regions. Additionally, the brain has "plasticity", meaning that if one region is affected or impaired, another region can often take over some of the functions.

In general, it is the pressure on the adjacent brain tissue or nearby nerves, caused by the hemangioblastoma and/or associated cyst/syrinx, which results in

symptoms. Although treatment may be deferred even in the setting of a growing tumor, it should be initiated before symptoms become severe. The timing of intervention is a delicate balance. Rarely can severe or long-standing symptoms be fully reversed, or diminished by tumor removal; however, symptoms of short duration can be reversed. Planning and timing the surgical removal of tumors is critical because there is risk associated with surgery on the brain or spinal cord, and asymptomatic tumors may never require removal. Thus, it is important to carefully consider both the benefits and risks. Further complicating the decision making is that many patients may have more than one hemangioblastoma and the growth of these tumors may be independent of one another. Finally, the status of other non-neurologic complications associated with VHL should be considered in the decision making process for hemangioblastomas.

Special Imaging Considerations for the Brain and Spinal Cord

T1-weighted contrast-enhanced MRI remains the imaging method of choice for determining the extent of nervous system hemangioblastomas and monitoring their growth over time. If possible, obtaining these with what radiologists refer to as a "3-D protocol" ensures that the image will be able to be compared to images from different centers with different imaging resolution and clarity. Contrast-enhanced MRIs are also recommended if symptoms or neurological signs develop. It can be difficult or impossible to accurately assess the extent and progression of hemangioblastomas using non-contrast enhanced MRIs. Some patients with sub-optimal kidney function may not be able to receive contrast dye. T-2 weighted and FLAIR MRI sequences are useful for determining the extent of swelling or cysts around a tumor, and for monitoring their progression over time.

Treatment Options

When considering treatment options, always explore the three main choices: surgery, radiation (primarily stereotactic radiosurgery), and medication (chemotherapy, currently in experimental stage for VHL).

The goal of all open surgical treatments is the complete removal of the hemangioblastoma. New surgical techniques and new surgical tools are being developed constantly, often to allow minimally invasive surgery. Regardless of the surgical technique that is used, the timing of surgery remains one of the most critical decisions to make. No one approach is always the right one, nor the best for every patient. It depends on the particular tumor, its location and size, the associated risks of each approach, and the general condition of the patient. It is important that options are thoroughly understood, and the patient works with their medical team to arrive at the right choice. Do not hesitate to ask for second opinions. VHL or not, hemangioblastomas are rare tumors and few surgeons have

a great deal of experience with them. It is helpful both for you and your neurosurgeon to have additional opinions on the best approach to your problem.

Considering Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS), sometimes called by the name of the device, such as Gamma Knife® or CyberKnife®, is a non-invasive surgical technique similar to laser surgery that does not require open surgery. Radiation is delivered to a very specific internal area where multiple beams of radiation meet and deliver a therapeutic dose. As with all other forms of radiation treatment, the tumor or lesion is not removed, but the DNA of the tumor cells is damaged. Radiosurgery can also cause direct blood vessel damage, especially in vascular tumors such as hemangioblastomas. Thickening and closing of the blood vessels can occur over a period of a few months, or for up to two years. Therefore, SRS is not effective instantaneously like surgery. Though the beneficial effects may be delayed, early side effects may occur and include swelling of the treated lesion due to loss of the cells' ability to regulate fluids, as well as swelling in the brain tissue adjacent to the treated tumor.

SRS is not appropriate in every case, as it may cause post-treatment swelling or scarring that could make future open surgery more difficult. SRS for any brain or spinal hemangioblastoma needs to be discussed carefully with a radiation oncologist, neurosurgeon, or neuro-oncologist knowledgeable about VHL.

There are three basic types of stereotactic radiosurgery: particle beam (proton—available only at a few hospitals), cobalt-60 (photon—Gamma Knife®), and linear accelerator (LinAc—CyberKnife®, Novalis Tx®).

VHL Alliance's Clinical Advisory Council has issued the following recommendations when considering the use of SRS to treat VHL-related brain and spine tumors:

- **SRS should not be used for hemangioblastomas of the brain** unless the tumor has been deemed unresectable by a surgeon with experience in VHL or if the patient is in very poor health and could not sustain open surgery.
- **SRS should not be used at all if the tumor is larger than 3 cubic centimeters** (about 1.7 cm measured diagonally), where a cyst is present, or when the patient is experiencing symptoms.
- **SRS should not be used at all in the spinal cord or CNS tissues other than the brain**, since there is still insufficient data on effectiveness or possible complications.

The best candidate tumor for SRS is a brain tumor less than 1.7 cm in size, which does not have an associated cyst and is not causing symptoms. Patients who have symptoms or cysts usually need to have standard surgical removal.

Because SRS works best with small tumors, some of the tumors chosen for treatment might, in fact, never have grown. Most doctors prefer to wait until the tumor shows some signs of enlarging but without development of a cyst before considering treatment with SRS. **The long-term efficacy of SRS is not yet known, but doctors have seen scarring following SRS treatment that may make some subsequent surgeries more difficult.**

Discuss with Your Doctor Usage of Stereotactic Radiosurgery (SRS) on the Brain and Spinal Cord

The following list of questions and advice has been compiled to help you engage in a discussion with your doctors to see if using SRS in your particular situation is the best choice:

- **Get opinions on both surgical techniques.** Consult with physicians about BOTH conventional micro-neurosurgery AND stereotactic radiosurgery. It is NOT enough to speak only with a radiation oncologist, or someone who practices only SRS. Be sure to talk with surgeons who are experts in each method and get both perspectives. It is also reasonable to discuss options with a neuro-oncologist with expertise in VHL. While conventional surgery has its own set of risks and drawbacks, in many cases, it is the safer approach. It is important to assemble a team of medical professionals who can help fairly evaluate the pros and cons of both procedures and decide which is better for you in this particular situation at this particular time.
- **How big is the tumor?** Recommendations are to NOT treat a hemangioblastoma larger than 1.7 cm diameter with SRS. The reason is that a larger tumor, with a greater surface area, requires significantly more radiation to treat. The additional exposure increases the risk and severity of post-operative swelling.
- **Is there a cyst or other source of mass effect?** Mass effect is the excess pressure in the brain caused by some additional mass inside your skull. This could be from a cyst, swelling, or from the tumor itself. If there already is extra pressure inside your skull, SRS may not be a good idea since the additional swelling caused by the procedure would compound the mass effect and make the symptoms worse.
- **Where is it?** Once treated, there will be swelling (edema) of the tumor and surrounding tissues. What this means to you is that the treated tumor may get bigger before it gets smaller. Depending on how much room there is for expansion, your symptoms may get worse before they get better. Where is the tumor located? When it swells, what symptoms may occur? How will the doctor propose to control the swelling? How can you work in partnership with the medical team to minimize the swelling and get through the swelling period? Note that this period of swelling is not measurable in days,

but in months. Ask your doctor how long you should expect this swelling period to last.

- **What are the dangers to surrounding tissues?** There is usually some margin of healthy tissue that will be irradiated with a therapeutic dosage. What tissue is within that margin? What would such damage do? If the tumor is in a position where there is fluid beside it, the n there is some "margin for error," but if it is in a critical spot, then its effect on the nearby healthy tissue can be significant.
- **How many tumors do they propose to treat?** What is the sum of the radiation to which you would be subjected? If more than one tumor is to be treated, is it wise to treat them all at this same time or is it better to treat them one at a time? Pacing the treatment can be critical to managing the post-treatment swelling.
- **What experience does this team have with treating hemangioblastomas, as opposed to other solid tumors?** Hemangioblastomas react differently to radiation treatment than other solid tumors do. It is important to get someone with experience in treating hemangioblastomas to participate in reviewing the treatment plan prior to the beginning of treatment. If you cannot find someone in your area, the VHL Alliance can suggest some sources for second opinions. This should be welcomed by your team as it is for their protection as much as for your own.
- **What follow-up care or treatment will be required?** Will a shunt need to be inserted to drain cerebrospinal fluid (CSF)? If so, what ongoing care might be required?

VHL IN THE PANCREAS

What and Where is the Pancreas?

The pancreas is an organ extending from the left to the midsection of the upper abdomen, in the back. It lies directly behind, and against the stomach and small intestine, measuring about 5-7 inches long (see Figure 5). The gallbladder and the liver connect to the pancreas by way of the common bile duct. The pancreas has a long tube that runs through it called the pancreatic duct. This duct connects to the common bile duct and then carries the products made by these organs to the beginning of the small intestine (called the duodenum).

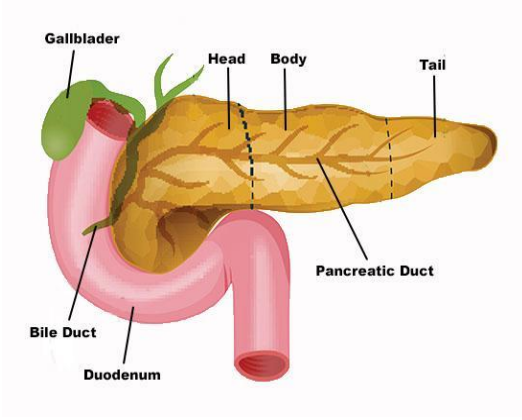


Figure 5. Diagram of the pancreas.

Functions of the Pancreas

The pancreas constantly regulates how the body's cells are nourished. The pancreas consists of two glandular parts, responsible for:

Producing digestive chemicals and enzymes to break food down into nutrients that can be absorbed through the walls of the small intestine and delivered to the cells. The digestive enzymes flow through the large pancreatic duct, together with bile produced by the liver, into the upper part of the digestive tract.

These three digestive enzymes are:

- Protease to break down protein foods
- Amylase to break down carbohydrates and sugars
- Lipase to help us absorb fats

Producing hormones (insulin and glucagon) that help regulate blood sugar and the body's ability to feed every cell. These hormones are created in the islet cells. After a meal, the pancreas makes insulin, which allows the sugar to travel from the bloodstream into the cells where it can be burned for energy or stored as fat for future use. When the blood sugar starts to drop between meals or during sleep), the pancreas makes glucagon, which tells the liver to release stored sugar, or to make sugar from fat and muscle cells. This prevents glucose levels from dropping too low, when the pancreas is functioning normally.

Lesions in the Pancreas

In patients with VHL, three types of lesions may be found commonly in the pancreas:

- Cysts
- Serous microcystic adenomas, or "cystadenomas"
- Islet cell tumors, or pancreatic neuroendocrine tumors (pNETs)

These lesions are very different from the common pancreatic tumors and cysts that may be detected among patients in the general population that are not diagnosed with VHL.

Pancreatic cysts may be found in a large number of people with VHL, with wide variation among families. About 75% of people with VHL develop pancreatic cysts. Many cysts, even very large ones, may be present without causing symptoms, in which case no treatment is required. In some cases, enlarged cysts may press against surrounding organs, such as the stomach, and cause discomfort. Surgical or endoscopic drainage of a large cyst may provide relief.

Pancreatic tumors are found in up to 17% of people with VHL. Serous microcystic adenomas are the most common. They are benign and appear as honeycombed clusters of small cysts that look solid on the scans. These generally do not need to be removed, unless they are causing obstructions to the normal flow of fluids and enzymes that cannot be managed otherwise.

VHL-related pancreatic lesions are generally considered to be one of the least symptomatic among the lesions associated with VHL. Depending on their size, type, and location, cysts and tumors of the pancreas can cause functional problems, as well as structural problems. The medical team may request additional tests to detect abnormal hormonal function. Cysts and tumors may block one or more of the ducts that carry essential fluids from the pancreas to the digestive tract, causing jaundice, pain, inflammation, infection, diarrhea, constipation, fatty stools, weight loss, and other digestive complaints. Blockage of the delivery of insulin may cause digestive problems, or diabetes. Fortunately, there are replacements that can be taken by pill or injection. Insulin or digestive enzymes may need to be prescribed to maintain health. Figuring how much of which enzyme is needed at what times is not an easy thing to calculate. A gastroenterologist, or naturopath, familiar with pancreatic insufficiency and digestive imbalance can assist in achieving the right balance to improve quality of life.

Pancreatic Neuroendocrine Tumors (pNETs)

Although rare, the most serious pancreatic issue is solid tumors, not cysts, arising within the islet cells of the pancreas. In VHL, these are most commonly pancreatic neuroendocrine tumors (pNETs). Most of these tumors do not metastasize. Although the minority, pNET that do metastasize typically spread to the liver, bone, or other organs. Hence, careful evaluation of pNETs, while they are localized, is necessary to allow timely resection. PNETs are almost never functional in VHL, meaning they do not release hormones that cause symptoms, so chemical blood or urine tests will not help to determine their nature. MRI using gadolinium as the contrast dye is the preferred routine surveillance method for the abdomen, unless MRI is contraindicated, in which case contrast-enhanced CT may be used.

Researchers have identified two variables that may be considered when deciding whether intervention is required: tumor size and genetics.

- **Size:** Size is the main criteria for determining approximate risk level for pNETs. Tumors that are greater than, or equal to, 3 cm should be considered high risk and be evaluated for surgery. pNETs with a diameter between 1.2-1.5 cm and 3 cm should be considered moderate risk and be monitored closely. Those smaller than 1.2-1.5 cm are considered low risk. The location of the tumor within the pancreas should also be taken into consideration, as tumors in the head of the pancreas are typically removed when they are smaller to allow for less extensive surgeries.
- **Genetics:** The *VHL* gene has three distinct parts, called exons. Two large studies have shown a higher rate of dangerous pNETs (those that may metastasize) among people who have an alteration in exon 3 of the *VHL* gene. The genetics of a patient may be used to better determine risk level in those patients who fall into the "moderate risk" category based on size (diameter between 1.2-1.5 cm and 3 cm).

It is important to note that the decision on when and how to intervene on a pNET is complex and requires a multidisciplinary team discussion that includes a VHL pNET specialist.

Possible Effects on Pancreatic Function

While cysts are benign, they may block one or more of the tiny tubules in the pancreas that deliver pancreatic enzymes to the gut. It is somewhat like stepping on a garden hose. Even though the pancreas is still making these enzymes, they are unable to get to where they need to go to aid digestion. In late stages, when the pancreas is widely replaced by cysts, the number of cells in the pancreatic islets may be low, leading to insufficient secretion of hormones and increase in blood sugar levels.

Tumors and/or cysts near the common bile duct can also block the gallbladder from delivering bile. Blockages near the liver can affect liver function. Be sure to discuss any pain or yellowing of skin or eyes with a doctor. These symptoms of jaundice may indicate a problem with liver function.

Diabetes is the condition that occurs when the pancreas does not make enough insulin to keep blood sugar within the normal range. Diabetes occurs rarely in non-operated patients. The risk increases in patients with repeated pancreatic tumor resections and especially among those with severe pancreatic cystic disease. This can be treated with pills that can help the pancreas make more insulin, pills that tell the liver to make less sugar, or injections of insulin to replace what is not being produced or delivered. An endocrinologist and a certified diabetes educator (dietitian or nurse) can help with the management of diabetes and help develop a personalized plan for meals and exercise.

Caution: Alcohol and Dehydration

If you have pancreatic disease, it is important to avoid drinking alcohol in excess. This is because drinking alcohol can lead to dehydration, which research has shown can cause the pancreas to flare. Always drink plenty of fluid. It has been recommended that a patient always have a bottle of water or any liquid with them at all times to keep from being dehydrated.

Taking a Break from Solid Food

Sometimes it is best to rest the pancreas and limit your food intake. If you are experiencing a flare, your doctor may even recommend no food for a day or two. A diet of clear liquids can be followed when pain is severe. Clear liquids include apple, cranberry, and white grape juice, gelatin, and broth. The clear liquid diet, however, is not nutritionally complete, and the diet should be advanced as soon as additional food is tolerated and according to the schedule given to you by your doctor.

Pancreatic insufficiency is when the pancreas is not making the digestive enzymes, or when their delivery to the gut is blocked. Removal of all or part of the pancreas reduces the ability of the pancreas to make and deliver these enzymes. When the food is not broken down, the nutrients cannot be delivered to the cells. The food simply goes right through and out the other end without being digested and absorbed. In other words, the cells are still starving. This condition is called malabsorption. One major sign of malabsorption is weight loss. It is critically important to your health to get your digestion back in balance. This is more than an annoyance; it is one of the keys to your health.

Symptoms of malabsorption include diarrhea, bloating, cramping, abdominal pain, fatty stools (appear frothy and oily on the top of the toilet bowl water, with a strong odor), and possible deficiencies of fat-soluble vitamins (A, D, K, and E). A registered dietitian who works with clients with cystic fibrosis, pancreatic cancer, or pancreatic insufficiency should be able to help with this problem.

Diet and the Pancreas

Heart-healthy fats are good in small amounts. Fats are the hardest type of food to digest and the amount of fat someone should eat varies depending on their weight, height, and activity level. People who have pancreatic insufficiency usually do best on a low-fat diet, However, this is not the case for everyone. You should consult a doctor or medical professional before making changes to your diet or fat intake. Potential solutions may include supplemental pancreatic enzymes, but this should be discussed with your physician. It is important to understand that lack of fat absorption is not a positive situation. Fat is required for building the body cells, hence we need to promote fat absorption and not avoid consuming it completely. However, reducing the fat portion in our diet is generally advised.

Diet Tips

Eating boneless chicken breasts and most fish keeps meals low in fat. Cooking with a cooking spray to minimize use of oils also helps. Fat-free chicken broth can be added when moisture is needed.

Red meat, processed meats, and cheese can be very high in fat. Buy only lean cuts of beef and pork (lean cuts have fewer white streaks of fat in the raw product). Reduce the portion size of meat and cheese to control the total amount of fat you are eating. All dairy products can contain as much as 10 grams of fat per serving. Reduce portion size or choose nonfat or 1% fat alternatives.

Avoid fried foods and learn to bake, broil, and grill your protein foods. One grocery tip is to buy all fat free, reduced fat, or “lite” foods, or use very small amounts of the regular full-fat variety. Caution: Many fat-free processed foods contain an excessive amount of sugar.

Nuts and avocados have a very high fat content but these fats are heart-healthy and not nutritionally bad for you when consumed in moderation. Fruits and most vegetables are naturally fat free, and their vitamins and fiber are essential to your health.

Because fats are not being digested, the fat-soluble vitamins are not being absorbed. Ask a dietitian about water-soluble vitamin supplements.

The most important thing to know is that it is possible to get things back into balance and eat what you want and be comfortable. Take the time to find the right professional to help you.

Pancreas and Nutrition FAQs:

Q: *What is pancreatitis? Is it a precursor to cancer?*

A: Pancreatitis is an inflammation of the pancreas. The pancreas secretes enzymes that help digest fats, proteins and carbohydrates in food. Normally these enzymes are not activated until they reach the small intestines. If they become activated inside the pancreas, they will begin "digesting" it, which causes damage and inflammation to the pancreas. There are different types of pancreatitis. In both chronic and hereditary pancreatitis, there is an increased risk of pancreatic cancer.

Q: *What is the first thing a new patient with pancreatitis should know?*

A: A new patient with pancreatitis should know that the goal is to adjust their diet to help their body absorb nutrients better.

Q: *What is the most important thing for patients to be aware of in terms of their diet?*

A: Patients may not be able to digest food well, especially fat, since the pancreas is responsible for releasing enzymes to help digest nutrients. With pancreatitis, this organ is not secreting enough enzymes to break down the food normally so malabsorption can occur. This can result in weight loss, indigestion, abdominal pain when eating, and oily stools.

Q: *Can following specific dietary guidelines help relieve symptoms?*

A: Following a low fat diet may help reduce the symptoms associated with chronic pancreatitis, by decreasing the amount of enzymes needed to digest meals. If significant symptoms are still present after making these diet changes, the patient should speak with their doctor to discuss the possible need for pancreatic enzymes.

Q: *What specifically should they eat? Avoid?*

A: Patients with pancreatitis should avoid high fat foods. This includes fried foods, most desserts, whole milk dairy products, fatty cuts of meats, nuts/seeds, and avocado. Additionally, they should limit fats (like butter, salad dressings, sour cream, and mayonnaise) and foods with added sugar (like desserts and sweetened beverages). Alcoholic beverages should also be avoided. Patients can include grains, fruits and vegetables, lean meats (like fish, skinless poultry, and eggs), beans, and low fat dairy products in their diet.

VHL IN THE KIDNEYS

The kidneys are organs located in the back (retroperitoneum) of the abdominal cavity, behind the rib cage. They have several functions including filtering the blood and making erythropoietin (a chemical that stimulates red blood cell production) and Vitamin D. The kidneys measure approximately 12 cm (4 inches) long, or about the size of a fist (see Figure 6). VHL may cause cysts or tumors to form in the kidneys. While it is common for any adult in the general population to have an occasional kidney cyst, VHL-related cysts are usually multiple and in both kidneys. The presence of one or more simple cysts is not a problem in itself. However, in VHL each cyst may contain a small tumor, and it is possible for these tumors to become renal cell carcinomas (RCC), a form of kidney cancer.

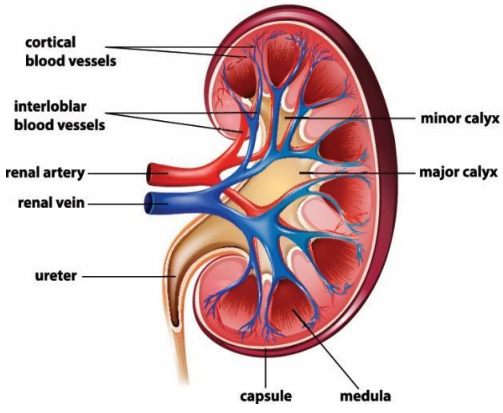


Figure 6. Diagram of a normal kidney

There is widespread agreement on the optimal approach to dealing with VHL kidney tumors. In VHL, a person with kidney involvement typically has a series of tumors on both kidneys, which develop over the course of several decades. Removing every little tumor as they appear is not possible because it would involve too many surgeries for the person and organ to endure. The goal of treatment is to maintain the patient's own kidney function throughout their lifetime, while minimizing the total number of surgeries and removing tumors before they can spread to other organs. The tricky part is to choose the right moment to operate—not too early and not too late.

Difference Between VHL-related RCC and Sporadic RCC

Once VHL-related kidney tumors appear, they act like clear cell renal cell carcinoma (ccRCC), which represents the most common form of kidney cancer in

the general population. The biggest difference is that in VHL, these tumors appear earlier in life than they do in the general public, as well as in both kidneys. If a VHL patient is following the recommended surveillance guidelines (vhl.org/surveillance-guidelines), the tumor is more likely to be detected earlier than it would be in people who have sporadic cases. That provides VHL patients with better options for dealing with the tumor early and allowing the kidney to function for as long as possible, while avoiding metastatic disease.

Symptoms

Nearly all small kidney cysts and tumors have no symptoms, so it is critically important to begin monitoring the kidneys long before any obvious physical symptoms or signs occur. The kidneys can continue to function while these changes are occurring without physical symptoms, and with normal blood and urine tests. Some of the possible symptoms of late-stage RCC are blood in urine, lower back pain, anemia (low red blood cell count), fatigue and unexplained weight loss. If you wait for symptoms, the tumor will usually be at a much later and more dangerous stage when it is found.

Monitoring

The objective of monitoring lesions in the kidneys is to track the progression of the cells from harmless (benign) to the point before they become capable of spreading (metastatic). CT or MRI imaging of the kidneys both with and without contrast agents as detailed in the VHL Surveillance Guidelines (vhl.org/surveillance-guidelines) is a reliable way to follow these tumors.

Figure 7. The dandelion effect: Dandelions demonstrate that cells need to mature to a certain point before they know how to send out seeds and plant more tumors in other places. There is no need to pull up every green one, but it is important to pick them while they are yellow.

Think of a dandelion. It begins as a bud, becomes a yellow flower, turns white, and one day the white seedlings are carried off on the wind to seed the lawn. If you pick the yellow flowers, the seeds are not mature and cannot spread. The cells have to mature to the point where they are able to seed themselves in the lawn.

The trick to living with dandelions is to pick them while they are yellow. There is a similar transition in cancer. Researchers have identified a series of distinct steps that the cells go through before they are capable of metastasizing.

It would be ideal if there were an easy blood or urine test—some biomarker—to check on tumor cell progression. Unfortunately, at this time, such a test does not exist, despite the fact there is a large research effort to find one. Meanwhile, clinical research has shown that the size of a solid tumor is one fairly reliable sign of its progress.

Biopsies are not usually called for with a diagnosis of VHL. The most valuable information to use when evaluating kidney tumors is their level of progression. This is not information that can be learned accurately through a biopsy. One exception to this is prior to a percutaneous ablation whereby the biopsy is the only method to 'prove' treatment of a cancer since it is not being removed and examined by a pathologist.

Imaging Considerations

In watching the kidneys, the medical team is working to evaluate whether there are cysts or solid tumors. Magnetic resonance imaging (MRI) is the best method of medical screening, as it does not use radiation and can detect even those tumors located within a cyst. The doctors will watch the tissue density, the position of the tumors, their size, and the rate of growth. The gadolinium contrast used in MRIs DOES NOT harm the kidneys and can be used in all patients except those on dialysis or are pregnant. CT scans are also good and are sometimes used in place of MRI. When used judiciously, the amount of radiation exposure due to CT scans is not problematic in adults. MRIs cannot be used in those with pacemakers or magnetic metallic material, or in cases of claustrophobia when anesthesia may be needed.

People with reduced kidney function, as indicated by low creatinine clearance, need to be protected from any side effects of the iodine contrast dyes used for CT scan. The principal goal is to ensure that the patient has sufficient fluid in the body to flush the contrast dye out in a timely manner. Generally, iodine contrast for CT scans can be given to those with an estimated GFR (glomerular filtration rate) of 40 or higher. Radiology teams may take certain safety steps, such as extra flushing or safer versions of contrast, depending on their hospital protocols.

For patients who are already on dialysis, it is generally safe to obtain a CT scan with iodine contrast, but they must have dialysis within 24 hours afterwards to avoid complications. The alternative is an MRI without contrast with T1, T2, and fat suppression sequences, which can help partially make up for the lack of contrast.

Criteria for gadolinium used based on Glomerular filtration rate (GFR):

- Patients with an estimated **GFR of less than 60 and greater than 30**, hydration with 1 liter of bicarbonate solution infused over the course of one hour immediately prior to when IV contrast injection is performed.
- For those on **long-term surveillance and estimated GFR over 60**, a full dose of gadolinium is used, for estimated GFR of 30–60, ½ dose, and no contrast agent is used if estimated GFR is less than 30.
- **People with renal failure (estimated GFR less than 30)** can be followed without use of contrast agents using non-contrast MRIs with T1, T2, and fat suppression sequences, which can help partially make up for the lack of contrast.

It is important that you understand the medical findings about which your physicians are concerned. This will allow you to participate in determining the right timing and treatment. Do not hesitate to get a second opinion. The distinction between a cyst and a tumor can be debatable depending on the clarity of the image and the experience of the radiologist who reviews the VHL tumors. Even among experts, there can be differences of opinion. This is an area where the perspective of one or more physicians with significant experience in VHL can make a world of difference. Films or CDs can easily be sent to a consulting physician far away, even in another country. **Contact the VHL Alliance for assistance in locating an expert who can assist you or visit vhl.org/ccc to find a VHL Clinical Care Center near you.**

Treatment

If a kidney tumor is large when discovered, it changes shape or size over time when being watched, or the rate of growth becomes suspicious, your medical team may recommend surgery. Not all kidney tumors require immediate surgery. Based on characteristics such as density, size, shape, and location, your medical team will recommend either a time to repeat the imaging tests or intervention with surgical resection (removal of the tumor) or ablation. Cysts are generally not considered sufficient cause to operate, even if large. In the rare event a tumor is present in the wall of a cyst, it will be important to watch the size of that solid tumor, not of the cyst.

The best practice in caring for VHL patients is to minimize the number of surgeries while preventing metastatic disease, in order to allow the kidneys to continue to function. Treatment is recommended when the largest tumor approaches 3 cm, known as the "3 cm Rule" (more of a guideline than a rule). This is because research has shown there to be nearly no potential for metastatic disease before the tumor reaches 3 cm.

In addition to the 3 cm guideline for the largest tumor diameter, doctors will look at tumor size over time, in order to determine its growth rate. A faster growth rate may indicate the need for surgery to remove a smaller tumor. Tumors typically grow in steps, with periods of little to no growth followed by periods of rapid growth. Looking at tumor growth over a number of years, NIH has found the average growth rate is 3-4 mm per year. Generally, growth greater than 5 mm over a year is considered accelerated.

Decisions about when to operate and the extent of the procedure need to be made by the entire team. These discussions should include the patient with full disclosure of all information. All points of view, the location of the tumor, the number of tumors, the patient's level of stamina and health, and even the possible desire of the patient to be free of the tumor, play a role in making the decision.

Kidney Transplant Considerations

In cases where the last remaining kidney must be removed, VHL patients have been proven to be good candidates for kidney transplant. VHL tumors grow from abnormalities within the cells of the VHL kidney itself. Since the new kidney has the donor's genetic structure with two healthy copies of the *VHL* gene, it is not at risk for VHL tumors. Immunosuppression for transplantation has not been seen to increase the growth of VHL tumors in other organs. Most transplant centers will require patients to be cancer-free for at least 2 years before being considered for transplantation, even if a donor is available. If you are considering transplantation, it is best to meet with a transplant team and have expectations established early.

Living Well with Reduced Kidney Function

Current management and treatment of VHL lesions in the kidneys allow most patients to retain normal kidney function throughout their lives. Your medical team will do everything possible to preserve your kidney function. However, if you have multiple operations or other procedures on your kidneys, or if the sheer number of renal cysts and tumors affects overall kidney function, you may develop reduced kidney function (also called Chronic Kidney Disease, or CKD).

Aggressively treating diabetes and high blood pressure are important as these two conditions are some of the greatest threats to kidney function.

Paying attention to diet and nutrition is important for the health of those with reduced kidney function, but it takes more than just good nutrition to live a healthy life. Here are the National Kidney Foundation's (kidney.org) top 10 tips for living well with chronic kidney disease (CKD):

1. **Learn it and live it.** Learn all you can about CKD then live the type of lifestyle that will promote optimum health and wellness.
2. **Have faith in yourself.** Having CKD is a challenge, but believing in yourself can help you to prevail. You can do this!
3. **Be your own best advocate.** Being well-informed will help you to lobby and obtain the treatments that are in your best interest.
4. **Keep tabs on your tests.** Because CKD is a progressive illness, you must monitor your symptoms on an ongoing basis and be up-to-date on all test results. That way you can match treatment and lifestyle options with your symptoms and stages.
5. **Be proactive, take control.** If you are considering a kidney transplant, conduct research and contact a transplant center. In addition, follow your doctor's recommendations along the way.
6. **Develop strong relationships.** Take time to build a connection with all of the members of your health care team. This will help you to have in-depth conversations and to ask tough questions. Also be sure to nurture your personal relationships and create a solid support network of friends and family.
7. **Exercise and eat right.** In addition to taking your medications or managing a treatment regimen, you must make daily exercise and healthy eating top priorities. Otherwise, you risk becoming sicker, faster.
8. **Recognize that work is good for you.** If you have a job, or if you spend your time volunteering, realize that having an outlet that enables you to feel competent and productive is positive for your total well-being. Of course, you may need to consider a reduced schedule or part-time work, but continuing your work schedule should help you stay connected and add to your quality of life.
9. **Make a plan.** Since CKD is a chronic health issue, you need a plan that looks ahead to the future. Know your treatment options and contemplate which ones will suit you best. Take time to consider what options you want to pursue if your condition worsens or your symptoms change.
10. **Make it a priority to enjoy each day.** Taking control of your health will enable you to feel your best. Recognize that feeling strong and well is what will allow you to do the activities that you enjoy most. So each day, make sure you take time to do just that!

Diet Tips with Reduced Kidney Function or Kidney Failure

When you have chronic kidney disease, you may need to make changes in your diet, including:

- Limiting fluids in some cases
- Eating a low-protein diet (this may be recommended)
- Restricting salt, potassium, phosphorous, and other electrolytes
- Getting enough calories if you are losing weight

Your recommended diet may change over time if your kidney disease gets worse or if you need dialysis. A nephrologist (a medical kidney doctor) can provide help in maintaining kidney function and can prescribe medication to manage some of the dietary problems, and dietitians can provide helpful guidance for what foods to avoid.

Reason for a Special Diet

The purpose of this diet is to maintain a balance of electrolytes, minerals, and fluid in patients who have chronic kidney disease or who are on dialysis. Patients who are on dialysis need this special diet to limit the buildup of waste products in their body. These waste products can also build up between dialysis treatments.

Most dialysis patients urinate very little or not at all. Limiting fluids between treatments is very important. Without urination, fluid will build up in the body and lead to excess in the heart, lungs, and ankles.

Diet Recommendations

Ask for a referral to a registered dietitian for diet information about kidney disease. Some dietitians specialize in kidney diets. They can help create a diet with a daily calorie intake that is high enough to keep you healthy and prevent the breakdown of body tissue.

Carbohydrates

If you are overweight or have diabetes, you may need to limit the amount and type of carbohydrates you eat. This is the single most important step you can—and should—take for your health. Talk with your doctor, nurse, or dietitian.

Otherwise, carbohydrates are a good source of energy for your body. If your health care provider has recommended a low-protein diet, you may replace the calories from protein with fruits, breads, grains, and vegetables. These foods provide energy, as well as fiber, minerals, and vitamins.

Fats

Fats can be a good source of calories. Make sure to use monounsaturated and polyunsaturated fats (extra virgin olive oil is the least processed source) to help

protect your arteries. Talk to your doctor, nurse, or dietitian about fats and cholesterol that may increase your risk for heart problems.

Protein

Low-protein diets may be helpful before you start dialysis. Your doctor or dietitian may recommend a moderate-protein diet (1 gram of protein per kilogram of body weight per day).

Once you start dialysis, you will need to eat more protein. In fact, a high-protein diet with fish, poultry, pork, or eggs at every meal may be recommended. This will help you replace muscles and other tissues that you lose.

People on dialysis should eat 8–10 ounces of high-protein foods each day. Your doctor, dietitian, or nurse may suggest adding egg whites, egg white powder, or protein powder to your diet.

Calcium and Phosphorus

Healthy Tip: Use non-dairy creamers and recommended milk substitutes (almond milk, rice milk, and soy milk) in place of milk as a way to lower the amount of phosphorus in your diet.

Calcium and phosphorus, two important minerals in the body, are also monitored closely. Even in the early stages of chronic kidney disease, phosphorus levels in the blood can become too high. High levels of phosphorus can cause chronic itching and can cause blood calcium levels to fall. This, in turn, pulls calcium from your bones, which can make your bones weaker and more likely to break.

You will need to limit the amount of dairy products you eat because they contain large amounts of phosphorus. This includes milk, yogurt, and cheese. Some dairy products or dairy substitutes are lower in phosphorus, including tub margarine, butter, cream cheese, heavy cream, ricotta cheese, brie cheese, sherbet, and non-dairy whipped toppings.

Fruits and vegetables contain only small amounts of phosphorus, but may contain large amounts of potassium (see below).

You may need to take calcium and vitamin D supplements to prevent bone disease and to control the balance of calcium and phosphorus in your body. If diet changes to lower your phosphorus levels are not enough, your doctor may recommend “phosphorus binders.

Fluids

In the early stages of chronic kidney disease, you do not need to limit how much fluid you drink. As kidney disease progresses or when dialysis is needed, it becomes necessary to monitor liquid intake. In between dialysis sessions, fluid can

build up in the body. Too much fluid will lead to shortness of breath, an emergency that needs immediate medical attention.

Your doctor and dialysis nurse will let you know how much you should drink every day. Do not eat too many foods that contains large amounts of water, such as soups, gelatin desserts, popsicles, ice cream, grapes, melons, lettuce, tomatoes, and celery.

Tips to keep from becoming overly thirsty include:

- Avoid salty foods
- Freeze juice in an ice cube tray and eat it like a popsicle (you must count these ice cubes in your daily amount of fluids)
- Stay cool on hot days
- Use smaller cups or glasses and turn over your cup after you have finished it

Salt or Sodium

Healthy Tip: Salt is not the only way to make your food flavorful.

Reducing sodium in your diet helps you control high blood pressure, keeps you from being thirsty, and prevents your body from holding onto extra fluid. You will probably need to eat a low-salt diet.

Look for these words on food labels:

- Low-sodium
- No salt added
- Sodium-free
- Sodium reduced
- Unsalted

Check all labels to see how much salt or sodium foods contain and look for those with less than 100 mg of salt per serving. Avoid foods that list salt near the beginning of the ingredients.

Try fresh or dried herbs and spices instead of table salt to enhance the flavor of foods. Also, try adding a dash of hot sauce or a squeeze of lemon juice for flavor.

Do not use salt when cooking and take the saltshaker away from the table. DO NOT use salt substitutes because they contain potassium. People with chronic kidney disease also need to limit their potassium.

Potassium

Normal blood levels of potassium help keep your heart beating steadily. However, too much potassium can build up when the kidneys no longer function well. Dangerous heart rhythms may result, which can lead to death.

Potassium is found in many food groups, including fruits and vegetables. Choosing the right item from each food group can help control your potassium levels.

When eating fruits:

- Choose peaches, grapes, pears, cherries, apples, berries, pineapple, plums, and tangerines.
- Limit or avoid oranges and orange juice, nectarines, kiwis, raisins or other dried fruit, bananas, cantaloupe, honeydew, prunes, and nectarines

When eating vegetables:

- Choose broccoli, cabbage, carrots, cauliflower, cucumber, eggplant, green and wax beans, lettuce, onion, peppers, watercress, zucchini, and yellow squash
- Limit or avoid asparagus, avocado, potatoes, tomatoes or tomato sauce, winter squash, pumpkin, and cooked spinach

Iron

Patients with advanced kidney failure often have anemia (low iron levels) and usually need extra iron supplements or a diet containing foods with high levels of iron (liver, beef, pork, chicken, lima and kidney beans, iron-fortified cereals). Talk to your doctor, nurse, or dietitian about whether or not you have low iron levels and need to add iron to your diet.

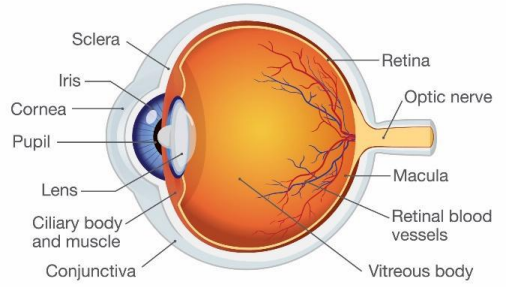
VHL IN THE EYES

Retina

The retina is the light sensitive tissue in the eye, sitting in the innermost layer in the back of the eyeball, akin to the film in a camera. The lens of the eye projects an image of what a person is looking at onto their retina, where it is converted into chemical signals by cells, known as rods and cones. These signals are transmitted to the brain, via the optic nerve, where they are translated into a recognizable image. The optic disc is the spot in the back of the retina, where the retina connects to the optic nerve. The macula is a small, oval-shaped, pigmented area near the center of the retina, responsible for high-acuity vision used for reading, color vision, and central vision in bright conditions.

In human biological development, the retina forms as an outgrowth from the brain, which is why it is considered to be a part of the central nervous system (CNS).

Figure 8. Diagram of the eye



Retinal Hemangioblastomas

Retinal hemangioblastomas are tumors in the retina, caused by the unchecked growth of leaky, irregular blood vessels. They are one of the most common VHL manifestations, affecting about 60% of VHL patients, and are frequently one of the earliest to present themselves.

Symptoms

Leakage or bleeding from hemangioblastomas can lead to retinal detachment and vision loss, so early treatment and careful management is very important. Untreated, or partially treated, hemangioblastomas that are not actively bleeding, or leaking, may stimulate the growth of fibrous tissue in the eye that can also endanger vision. Therefore, the retina needs to be regularly assessed.

Surveillance

Not all ophthalmologists are familiar with VHL. It is best to work with an ophthalmologist that is familiar with VHL and qualified to perform a thorough dilated retinal examination with an indirect ophthalmoscope.

The VHL Active Surveillance Guidelines (vhl.org/surveillance-guidelines) call for a **DILATED** retinal exam, performed by an ophthalmologist, retina specialist, or ocular oncologist familiar with VHL, every 6-12 months, starting before age 1. Beginning at age 30, these dilated retinal exams can be performed annually. During the exam, the doctor will use magnifying lenses to look at the retina from all angles. For young children who may not be able to tolerate the examination, anesthesia may be considered. Ultrawidefield photography and fluorescein angiography can also be valuable diagnostic tools, but they should not replace a dilated retinal examination by a specialist with experience in the retinal manifestations of VHL.

Identifying and treating retinal lesions in the early stages is extremely important. New hemangioblastomas can occur throughout life; therefore, regular surveillance to identify and treat lesions in the early stages is extremely important.

Treatment

Fortunately, retinal hemangioblastomas can be treated effectively and positive outcomes are possible with proper management. A referral to a retina specialist or ocular oncologist may be required, if treatment is necessary.

The objective of treatment is to destroy the hemangioblastoma while it is still so small that it does not affect the patient's vision. While a number of treatment methodologies have been used to treat retinal hemangioblastomas, laser therapy (light surgery) and cryotherapy (freezing) are most frequently used, depending on the size, location and presentation of the lesion. Generally, smaller lesions can be treated more successfully and with fewer complications than larger ones. Laser therapy works best on smaller tumors that are located more posteriorly, while those that are medium-sized or farther in the periphery may respond better to cryotherapy. There is no consensus on how to treat large lesions, although photodynamic therapy, a type of "cold laser" which is combined with an intravenous photosensitizing dye, may be useful.

Vitreoretinal surgery may be necessary if the retina is detached from the back of the eye, as a result of leakage from a hemangioblastoma, or as a result of fibrous tissue that has grown in the eye and is pulling on the retina.

Lesions on or near the optic nerve are very difficult to treat successfully without damaging the optic nerve itself. If they are not actually affecting vision, they should be monitored. There is no consensus among doctors on the best treatment approach if they do start to leak and affect vision. Fortunately, these lesions tend to grow slowly, and can often be watched for years.

Contact the VHL Alliance for the latest recommendations. The National Eye Institute (nei.nih.gov) and the National Library of Medicine (nlm.nih.gov) are also excellent resources for new terms and treatments.

VHL IN THE ADRENAL GLANDS

The adrenal glands are glands in the body that are approximately 3 x 2 x 2 cm (1 in long) and sit on top of each of the kidneys (see Figure 9). They produce hormones that are involved in the regulation of critical body functions, including:

- **Catecholamines:** This is predominantly epinephrine, but also some norepinephrine. Epinephrine helps to regulate the "fight or flight" response to stress (also known as adrenaline. It is the main catecholamine produced by the adrenal glands).
- **Glucocorticoids:** The most important glucocorticoid is cortisol. Cortisol helps to regulate blood sugar, blood pressure, fat and protein metabolism, and the immune system. Cortisol is known as the 'stress hormone.'

- **Mineralocorticoids:** The most important mineralocorticoid is aldosterone. Aldosterone works mainly in the kidneys by maintaining salt and water balance within the body. This is important for blood pressure regulation and proper cardiovascular function.
- **Adrenal androgens:** These are precursors to sex hormones (i.e. testosterone, estrogen).

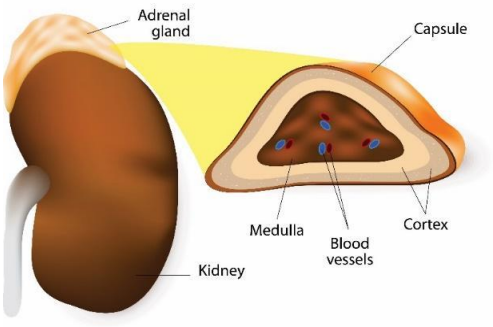


Figure 9. Diagram of an adrenal gland with cross-section: the figure shows the relative positions of this organ.

Pheochromocytomas and Paragangliomas

VHL is associated with a usually benign type of tumor occurring in the adrenal glands, called a pheochromocytoma (pheo). Pheos occur more frequently in some families than others. They are rarely malignant (less than 7% of the time) among people with VHL. Detected early, pheos do not cause problems, but they are potentially lethal if not treated. This is especially true during times of heightened stress (surgery, accidents, childbirth, etc.).

Pheos that develop outside of the adrenal glands are called paragangliomas (paras) and are very rare, even in VHL patients. Paragangliomas may occur anywhere on the sympathetic nervous system, which includes anywhere along a line drawn from the groin to the ear lobe, on either side of the body. Multiple tests may be needed to find them.

Research indicates that adrenal tumors are as much as four times more common among people with VHL than previously thought. Even in families that have not previously had a pheo, it is still important to test for the presence of these tumors. In one large progeny in France where there were no pheos for three generations; there are now pheos in two branches of that family.

Symptoms

The primary clinical sign of a pheo is high blood pressure, especially spiking blood pressure, that can put strain on the heart and vascular system, potentially causing a heart attack or stroke. However, blood pressure in some patients may

be normal, despite the presence of a pheo. Patients may notice headaches, irregular or rapid heartbeat, or what feels like a panic attack, fear, anxiety, or even rage. There may be unexplained heavy sweating and sometimes people experience hot and/or cold flashes. There may also be abdominal pain or unexplained weight loss. It is recommended that all people with VHL be screened regularly for pheos.

Testing for a Pheochromocytoma

It is extremely important to test for pheochromocytomas before undergoing surgery for any reason, as well as before going through childbirth. Undergoing either of these stressful experiences with an undiagnosed pheo can be extremely dangerous. If the doctors are aware that the pheo is there, they can take preventive action that will ensure the safety of the patient and of any unborn child.

Traditional blood or urine tests that measure only catecholamines are inadequate to find most pheos. In order to diagnose a pheo, an initial biochemical test is done to measure blood or urine metanephrines. The preferred test is a plasma free metanephrines test, due to its higher sensitivity. This involves taking a sample of blood and measuring the levels of metanephrine, the metabolite of adrenaline, and normetanephrine, the metabolite of noradrenaline. More widely available is the fractionated 24-hour urinary free metanephrines test, which includes collecting a 24-hour urine sample and analyzing it for fractionated metanephrines and normetanephrines.

The measurement of normetanephrine is most important, since VHL-related pheos usually do not produce adrenaline or its metabolite, metanephrine, in significant amounts. Testing for methoxytyramine (a metabolite of dopamine) levels may be useful in evaluating metastatic status, although only 17% of VHL patients with pheos produce it. If additional information is required, or if there are symptoms of a pheo, but the blood and urine tests are negative, anatomical imaging scans should be used.

Testing Standards for Pheochromocytomas and Paragangliomas

Below are the clinical guidelines that were approved by the Endocrine Society for testing for the presence of pheochromocytomas and paragangliomas (together known as PPGLs):

- **Surveillance for PPGLs** should always include measurements of plasma metanephrines (obtained from a blood sample) or urinary fractionated metanephrines (obtained from a urine sample).
- **For a blood sample**, it is recommended that patients be supine (lying down) for a minimum of 20-30 minutes between the time the needle is inserted and the time the blood is drawn. Studies have shown that seated

blood testing more often results in false positives. The reason for this is that the release of catecholamines by peripheral nerves and the adrenal gland is stimulated by an upright posture. Sitting upright results in increased blood levels of metanephrines compared to being in a supine position.

- **For blood sample analysis**, upper reference intervals (the test result above which a pheo is determined to be present) should be established from supine tests, not seated tests, in order to minimize the chance of a false negative result (missing a PPGL that is present).

Analysis is performed using liquid chromatography (LC-MS/MS) with mass spectrometric, or electrochemical detection and using supine norms for plasma test results. All positive test results should be followed up. Follow-up may involve repeated biochemical studies (e.g. a clonidine test), or a CT scan or MRI (if a CT scan is not appropriate).

In VHL, it is only necessary to consider elevations of normetanephrine. For plasma in an adult patient with VHL, anything over 112 picograms/milliliter (0.61 nanomoles/liter, the NIH upper reference limit) should evoke suspicion. Anything over 400 pg/mL (2.2 nmol/L) for a sample that is taken with the patient lying down and relaxed (no stress) and on no antidepressants is immediately highly suspicious (close to 100% likelihood). Imaging is then warranted. Between those ranges, the likelihood of a pheo increases with increased level and follow-up tests, such as imaging, should be considered.

If these chemical tests indicate the presence of a pheo, but it cannot easily be located on MRI or CT, an MIBG or PET scan may be recommended. These scans help to locate a pheo, even if it is outside the adrenal glands.

According to research at the U.S. National Institutes of Health, different tests have different success rates in locating a pheochromocytoma or paraganglioma:

- 18F-FDA PET scan finds 75–92%
- 18F-FDOPA PET scan finds 67–93%
- 123I-MIBG scan finds 67–86%
- 18F-FDG PET scan finds 83–93% (adrenal: 67%)
- Octreotide scan finds fewer than 50% of these tumors. Please note that the Octreotide scan will soon be replaced by 68Ga-DOTA analogs used with PET scans.

The choice of one of these tests is often made depending on the availability of a particular technology at that center. However, it is important to note that if the test chosen does not find the pheo, there is still some chance that the pheo is there but cannot be detected by that particular test. A second opinion should be requested from a VHL or pheochromocytoma expert.

Preparing for Pheochromocytoma Testing

The accuracy of the urine and blood tests for pheo activity will be determined in large part by your own cooperation in preparing for the test. The tests are most reliable when care is taken in two areas—diet prior to testing and preservation of the urine sample from the start of the test until the lab processing is complete.

For a reliable measurement of plasma and urinary free metanephrines, no specific diet is required. Testing for plasma or urinary 3-methoxytyramine requires a diet poor in catecholamines to prevent false-positive results. Catecholamines can be found in fruits (such as bananas), fruit drinks, and nuts.

While there is no strong data that suggests that regular use of tobacco or alcohol may be linked to inaccurate results, caffeine should be avoided because it can cause false-positives on some tests. Certain drugs and medications can interfere with the measurement method being used, while others, like antidepressants, can cause false-positives. Be sure to tell your doctor and the technician if you are taking any medications. If possible, testing for pheos should be done before beginning any medications.

Specific instructions may differ slightly from center to center, due to different methods of analysis. Follow any instructions carefully to avoid a false reading.

Preparation for Blood Testing

The procedure usually takes about 45 minutes. It is important that you be quiet and calm for 20–30 minutes prior to the blood draw to ensure accurate results. Bring something with you to keep you occupied and relaxed as you will be asked to lie quietly on a table for 20 minutes after the needle is inserted before the test begins.

	UPPER LIMITS	
	Normetanephrines	**Metanephrines**
Boys (ages 5-18 years)	97 pg/mL (0.53 nmol/L)	102 pg/mL (0.52 nmol/L)
Girls (ages 5-18 years)	77 pg/mL (0.42 nmol/L)	68 pg/mL (0.37 nmol/L)

Table 4. Published upper limits for reference intervals of plasma concentrations of metanephrines in children (from samples collected lying down with an indwelling i.v.). Reference intervals for each lab may be slightly different due to variations in processing.

If there are concerns about interactions with medications, it is important that the laboratory use LC-MS/MS techniques to analyze the sample, in order to achieve the highest sensitivity and selectivity in checking fractionated metanephrines, especially normetanephrine.

Preparation for 24-hour Urine Testing

Pro Tip: Do not begin collection on Friday or Saturday. This ensures that your sample will be delivered to the lab on a working day and can be processed promptly.

1. Start the collection in the morning. Empty the bladder; do not save this urine specimen.
2. Write the date and time on the jug. (If there is a preservative added to the jug, be careful not to get it on the skin. If this happens, wash the area immediately with water.)
3. Save all the urine passed for the next 24 hours in the jug provided including the final specimen passed exactly 24 hours after beginning the collection.
4. Keep the urine refrigerated at all times. You might keep it in a paper bag in the refrigerator. If you must be out, you could carry it in a bag or backpack with plastic ice packs against the jug.
5. Write this date and time on the jug when the collection is finished.
6. Bring the collection and the paperwork to the lab as soon as possible after collection. (Labs are usually open early in the morning or have a place where you can arrange to drop it off early.)

Treatment

If surgery is required, the preferred method is a cortical-sparing partial adrenalectomy. Studies have shown that keeping even a small amount of the cortex of the adrenal gland, if surgery on both glands is required, makes it easier to manage post-surgery. It also usually avoids the need for steroid replacement. On the other hand, it must also be recognized that the remaining adrenal tissue can be associated with recurring pheos. Removal of the entire adrenal gland is rarely required to manage VHL-associated pheos.

The "key hole" operating technique (laparoscopy) is currently used to treat pheos. With this technique, there is less risk of infection and the recovery is much faster. Some surgeons have the technology to simultaneously remove pheos located on each of the two adrenal glands. Laparoscopic or robotic surgery should be discussed with your doctor.

Prior to surgery, the medical team will prescribe "blockers" (alpha blockers, sometimes followed by beta blockers), or drugs that inhibit the formation of catecholamines. These medications will calm the effects of the chemicals produced by the pheo and allow the surgery to proceed calmly, without causing a

pheo crisis. While the blockers will make you tired, they are critically important. They may be prescribed for two or more weeks before the planned surgery.

Another important consideration before surgery is to make sure that the anesthesiologist working with your surgeon has experience with pheos. The anesthesiologist is responsible for managing your blood pressure during the surgery. Your endocrine surgeon should be able to let you know who will be part of your surgical team.

Adrenal Dietary and Lifestyle Management Strategies

Maintain a healthy diet. Chronic stress is associated with increased levels of cortisol, a hormone related to stress which helps regulate blood sugar, blood pressure, fat and protein metabolism, and the immune system. High levels of cortisol can promote overeating and lead to weight gain. Eating a balanced and nutritious diet supplies the body with all its essential nutrients and can be useful for controlling weight, reducing stress, and improving performance.

A clinical study evaluating the effect of calorie restriction for one month in otherwise healthy overweight women aged 20–36 found that, along with an average weight loss of almost 13 pounds, there was a significant decrease in blood pressure, heart rate, and cortisol hormone levels, improved hand-eye coordination, and no evidence of increased physiological or psychological stress. Work with a dietician to develop the most appropriate diet for you.

Eat salt and stay hydrated. Those who have had their adrenal glands removed due to pheochromocytomas or who have adrenal insufficiency (or Addison's Disease) generally need more salt in their diet. This is because they do not have enough of a hormone called aldosterone, which regulates sodium and potassium (salt and electrolyte) levels in the body. Aldosterone is produced by the adrenal glands, and without functioning adrenal glands, there is very little or no aldosterone production. If aldosterone levels get too low, the body loses too much sodium.

People who produce low or no amount of aldosterone are often categorized as "salt-wasters" because they cannot maintain salt (sodium) levels. These individuals must take supplements to replace aldosterone. Even with replacement, maintaining optimal levels of aldosterone can be a challenge. When these "salt wasters" exert themselves heavily or spend enough time in hot temperatures, there is a good possibility of their losing too much salt in sweat and urine, putting them at a higher than normal risk for dehydration. Therefore, "salt wasters" should be sure to drink enough non-sugar-loaded liquids and supplement with enough salt to alleviate this dangerous situation. Good liquid options include water (always the best choice), seltzer or soda water, tea of any type, fruit juice, milk, broth, etc.

Avoid simple carbohydrates. Cortisol is released by the adrenal glands if the body has low blood sugar. Low levels of glucose can occur when meals are skipped or taken at irregular intervals. Eating simple or refined carbohydrates (such as sugar, corn or table syrup, or white flour) can also cause low blood sugar levels, since they are digested and absorbed very quickly by the body. Instead of a gradual rise in blood sugar, this quick absorption triggers a quick spike in blood sugar levels that is followed by a quick decline. This rapid increase and decrease in blood sugar causes an increase in cortisol levels, which triggers the stress response mechanism.

Eating meals at regular intervals and consuming foods other than simple carbohydrates can prevent this increase in cortisol levels. Proper diet is important not only to control blood sugar and reduce spikes in stress hormone levels, but also to reduce risk factors for disease.

Limit stimulants. Consumption of stimulants, such as energy drinks, coffee, or soft drinks has been linked to feeling stressed. The effect of caffeine is known to increase cortisol hormone production and intensify the stress response. Therefore, caffeine should be consumed in moderation or avoided by people exposed to chronic stress or with impaired adrenal function. Smoking cigarettes can also increase stress; nicotine exposure is known to increase cortisol levels.

Stay positive, practice self-care. Low self-esteem and loneliness are known to increase cortisol levels, while maintaining a positive outlook on life and a good social support system is associated with lower stress hormone levels.

Sleep. There is a known association between sleep and levels of cortisol, the stress hormone. While getting enough quality restful sleep can slightly decrease cortisol levels, disturbed sleep or not getting enough sleep can lead to mildly increased cortisol levels. For this reason, sleep deprivation may be an important risk factor leading to stress-related disorders.

Medication. Please note that if you have had both of your adrenal glands completely removed, it is important to follow your prescribed daily doses of hydrocortisone and fludrocortisone, and to be checked regularly by your endocrinologist. These medications work to replace the functions of your missing adrenal glands to manage the balance of fluids in your body, maintain kidney function, control blood pressure, and maintain cardiovascular health.

VHL IN THE REPRODUCTIVE SYSTEM

VHL lesions in the reproductive system are classified as cystadenomas. A cystadenoma is a benign tumor with one or more cysts inside it, having more density than a simple cyst.

Epididymal papillary cystadenomas may occur in as many as 50% of VHL patients with male reproductive organs. Similarly, VHL patients with female

reproductive organs may develop cystadenomas of the broad ligament. Both lesions are benign, although they may sometimes cause pain or discomfort.

Manifestations in the Male Reproductive System

Epididymis

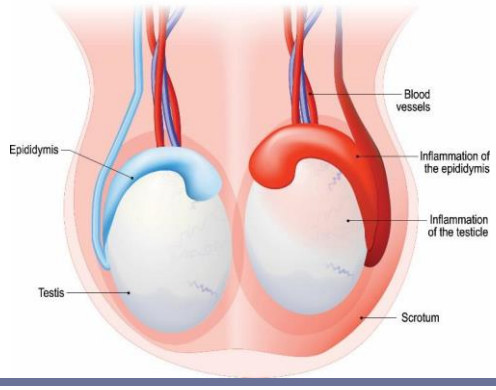


Figure 10. Diagram of testicles demonstrating position of epididymis.

The epididymis is a small coiled conduit that lies above and behind the testicle on the path to the vas deferens, the tube that carries the sperm from the testicle to the prostate gland.

The epididymis is as long as the testicle, lying in a flattened C shape against one side It is a complex tubular system that gathers the sperm and stores them until needed. After having been stored in the epididymis, sperm moves through the vas deferens to the prostate, where they are mixed with seminal fluid from the seminal vesicles, and then move through the prostate into the urethra during ejaculation.

Epididymal Papillary Cystadenomas

About 25% of people with male reproductive organs in the general population will develop a small number of cysts in the epididymis. By themselves, cysts are not cause for concern and are not even particularly noteworthy. VHL is associated with a specific type of cyst, known as a papillary cystadenoma.

Papillary cystadenomas of the epididymis are a rare occurrence in the general population. In VHL, they are benign, can range in size from 1 to 5 cm (0.3 to 1.7 in), and can occur on one, or both, testes. When they occur on both sides, it almost always means a definite diagnosis of VHL.

Symptoms

Epididymal cystadenomas have been described by patients as:

- A lump in the tube leading to a testicle
- A small, hard lump on the epididymis
- A rice-like lump under the skin on the epididymis
- A "pebble" in the scrotum

They are usually not painful and do not continue to enlarge. If it is painful, check with a doctor, since on rare occasions they can become inflamed and even rupture. These lesions usually develop during the teenage years, or later in life. It is not unusual for them to occur for the first time in one's forties.

Sexual Function and Fertility

Epididymal papillary cystadenomas do not interfere with sexual function. In most cases, the only "problem" associated with cystadenomas is the minor annoyance of knowing it is there.

Depending on their position, cystadenomas may block the delivery of sperm resulting in infertility. In some cases, they may cause atrophy of the vas deferens, also resulting in infertility. Patients who have epididymal papillary cystadenomas and wish to keep their childbearing options open may want to bank sperm for possible later use.

Monitoring

The best way to keep track of epididymal papillary cystadenomas is with a monthly testicular self-exam (TSE) monthly, as recommended in the general population. A TSE helps you become familiar with the size and shape of any epididymal cystadenomas, and make sure there are no unusual bumps or lumps in the testicles.

1. Check yourself right after a hot shower. The skin of the scrotum is then relaxed and soft.
2. Become familiar with the normal size, shape, and weight of your testicles.
3. Using both hands, gently roll each testicle between your fingers.
4. Identify the epididymis. This is a rope-like structure on the top and back of each testicle. This structure is NOT an abnormal lump, but epididymal cystadenomas may occur in this structure. Note their size and shape; keep a record for comparison in the future.
5. Be on the alert for a tiny lump under the skin, in front or along the sides of either testicle. A lump may remind you of a piece of uncooked rice or a small cooked pea.
6. Report any swelling to your health care provider.

Treatment

Although rarely necessary, epididymal cystadenomas can be surgically removed if they are causing discomfort to the patient.

It is important to note that epididymal cystadenoma surgery does not necessarily cause infertility. However, the removal procedure is similar to a vasectomy and may result in the disabling of the delivery of sperm from the operated side. The non-operated side will continue to function as normal.

Epididymal Cystadenomas and Testicular Cancer

VHL does not increase the risk of testicular cancer. Lumps or swelling on the epididymis does not necessarily mean that there is testicular cancer, but the patient must be checked by a healthcare provider.

Manifestations in the Female Reproductive System

Broad Ligament

The broad ligament is a folded sheet of tissue that drapes over the uterus, fallopian tubes and the ovaries (see Figure 11). It connects the uterus to the walls and floor of the pelvis. Cells in this area are from the same origin in the development of the embryo as the epididymis in people with male reproductive organs.

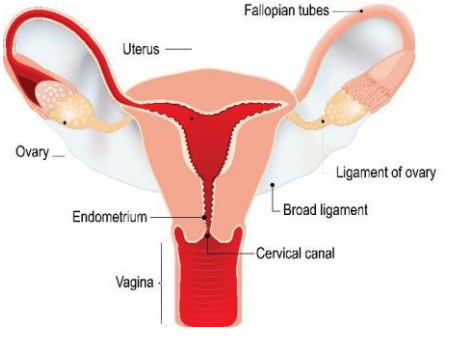


Figure 11. Diagram showing the broad ligament. The broad ligament is a large area of tissue that lies on top of the uterus, fallopian tubes, and ovaries.

Papillary Cystadenomas of the Broad Ligament

The VHL-related tumor that occurs on the broad ligament is called an Adnexal Papillary Cystadenoma of Probable Mesonephric Origin (APMO), also known as broad ligament tumors.

Cysts in this area are very common in the general population. However, papillary cystadenomas are a rare occurrence. If an unusual cyst or tumor is seen in the area of the broad ligament or fallopian tubes, a cystadenoma associated with VHL should be considered.

It is important for the doctor to do a careful differential diagnosis in order to prevent the over-treatment of benign tumors, which are sometimes confused with ovarian cancer. executiveresponse@endurance.com

Treatment

Although symptoms are rare, broad ligament cystadenomas can be surgically removed if they are causing discomfort to the patient, or increase the risk for infertility.

Note: The information above is related to a person's biological reproductive system at birth and is not related to gender identity. Transgender VHL patients should monitor for the manifestations related to the reproductive organs that they were born with.

In order to learn more about VHL in the reproductive system, especially in transgender and transsexual patients, everybody with VHL is encouraged to share their experiences by participating in the MyVHL: Patient Natural History Study at vhl.org/MyVHL.

Family Planning

Family planning is a very important and personal topic for people with VHL and their partners to consider, since every person who has VHL has a 50% chance of passing it on to each child. Some people feel more accepting of the idea of having children affected with VHL; other people feel worried and anxious about the risk of passing on the mutation. Different people act and feel differently; there is no "right" way to feel about having a child with VHL.

There are different family planning options available to individuals who have VHL, or a partner with VHL, and are considering having children. Some of these options allow someone to have a child unaffected with VHL; others simply help provide more information about a pregnancy. These options are a choice, not a requirement; many people choose to start a family without doing any genetic or prenatal testing. It is important, however, to know that these options are YOUR choice, and they are available should you choose them.

Meeting with a genetic counselor will help you understand all the options available to make the best decision for you and your family. Genetic counselors work as part of a healthcare team; they provide information and support to individuals and families affected by, or at risk for, a genetic disorder. Genetic counselors are trained not only to present complex information about genetic

risks, testing, and diagnosis, but also to provide supportive counseling and referrals to other sources of information and support. They serve as a central resource of information about genetic disorders for other health care professionals, patients, and the general public. To find a genetic counselor in your area, go to a VHL Clinical Care Center (vhl.org/ccc), visit the National Society of Genetic Counselors website (nsgc.org), or talk to your health care provider.

Birth Control and VHL

While there is no conclusive data that suggests that birth control that uses hormones has any impact on VHL or tumor growth, many physicians may recommend that a patient with VHL limit their contraceptive choices to those that are non-hormonal, or very low in progesterone. The rationale is that hemangioblastomas associated with VHL may be sensitive to the progestin contained in birth control pills, patches, rings, implants, and long-acting injections. Some IUDs contain copper and others have a low dose progestin. The copper IUDs are a non-hormonal contraceptive. The progestin IUD has a low dose of progestin and may also be considered. Talk with your doctor about what options are right for you.

Preimplantation Genetic Diagnosis

Preimplantation genetic diagnosis (PGD or IVF-PGD) was developed in the United Kingdom in the 1980s as an alternative to prenatal diagnosis. PGD allows a couple to select an embryo without the *VHL* mutation. in vitro fertilization (IVF), or fertilization of the egg and sperm, is performed in a laboratory. A few days after fertilization, a single cell is teased out of the developing embryo. The single cell sample is sent to a genetics lab for analysis. Usually samples from at least 4–8 developing embryos are analyzed; the results specify which of the embryos are affected with the *VHL* mutation and which are not. A small number of unaffected embryos can then be implanted into the uterus and the pregnancy proceeds forward normally. Embryos free of the *VHL* mutation that are not implanted can be frozen for future use. At this time, genetic testing must be done from embryos, not from banked eggs or sperm.

It takes pre-planning to accomplish this. Before the IVF process can be started, a test must be prepared to analyze the VHL status of the embryonic sample. This will require sending DNA samples to the testing lab. If the parent with VHL has not had previous genetic testing, samples from them and sometimes also from other close relatives are needed to determine their specific *VHL* mutation. Once the *VHL* mutation has been determined, the IVF process can be started. It is now possible to develop a genetic test for most, but not all, *VHL* mutation types. Each embryo to be implanted must be screened for the *VHL* mutation that is present in the affected parent.

IVF-PGD can be costly: check with your health insurance about coverage specifically for VHL. It is important to confirm that insurance will cover both the fertility treatment required to obtain the embryos for testing and the genetic testing fee. It should be noted that the process may take several cycles before it succeeds.

Some studies have demonstrated that the experience of IVF-PGD is a challenging process, full of uncertainty, with difficult decision-making required at particular points in time. It is important that couples pursuing PGD receive appropriate genetic counseling.

Many couples with VHL have used IVF. If you would like to explore this option, please contact the VHL Alliance or a certified Fertility Clinic offering in vitro fertilization with preimplantation genetic diagnosis (PGD). Please help us learn more by sharing your experiences with PGD in the MyVHL: Patient Natural History Study at vhl.org/MyVHL.

Pregnancy and VHL

There is no clear answer as to whether pregnancy impacts tumor growth. It is important for people with VHL to discuss a possible pregnancy with their doctor and medical team, including what might happen if tumors grow during pregnancy. Since it is preferable not to use tests that involve radiation while pregnant for fear of harming the baby, it is best for testing to be performed in advance. It is also important to discuss possible risk factors before making the decision to get pregnant.

If a VHL patient is are already pregnant, tell your obstetrician and connect them with the other members of their VHL medical team. Watch for symptoms and report anything to the doctor. Pregnancy is accompanied by multiple changes in the body. While some are normal in any pregnancy, they can be of particular concern for someone with VHL.

- **Vomiting and headaches:** This will take more watching than for most pregnant people, since these can also be signs of brain and spinal tumors. Do not ignore or discount them, particularly if they are excessive or persistent. A little morning sickness is normal as the amount of vomiting is variable within a pregnancy. Always check with your medical team if there is cause for concern.
- **Doubling of blood volume:** If a hemangioblastoma in the brain, spinal cord or retina, is present, the increased blood flow caused by the preganancy may expand the tumor for a period of time. Some pregnant VHL patients have reported worsening of symptoms during the pregnancy followed by a lessening of symptoms after delivery. In some cases, the expansion took mild or non-existent symptoms and expanded them to a critical level.

- **Possibility of triggering an existing pheochromocytoma (pheo):** It is important to have a thorough test for a pheo before planning a pregnancy, or as soon as pregnancy is determined. This is especially important before going through the birthing process. An active pheo can be life-threatening to the parent and their baby. Be sure to get checked—and rechecked—for a pheo during the pregnancy to avoid these complications. Pheo symptoms can be overlooked during pregnancy, with the assumption that high blood pressure is due to preeclampsia or another issue. Undiagnosed pheos can increase risk of parental death. This higher parental mortality arises from pheo-related difficulties in controlling blood pressure. For example, elevated blood pressure can result in the premature separation of the placenta from the uterus, posing a life-threatening problem for the parent and the fetus. Pheos have been safely removed during some stages of pregnancy, but it is preferable to remove them prior to pregnancy.
- **Additional strain to your spinal column due to the extra weight of the fetus:** Depending on what cysts or tumors are already present in the spinal cord, this additional stress may cause a worsening of symptoms.
- **Increased fluid load on your kidneys:** Make sure that kidney function is normal.

Because some changes from pregnancy can mask symptoms and signs of tumors, it is important to know what is going on before those changes begin. The surveillance guidelines regarding pregnancy include:

- Going for a generalized physical exam, with a medical history taken, as well as blood pressure and heart rate checked, prior to conception.
- Having an abdominal, brain, and spine MRI—with and without contrast—prior to conception. If already pregnant, any necessary MRIs should be performed WITHOUT contrast only.
- Getting tested for pheochromocytomas, via a plasma free metanephrines test (blood) or urinary free metanephrines test (24-hour urine) prior to conception.
- Undergoing a dilated retinal exam for hemangioblastomas prior to conception, and every 6-12 months thereafter.

Anesthesia during labor: There is a theoretical risk that spinal hemangioblastomas may rupture with anesthesia; however, very few VHL lesions are in the lumbar region of the spine. Thus, if the hemangioblastomas are not in the lumbar region, the risk during epidural anesthesia is likely low. It is important to have imaging done before administering anesthesia. Some anesthesiologists will not offer epidurals to patients who have spinal hemangioblastomas. General anesthesia appears to be safe when used in an emergency.

Approximately 2–3 months after the baby is born, have another thorough check-up to evaluate any changes in your own health. New symptoms or complications of central nervous system (CNS) lesions could occur postpartum and thus the patient with VHL should be examined carefully, especially if any new symptoms arise.

In order to better understand any effects of contraception, pregnancy and childbirth, and hormone replacement therapy on VHL lesions, you are encouraged to share your experiences by participating in the MyVHL: Patient Natural History Study at vhl.org/MyVHL**.**

VHL IN THE EARS

Endolymphatic Sac

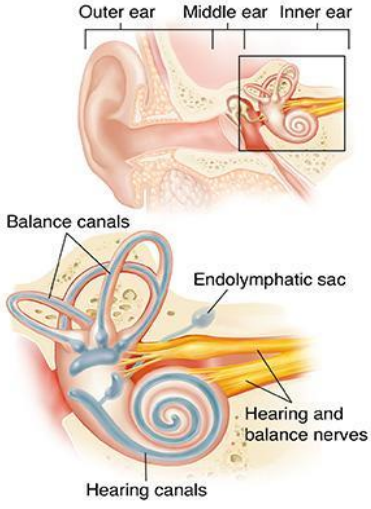


Figure 12. Diagram of the inner ear, showing the endolymphatic sac (ELS). Illustration courtesy of StayWell's image "Anatomy of the Inner Ear" (83596)

The endolymphatic duct runs from the inner ear to the back surface of the petrous bone at the base of the skull, and ends beneath the dura, as a flattened expansion, called the endolymphatic sac (see Figure 12). This tiny structure is filled with fluid (called endolymph) and has a delicate system of pressure regulation that is responsible for balance and equilibrium.

An ELST is a lesion that forms in the endolymphatic sac behind the inner ear. They occur in about 15% of people with VHL. It is often misdiagnosed as Menière's disease, another condition that is caused by a disturbance in this area.

Surveillance

The VHL Surveillance Guidelines (vhl.org/surveillance-guidelines) include a recommendation that everybody with VHL should go for an audiogram examination by an audiologist every two years, beginning at age 11, to document their state of hearing and verify that it has not changed. Additionally, every person with VHL should get a baseline high-resolution MRI, with 1 mm slice thickness, of the internal auditory canal, after age 15 (once the temporal bones have matured). This scan should be added to a brain and spine MRI for those patients who are between ages 15-20.

If you sense changes in your hearing or other indications of inner ear problems, you should follow up with a neurotologist. Patients who have never had any signs or symptoms of an ELST may stop audiogram testing beginning at age 65.

Symptoms

People with ELSTs report hearing changes, ranging from subtle changes in the "texture" of the hearing to profound hearing loss. Hearing loss may occur suddenly, or gradually over a period of months. If there is a loss of hearing, swift action is needed if there is to be any hope of preserving it. Once hearing is lost, it is very difficult to regain. Other symptoms may include tinnitus (ringing in the ears), vertigo, dizziness, fullness in an ear, or facial weakness.

There is one case reported where chronic ear infections were the first sign of an ELST in a 6-year-old child with VHL.

Treatment

When an ELST is visible on an MRI, surgery should be considered to prevent disease progression and hearing loss. Careful surgical removal will stop further damage and can occasionally be done without damaging hearing or balance. This delicate microsurgery usually requires a team made up of a neurosurgeon and a neurotologist, in a practice that performs a lot of inner ear surgery.

There are occasionally situations where hearing may be affected, even though there is no tumor visible by MRI. Tumors as small as 2 mm, found during surgery, have been seen to affect hearing. Please help us learn more about ELSTs by participating in MyVHL at: vhl.org/MyVHL.

VHL IN THE LIVER

The liver is an organ located in the upper abdomen. It produces biochemicals and hormones that are involved in digestion, metabolism, detoxification, glycogen storage and the decomposition of red blood cells. Bile, produced by the liver, is stored in the gallbladder, which sits just below it (see Figure 13)

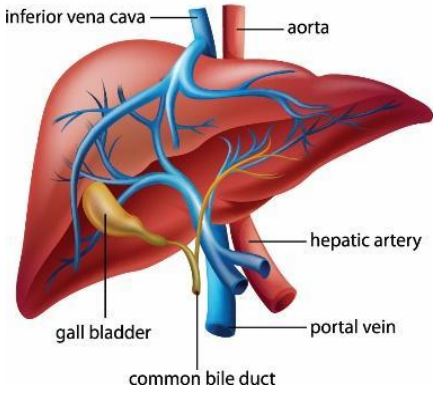


Figure 13. Diagram of the liver.

VHL-Related Manifestations

Studies have found that about 17% of people with VHL will develop multiple cysts in the liver, called simple hepatic cysts. These relatively common lesions are asymptomatic and do not become malignant. They can be seen using MRI, CT, or ultrasound imaging.

About 2–7% of the general population have simple hepatic cysts, but the appearance of multiple cysts are more common in patients with certain diseases, including VHL, polycystic liver disease and polycystic kidney disease. Liver hemangioblastomas are very rare, but may occur in VHL patients.

Other non VHL-related, benign, asymptomatic lesions that have been found in the liver include liver adenomas (3%) and liver hemangiomas (7%). Please note that liver hemangiomas may occur in the general population, or in VHL patients, and are distinct from true liver hemangioblastomas.

Pay it forward to the VHL community and help us learn more about VHL in the liver by participating in MyVHL, vhl.org/MyVHL.

VHL IN THE LUNGS

The lungs are located in the chest and are the primary organs of the respiratory system, allowing people to breathe (see Figure 14). Breathing is the process by which oxygenated air is drawn in through the lungs, followed by the expulsion of carbon dioxide.

VHL-Related Manifestations

VHL is associated with benign cysts in the lungs. When first noted at the National Institutes of Health, biopsies were performed. All of the lesions were benign, with no metastases from other organs. The presence of a lung hemangioblastoma is a possible rare manifestation in VHL patients.

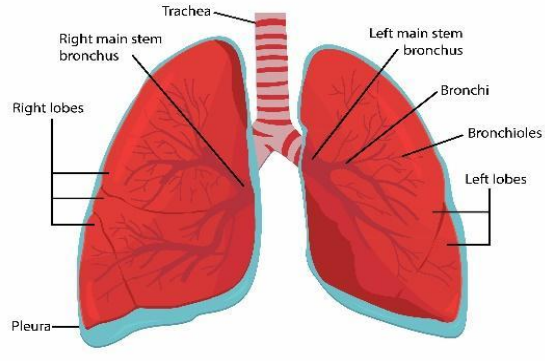


Figure 14. Diagram of the lungs.

At this point, the percentage of VHL patients who have these benign cysts is unknown, as there have been just a few cases reported in medical literature. Please add to the knowledge about the VHL manifestations in the lungs by participating in MyVHL, vhl.org/MyVHL.

SECTION 3

HEALTHY LIVING FOR THE VHL FAMILY

Whether a patient, a caregiver, or a family member, there are many factors that affect one's health. Some of these cannot control such as genetic makeup or age, while some lifestyle changes can be control.

There are three factors that can be controlled and can impact one's health status are:

1. How much one moves
2. What one eats
3. How one cares for their emotional health

Every day choices affect one's health and wellness. Choosing to be active, eat healthy foods, and improve one's emotional wellbeing are the most important investments to make in life. Strive for the best health possible in all areas of life by making mindful, healthy choices. Take charge of life!

Nothing is more important than taking care of oneself. Set aside time every day for this purpose—be active, enjoy hobbies, and share time with family and friends.

- Strive for balance in both personal and work life
- Make time for important relationships in life
- Ask for help whenever support from others is needed
- Find ways to relieve stress, such as physical activity and relaxation techniques
- Be open-minded to try something new, like a hobby or activity
- Be open to speaking with a doctor, who can provide resources and advice when needed. Such a doctor may be a family doctor or PCP.

Keep in mind that any lifestyle change is a "work in progress" and that lasting changes take time. Set small goals that are easy to add to daily life and take charge in order to accomplish them.

VHL puts a person at greater risk for cancer, particularly renal cell carcinoma (RCC). An individual affected with VHL will have a higher baseline risk than someone in the general population because of their genetics. It has also been noted that taller adults (4 inches/10 cm taller than average) are at increased risk for RCC. Additional environmental and lifestyle factors can also contribute to RCC

risk level. Smoking, hypertension, and obesity (as defined by waist size or waist-hip ratio) are major environmental and lifestyle risk factors associated with RCC, while diets rich in vegetables and low in red meat lower the risk. By taking steps to live a healthy lifestyle and avoid known risk factors, the risk of cancer can be reduces as much as possible.

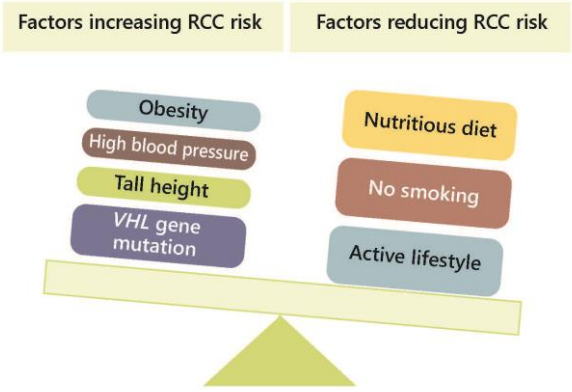


Figure 15. Factors increasing/decreasing RCC risk: Diagram by the VHL Alliance ©2015

Speak with a medical professional before making major lifestyle changes. It is important to live a healthy lifestyle, but being healthy means different things for different people. Certain diets might not be appropriate for individuals with VHL, including those who have adrenal, pancreas, or kidney function problems. Someone with physical disabilities may be limited to moderate exercise. Meet with a doctor or health care provider before making significant lifestyle change, or about concerns related to physical capabilities.

SMOKING AND VHL

One of the greatest known risk factors for many medical conditions is smoking. People who smoke are also at higher risk for a number of post-operative complications. Smoking is not only hazardous to the user, but second-hand smoke is dangerous for those nearby. According to the U.N. World Health Organization (WHO), tobacco use kills six million people each year, of which more than one tenth die from second-hand smoke. For everyone in the household, it is important to remove the contamination of the many toxic gases released in cigarette smoke from over 4,000 chemicals, of which at least 50 of which are known carcinogens.

Smoking is known to accelerate cancer, kidney cancer, in particular. Studies on kidney tumors in the general population indicate that patients who smoke, especially men, have more tumors than those who do not, and that those tumors grow more rapidly. Once an individual has stopped smoking for over 10 years, these elevated risks are reduced.

Vaping and e-cigarettes should not be considered a risk-free alternative to smoking. They also should not be considered as a smoking cessation device. Studies show a wide variability in nicotine levels and other chemicals, which cause them to be hazardous to the user.

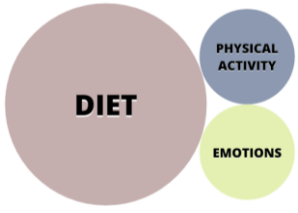
People often use smoking as a method of stress control. Smokers who have VHL and their family members, especially if there is something tense going on, will need to replace smoking with another healthier method of stress management. Support groups, a telephone buddy, or daily text messages are a way of keeping on track. Healthy snacks can help to ease the hand-mouth habit that often accompanies smoking.

The bottom line is getting tobacco smoke out of the house and out of everyone's life is important to the health of the individual as well as the health of the entire family.

DIET

Note: These are general suggestions and may not be appropriate for those with compromised adrenal, kidney, or pancreas function. Please see specific suggestions under each of those sections and work with your medical team.

General Nutrition



The role of diet and nutrition in lowering the risk of developing cancer has been discussed and studied for nearly a century. The American Cancer Society's published guidelines include recommendations for healthy living for reducing cancer risk. Obesity assessed using Body Mass Index (BMI) increases risk of renal cell carcinoma. Consumption of antioxidants (vitamins C, E, and carotenoids), vitamin D, and alcohol in moderation along with increased physical activity or exercise have been reported to protect against RCC. Higher intakes of fruits and vegetables guard against both RCC and pancreatic cancer. Unless recommended by a health care team, it is best not to use supplements, but to rely instead on whole foods to get the appropriate balance of essential vitamins and minerals.

Healthy eating is not about strict nutrition philosophies, staying unrealistically thin, or depriving oneself of one's foods favorite foods. Rather, it is about feeling great, having more energy, stabilizing one's mood, and keeping oneself as healthy as possible—all of which can be achieved by learning some nutrition basics and using them in a way that works. Try expanding the range of healthy food choices and learn how to plan ahead to create and maintain a tasty, healthy diet. To set up for success, think about planning a healthy diet as a number of small

manageable steps rather than one big drastic change. If one approaches the changes gradually and with commitment, they will most likely have a healthy diet sooner than anticipated.

People often think of healthy eating as an all or nothing proposition, but a key foundation for any healthy diet is moderation. The goal of healthy eating is to develop a diet that one can maintain for life, not just a few weeks or months, or until a predetermined weight is reached. Try to think of moderation in terms of balance. Everyone needs a balance of carbohydrates, protein, fat, fiber, vitamins, and minerals to sustain a healthy body.

Healthy eating is about more than the food on one's plate—it is also about how one thinks about food. Healthy eating habits can be learned, and it is important to slow down and think about food as nourishment rather than just something to gulp down in between meetings or on the way to pick up the kids. Food should not be a reward for oneself or others.

The Healthy Eating Plate from the Harvard School of Public Health incorporates new learning about nutrition, health, and cancer prevention. What one eats affects how one feel.

Basing a diet on plant foods (like vegetables, fruits, whole grains, and legumes (such as beans) and choosing nutritious foods and drinks is one of the best ways to stay healthy.

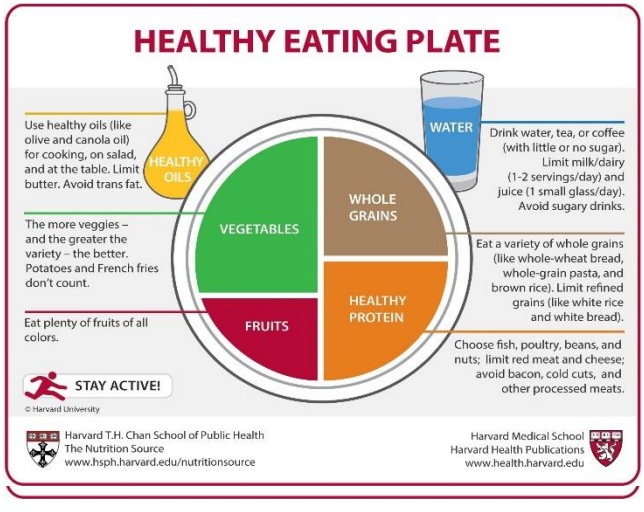
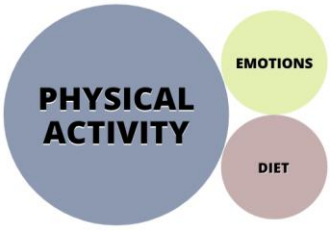


Figure 16. Healthy Eating Plate: Source: Willett et al., Harvard School of Public Health, 2011.

Sugar and Cancer: Is There a Link?

Not a direct link, no. Sugar does not cause cancer to grow or spread more quickly. However, a diet that leads to rapid changes in blood sugar level has been associated with both increased cancer risk (colorectal and endometrial cancers) and poorer outcomes. The effect of foods on blood sugar levels is measured by the glycemic load. Glycemic load is based upon the serving size of the food, so a food such as an orange may have sugar (measured as glycemic index), but the amount eaten in one serving will not require your body to release much insulin to handle it. Foods with a lower glycemic load provide a steadier release of energy and may keep you from feeling hungry soon after eating. These foods also do not cause spikes in your blood insulin levels which may be a risk factor in the development of Type 2 diabetes.

PHYSICAL ACTIVITY



Be physically active for at least 30 minutes every day.

Regular activity has been shown to decrease cancer risk and improve outcomes for those with cancer. Physical activity also improves cancer-related fatigue, anxiety, self-esteem, physical functioning, and various aspects of quality of life, including stress relief. Exercise can also improve muscle strength and body composition, while reducing the risk of heart disease and diabetes.

There is no evidence to indicate that VHL patients should limit their physical activities in any way, except for short periods following treatments or surgery. Speak with a healthcare provider about exercise tolerance. Moderate exercise, however, is good for everyone, but it is not good to overdo it.

Exercise is important for everyone at every age. It is important to begin the habit of regular physical activity in childhood. The Centers for Disease Control and Prevention (CDC) recommends one hour or more of physical activity per day for children and adolescents. This physical activity needs to include aerobic activity (walking, running, or swimming), muscle strengthening (gymnastics or calisthenics), and bone strengthening (weight-bearing). Although many children and teens already meet this guideline, a substantial portion do not; efforts are needed to engage them in the many sports and fun activities that will ensure that they meet these goals.

Guidelines for adults from the American Heart Association recommend at least 30 minutes of aerobic activity, 5 days per week, plus moderate to high intensity muscle-strengthening activity at least 2 days per week. The

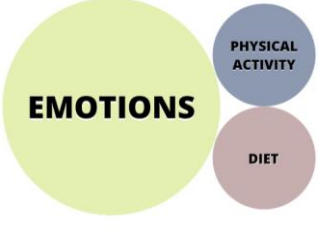
recommended total time can be split up into two or three segments of 10 or 15 minutes, allowing short walks to meet your aerobic exercise goal.

A study published in the journal Medicine & Science in Sports & Exercise found that people aged 60 and over have to work out more than people under the age of 60 to maintain muscle mass. However, workouts can be tough for those in that age group (ages 60–75, in the study), especially since joints are often more susceptible to injury at older ages. Low impact activities and exercises that do not require a gym or special equipment can help with this problem and provide opportunities for exercise that are accessible and feasible for everyone.

Regular physical activity can help keep your thinking, learning, and judgment skills sharp as one ages. It can also reduce risk of depression and may improve sleep. Research has shown that doing aerobics or a mix of aerobic and muscle-strengthening activities 3–5 times a week for 30–60 minutes can provide mental health benefits. Some scientific evidence has also shown that even lower levels of physical activity can still be beneficial.

Recent research indicates that in addition to regular exercise, it may also be important to avoid long periods of sitting. This means that as much as possible, it is important to stand or move instead of sit. Exercising can be performed watching television or by standing while working at the computer, or having a meeting while walking. It is recommended to get up and move for 1–3 minutes every half hour.

EMOTIONAL HEALTH



Stress can creep up everywhere in life.

It can come from the frustration of a traffic jam or a confrontation with a partner. Stress can be spurred by money worries or spiked by a sudden health scare. It is inevitable for anyone, particularly someone, directly or indirectly, impacted by a long-term medical condition such as VHL. Feelings of anxiety or worry can arise in response to our perceived stress. Anxiety or worry may be triggered by events such as the diagnosis, decisions on when to operate, and thoughts about future health. "Scanxiety" is a known phenomenon that occurs when preparing for annual scans, as well as while waiting for the follow-up reports. It can exact a toll—physically and emotionally.

The human brain is hard-wired with an alarm system for your protection. When the brain perceives a threat, it signals the body to release a burst of hormones to fuel its capacity for a response. This has been labeled the "fight-or-flight" response; a physical reaction is triggered by the brain in response to a stressor. Once the threat or source of stress is gone, the body is meant to return

to a normal relaxed state. Unfortunately, the nonstop stress of modern life (particularly when dealing with a long-term medical condition) means that the alarm system rarely shuts off. Stress management provides a range of tools to reset the alarm system.

Stress is a fact of life. But you determine how it affects your life. You can counteract the damaging effects of stress by calling upon your body's rich potential for self-healing. The VHL Alliance's Wellness Coaching program can help can you develop valuable techniques to deal with stress (vhl.org/wellness-coaching).

Stress

What is Stress?

Stress describes what people feel when they are under mental, physical, or emotional pressure. Stress is the demands that people perceive, whereas distress (anxiety, depression, worry) is the emotional response to these stressors. Although it is normal to experience some mental stress from time to time, people who experience high levels of stress or who experience it repeatedly over a long period of time may develop health problems (mental and/or physical).

The body responds to physical, mental, or emotional pressure in the same way: by releasing stress hormones (such as epinephrine and norepinephrine produced by the adrenal glands) that increase blood pressure, speed heart rate, and raise blood sugar levels. These changes help a person act with greater strength and speed to escape a perceived threat. Cortisol is a hormone that helps regulate the inflammatory response in the body. Cortisol is produced by the adrenal glands in response to stress. Under normal circumstances, cortisol levels should be high in the morning and drop throughout the course of the day. But studies have shown that among people experiencing chronic stress or depressive symptoms, cortisol levels can remain sustained throughout the day, with less of a decrease than normal in the evening. For people who are living without adrenals or adrenal function, supplementing with a replacement steroid is mandatory.

Everyone Experiences Stress

While some events can be more stressful than others, the average person faces stress on a daily basis. The stress of typical daily activities and responsibilities is often intensified by the stressor of chronic, genetic conditions like VHL.

Living with VHL or having a loved one affected with VHL can be a significant source of stress. VHL is a lifelong challenge that is taxing not only for the patient, but for every member of the household. While symptoms of and issues related to VHL may not affect one's life on a day-to-day basis, every once in a while they will come up and demand attention. Feeling out of control and not knowing what to expect can put a significant amount of stress on someone which, in turn, sustains

the health problems that come with VHL. Managing the stress of living with VHL and/or caring for someone affected with VHL is an important part of self-care.

Join a discussion call to talk out frustrations with other people in your situation and to get helpful ideas. Patient support groups are available online such as the VHLA Facebook group (facebook.com/groups/VHLawareness). The VHL Alliance also offers numerous support discussion calls, including a:

- VHL Patient/Caregiver Call - vhl.org/ptcgcall
- Parents of VHLers Call - vhl.org/parentscall
- VHL Low/No Vision Call – vhl.org/lownovisioncall

To learn more about support offerings, visit the website at vhl.org/support or contact VHLA (617.277.5667 x4).

How Does Stress Affect Health?

Research has shown that people who experience intense and long-term stress can have digestive problems, fertility problems, urinary problems, and a weakened immune system. People who experience chronic stress are also more prone to viral infections such as the flu or common cold and are more likely to have headaches, sleep trouble, depression, and anxiety. Stress makes the body unresponsive to cortisol and the hormone loses its effectiveness in regulating inflammation. Inflammation is a good thing when it is triggered as part of the body's effort to fight infection, but chronic inflammation can promote the development and progression of many illnesses, including depression, heart disease, diabetes, and cancer.

The buildup of stress can often feed or cause anxiety and depression. Practicing stress management techniques may bring some relief from anxiety and symptoms of depression; however, it is important to seek advice from a licensed social worker or medical professional, including your primary care physician. They may be able to recommend a combination of medications and counseling, as well as a mind-body program or other stress management approaches.

Is There a Link Between Cancer and Emotional Stress like Anxiety and Depression?

Although the research linking stress and risk factors for cancer is controversial, stress is known to affect biological processes that are critical to help control cancer growth.

A team of researchers led by Dr. Lorenzo Cohen, Professor and Director of the Integrative Medicine Program at The University of Texas MD Anderson Cancer Center, found that symptoms of depression among a group of patients with late-

stage RCC were associated with an increased risk of death. The probable mechanism found by the study was that the patients with chronic stress and depressive symptoms had higher cortisol levels than normal, which were also associated with an increased risk of mortality. The team also found increased inflammatory gene expression in the most depressed patients.

VHL and Family Distress

It is important to talk with one's family about how one is feeling. Generally speaking, these discussions are not a burden to other; it is an approach for helping others to understand, help, and participate. In general, it can be less stressful for everyone if everyone is dealing with VHL together. One shouldn't always feel obligated to shy away from asking for help or counseling. VHL is not a punishment; it is a medical condition. It is not one's fault and it is not something one can control.

A 2010 study in the Netherlands evaluated the prevalence of distress among VHL family members and identified factors that are significantly associated with such distress. Approximately 40% of the VHL family members reported clinically relevant levels of distress. These levels of distress were reported by 50% of the carriers and, interestingly, by 36% of the non-carriers. Having lost a first degree relative due to VHL during adolescence was a significant factor in heightened levels of distress. For this reason, the authors recommended that special attention be given to individuals who have lost a close relative due to VHL during adolescence.

Stress on Relationships

Living with VHL can be a very stressful experience. There are very real mental and physical challenges that come with the disease, its effects, and its treatment. Individuals who are affected with VHL may feel the strain in different ways. It is normal to go through stages of denial, anger, guilt, and other painful emotions. It is normal to feel more needful and to be angry when your family does not automatically understand your needs.

Unaffected members of the family will feel their own strains, anger, and guilt. Unaffected children may be angry that the affected child gets all the attention, or may feel guilty that they do not have VHL. Affected or not, children often harbor unspoken fears for themselves or for their family members, which may come out as misbehavior or school performance issues. Schools often have social workers or psychologists who can be called upon to assist children. In some areas there are support groups for children whose families are affected by cancer or chronic illness. The VHL Handbook Kid's Edition (vhl.org/product/vhl-handbook-kids-edition) can be used to help explain VHL to all of the children in your family.

Caregiver Needs and Stress

A chronic disease like VHL can put strain on even the healthiest of relationships. Partners are often the main suppliers of social support for patients and those at high risk, and social support is known to be a buffer for distress.

Therefore, if partners are distressed, they may be incapable of providing sufficient support to the high-risk spouse and vice versa. For this reason, it is important to address the emotional and psychological well-being of both.

The 2011 study in the Netherlands asked partners of individuals diagnosed with VHL to complete a questionnaire assessing distress, worries, and health-related quality of life. Of the 50 respondents, 25% showed signs of clinically relevant levels of distress and in need of emotional support or counseling. The majority (76%) of partners in the study believed that such support should be made available to them and be routinely offered to both individuals with VHL and their partners.

In general, emotional support is directed toward the patients; as such, distress experienced by partners may remain undetected and untreated. It is important to acknowledge and be aware of the needs of the partner, allowing them to seek needed support.

Additional studies further illustrate the personal challenges of caregiving. The results of a national poll conducted in 2013 by AARP found that, of the 1,036 adult caregivers who responded to the poll, one-third reported feeling sad or depressed and 44% reported ignoring or bottling up their emotions. Additionally, 38% of respondents said they slept less since becoming a caregiver, 24% ate more, 33% reported avoiding decision-making, and a third of caregiver respondents reported isolating themselves by avoiding people or social situations.

Caring for others is not easy and burnout is common. Caregiver may often wrestle with stress as well as exhaustion, anger, guilt, grief, and other difficult emotions. It is common to feel stressed and overwhelmed.

Studies show that those responsible for the long-term care of relatives show higher rates of illness, suppressed immune response, slower healing, and there is even increased mortality among caregivers. In order to give care, everyone needs stress relief, support, and time for themselves and the family.

It is important to share one's feelings with others who can help, or speak with a counselor or social worker. The VHL Alliance has some great support resources for caregivers, including the:

- VHL Caregiver Connect Facebook group (facebook.com/groups/vhlcaregivers)
- VHL: Parents to Parents Facebook group (facebook.com/groups/VHLparents2parents)
- Parents of VHLers Call (vhl.org/parentscall)
- VHL Patient/Caregiver Call (vhl.org/ptcgcall)
- VHLA Wellness Coaching Program (vhl.org/wellness-coaching)

Many people who were once caregivers say they did too much on their own. Some wished that they had asked for help sooner. Be honest about what and how

much one can do. Think about tasks can be given to others and let go of tasks that aren't important at this time.

- **Protect one's own health.** Boost resistance by eating well, getting enough rest and exercise, and pursuing activities that bring pleasure.
- **Practice self-care.** Make time for oneself and one's needs. Consider the airplane analogy—Put on your own oxygen mask before helping others. It is important to take care of oneself before one can effectively care for others. It is not selfish, it is vital.
- **Combat caregiver stress**. Relaxation response techniques and self-nurturing techniques will enable one to feel calmer, happier, and better able to help others.
- **Make time for relationships**. Nearly all caregivers and their partners feel more stress than usual in their relationship. A couple can stay close in spite of dealing with medical issues. Staying close is also about sharing feelings and understanding.
- **Accept help**. If no one offers help, ask for it. When someone offers help, accept it. Spell out to family members what needs to be done and what sort of help would be best. Sometimes it is hard to ask or accept these types of offers of help, but it is important to do. In many ways, by accepting this incredible personal gift, one is actually helping the giver.
- **Find support**. Join a support group to talk out frustrations with other people in your situation and to get helpful ideas. Some caregiver support groups are available online. Contact the VHL Alliance to learn more about their discussion group offerings including the VHL Partners program and the Telephone Discussion Groups (617.277.5667 x4 or info@vhl.org).

Stress Prevention and Management

In looking at the causes of stress, remember that the brain comes hard-wired with an alarm system for one's protection. When the brain perceives a threat, it signals the body to release a burst of hormones to fuel its capacity for a response. This has been labeled the "fight-or-flight" response.

Once the threat is gone, the body is meant to return to a normal relaxed state. Unfortunately, the nonstop stress of modern life means that the body's alarm system rarely shuts off. That is why stress management is so important; it provides a range of tools to reset your alarm system. **Without stress management, all too often the body is always on high alert.**

There are healthy and unhealthy ways to respond to stress. Healthy ways to deal with stress include exercise, relaxation techniques like meditation, yoga, etc., spending time outdoors, speaking with a friend, or playing with a pet. Unhealthy behaviors can include overeating or under-eating, sleeping too much, drinking too much alcohol, smoking, lashing out at others in emotionally or physically violent

outbursts, taking illegal drugs or self-medicating with prescription or over-the-counter drugs, and withdrawing from friends or partners. Becoming aware of how one typically handles stress can help one make healthy choices.

Emotional and social support can help patients learn to cope with psychological stress. Such support can reduce levels of depression, anxiety, and disease and treatment-related symptoms among patients. Approaches to stress management can include the following:

- Training in relaxation or stress management
- Techniques such as meditation, prayer, yoga, chi gong, tai chi
- Counseling or talk therapy
- Social support in a group setting
- Medications for depression or anxiety
- Exercise
- Learning various techniques that elicit the relaxation response such as breath focus and guided imagery
- Using cognitive restructuring, a method of helping reframe negative thoughts in order to cope more effectively with a difficult situation
- Nurturing yourself by setting aside time for socializing, relaxing, connecting with others, and pursuing activities that add joy to your life

Depression

Depression is a condition in which a person feels discouraged, sad, hopeless, unmotivated, or disinterested in life in general. When these feelings last for a short period of time, it may be a case of "the blues." When such feelings last for more than two weeks and when the feelings interfere with daily activities such as taking care of family, spending time with friends, or going to work or school, it is likely a depressive episode.

Depression is the most common mood disorder. According to estimates by the U.S. Centers for Disease Control and Prevention (CDC), approximately 1 in every 10 adults reports some level of depression. Fortunately, depression is treatable. A combination of therapy and antidepressant medication can help ensure recovery.

People with depression may experience the following signs and symptoms:

- Sad or low mood most of the day, nearly every day
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day nearly every day
- Significant weight loss or gain when not dieting or decrease/increase in appetite nearly every day
- Inability to sleep or sleeping too much

- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt nearly every day
- Diminished ability to think or concentrate
- Recurrent thoughts of death (not just fear of dying) or of suicide without a specific plan, or a suicide attempt or specific plan for committing suicide

Depression and Chronic Illness

Depression is one of the most common complications of chronic illness. Even a person who is successfully managing their chronic illness may still be at risk for depression.

The Rare Disease Impact Report published research showing that 75% of rare disease patients report that their disease caused their depression. Interestingly, 72% of caregivers to rare disease patients also reported feelings of depression.

Facing a chronic illness naturally leads to feelings of uncertainty, grief, sadness, anger, or fear. When these feelings continue and disrupt quality of life and day-to-day functioning, depression may be the culprit. Chronic illness and depression are sometimes related to each other and can be thought of as a two-way street—a diagnosis of a chronic illness can be depressing and the increase in depressive feelings can exacerbate the illness. The risk of depression increases in proportion to the severity of the illness and the life disruption it causes.

When symptoms of depression are present alongside symptoms of chronic illness, it is necessary to treat both—not just the symptoms of chronic illness. The treatment is similar to the recommended treatment for other people with depression.

Anxiety

Most people feel depressed or anxious at times. Losing a loved one, getting laid off from a job, going through a divorce, living with life-long health issues, and other difficult situations can lead a person to feel sad, lonely, scared, nervous, or anxious. These feelings are normal reactions to life's stressors. However, some people experience these feelings daily or nearly daily for no apparent reason, making it difficult to carry on with normal everyday functioning. These people may have an anxiety disorder, depression, or both.

Depression and anxiety disorders are different, but people with depression often experience symptoms similar to those of an anxiety disorder, such as nervousness, irritability, and problems sleeping and concentrating. Each disorder has its own causes and its own emotional and behavioral symptoms.

It is not uncommon for someone with an anxiety disorder to also suffer from depression or vice versa. Nearly one-half of those diagnosed with depression are

also diagnosed with an anxiety disorder. The good news is that these disorders are both treatable, separately and together.

The MyVHL: Patient Natural History Study (vhl.org/MyVHL) has identified that about 23% of VHL patients suffer from moderate to severe anxiety, while 16% suffer from mild anxiety. Post-traumatic stress disorder (PTSD) is also a common mental health diagnosis among people with VHL.

People with generalized anxiety disorder (GAD) experience exaggerated worry and tension, often expecting the worst, even when there is no apparent reason for concern. They anticipate disaster and are overly concerned about money, health, family, work, or other issues. People with GAD cannot seem to get rid of their concerns, even though they usually realize that their anxiety is more intense than the situation warrants. They cannot relax, may startle easily, and/or have difficulty concentrating. Often they have trouble falling asleep or staying asleep.

GAD is diagnosed when a person worries excessively about a variety of everyday problems for at least 6 months. GAD affects 6.8 million adults, or 3.1% of the US population, in any given year. The disorder develops gradually and can begin at any age, although the years of highest risk are between childhood and middle age.

Physical symptoms that often accompany the anxiety include:

- Headaches
- Muscle tension
- Muscle aches
- Difficulty swallowing
- Trembling
- Twitching
- Irritability
- Sweating
- Nausea
- Lightheadedness
- Having to go to the bathroom frequently
- Feeling out of breath
- Hot flashes

Treating Depression and Anxiety

All VHL Clinical Care Center (CCC) specialists, regardless of specialty, should be evaluating each patient's emotional health and wellbeing at each appointment.

Deciding Whether or Not to Seek Professional Help

Anyone who feels like they may have challenges managing the stress associated with life in general and/or VHL specifically should consider getting psychosocial support. This offers people the opportunity to meet with someone who can validate their concerns and also provide them with tools to manage their stressors and distress.

There are times when a person who is experiencing depression will get better on his own, but how does a person decide whether to seek professional help? Below are some questions for the person to consider:

1. Is the distress level intense enough that they want to do something about it?
2. Do they feel that they are no longer able to problem-solve on their own? Do they feel the need for more support?
3. Is the level of distress such that it is negatively affecting their relationships, usual activities, or work?
4. Are they contemplating suicide?

A person who answers yes to one or more of these questions may benefit from entering a counseling relationship with a professional. Individual counseling that includes talk therapy is beneficial for anyone living directly or indirectly with a chronic disease.

Who Treats Depression and Anxiety?

Clinical social workers, psychologists, psychiatric nurses, and psychiatrists are the primary treatment providers for depression and anxiety. Each takes a different treatment approach, so it is important that each person finds what works best for them and meets their needs. In addition, there is a wide range of other professionals who can also help, including primary care provider or internal medicine doctor, members of the clergy, and school guidance counselors.

Treatment Options

There are a wide range of treatment options for depression and anxiety, but they can generally be divided into three categories: Antidepressant medication (also used for anxiety) alone, counseling alone, or a combination of antidepressant medication and counseling.

Medication: There are a variety of antidepressant medications available, but they can be separated into two main categories: Tricyclic antidepressants (TCA's) and selective serotonin reuptake inhibitors (SSRIs) are frequently used to treat anxiety. Medications within these categories work differently on the brain and have different side effects. Unfortunately, there is not a definitive way of knowing beforehand which medications will be most effective. A person may have to try a few different medications before finding one that is effective. This is not to say that

prescribing medications is just educated guesswork. It is important that the physician and patient work closely together in order to determine an appropriate regimen.

Counseling or Therapy: There are many different approaches to counseling and therapy, so it is important to determine what you are looking for. The two main categories of counseling are cognitive-behavioral therapy and insight-oriented therapy. Cognitive-behavioral therapy is more focused on the present; looking at current behavior and thought processes, and how to change behavior and thinking that may be contributing to depressive or anxious feelings. Insight-oriented therapy is a longer-term process. It is focused on helping the patient to gain a greater understanding of their unconscious motivations and increase insight into the root of the problem.

SECTION 4

DISCUSSING VHL

FAMILY MEMBERS AND VHL

Genetic disorders can affect families in significant ways. Since DNA is inherited and passed down through families, a genetic disorder can impact the health of many family members. A genetic diagnosis for one family member may mean other blood relatives are also at risk, even if they currently show no symptoms or have no apparent health problems. Genetic disorders also present emotional challenges and special reproductive considerations. Families may be concerned about the risk that additional children will inherit the condition and worry about the decision have a child undergo a genetic test for VHL.

Given that genetic information affects family members, it is important to consider the family unit and the impact a genetic diagnosis can have on everyone. Family members who do not have the *VHL* mutation and are thus unaffected often feel guilty that loved ones have to deal with the manifestations of VHL while they do not. Unaffected siblings of children with VHL may feel neglected because their parents need to focus more time and attention on their siblings.

The appropriate timing of this conversation is very personal and may vary significantly between individuals. When communicating information about VHL to adult family members, you may want to give them the name and contact information of your genetic counselor. This will give them a knowledgeable third party to contact with questions that they may not want to ask you. It may also be especially beneficial when communicating information about VHL to teens.

Communication

Research shows that children and teenagers want their parents to engage in open and honest discussions about genetic conditions. Having a conversation about VHL means children can ask questions and have their parents answer them informatively and accurately. Openness also provides opportunities for children to use their parents as role models for their own coping with VHL.

While disclosure of a genetic condition may improve family cohesion and strengthen familial bonding, it can be hard for parents to talk about something like VHL with their children. They might feel guilty, afraid, or just not know how to bring it up.

Talking with Children About VHL

Regardless of whether the child has VHL, or a sibling and/or parent has VHL, talking with children about VHL can be a difficult and emotional conversation to have. There can be many reasons why a parent would not want to talk to their child about VHL. Many feel that they need to protect their child from this type of information. Parents may also feel guilty or like they have no control over the situation. There are always things that are out of our control, such as whether or not a parent passes on a *VHL* gene mutation to their child, but it might help to focus on the things one can control. Work on being present within relationships, using good coping skills, and taking care of oneself. Teach children valuable skills and lessons about coping with VHL by setting a good example; children tend to model the behaviors of important adults in their lives.

While one may feel guilty about taking any time for oneself, but it is nearly impossible take care of others effectively if not also taking care of oneself. Focusing on one's needs and health will not only help one to be a better parent, it will also help teach children about the importance of self-care.

Someone might have good intentions for why they do not want to tell their child about VHL, but it is important to understand that keeping secrets can do more harm than good and lead to feelings of isolation, betrayal, and, ultimately, stunt the family relationship instead of protect it. Children start to understand the world around them at a very young age. It is important to be honest with them. They need to know the truth about their health or the health of a loved one. Otherwise, they will think the worst.

Being Ready to Talk to Your Child?

There is no right or wrong answer for how and when to have this conversation. A parent knows their child best; it is up to the parent to decide when it is the right age for that individual child to learn about VHL.

If the patient has been diagnosed with VHL very recently, they might not be ready to talk. Wait until everyone is over the initial period of shock. Time is needed to process this news first before one can talk to them in a helpful or meaningful way.

Is it possible to easily describe why telling the child will be beneficial? If one is able to acknowledge and verbalize the benefits of telling the child, they are ready to have this conversation.

Is it possible for the child to have emotional space? The child needs to be listened to. One cannot just talk at them and try to fix the problem with words and reassurances. This needs to be a two-sided conversation.

Tips for talking with kids:

Listen and build on what the child already knows. Have the child tell you what they know or think they know; then correct any misinterpretations they might have.

Let them know their feelings are okay. Be understanding if they are upset, angry, sad, or scared. Remind them that no matter what happens, they are loved. Ask them how they feel and what they are worried about. If they are young, ask them to draw a picture or play with dolls to show how they feel.

Use honest, simple, and age-appropriate language. Avoid euphemisms (such as calling a tumor a "boo boo"). If someone has passed away, do not say that they are "sleeping." Do not give false hope or make promises that can't be kept.

Allow the child to tell you how much, or how little, they want to know. This conversation does not need to be one big talk. There might have one initial conversation about VHL, followed by other shorter conversations.

A small card with a brief description of VHL. Consider giving children who may not be able to describe VHL, but are living with effects that are apparent to others, a small card with a brief description of VHL and how it has affected them. You may also want to include a link to vhl.org.

BEING A SELF-ADVOCATE

An effective self-advocate is someone who is good at letting other people respectfully know what he or she is thinking, feeling, and needing. Sometimes self-advocacy means helping other people understand what is important to you, other times it can mean asking for help when you really need it. Being a self-advocate means understanding one's own wants and needs. Things might not always work out, but having the skills and confidence to communicate any needs is an important first step in reaching a goal.

Tips for Talking with Doctors

Take control. Patients may want to talk to their parents about practicing independence during medical visits. The patient can let their parents know that they would like to be more involved medical appointments, answer the doctor's questions, and help make health decisions. Patients should ask for help if they need it. One can practice being independent by spending time alone with their doctor.

How to be a healthcare advocate:

- Communicate about needs and feelings.
- Ask questions and keep asking them until the information is clear.
- Ask for help when needed
- Become an expert. Learning about VHL is the best way to be an advocate.
- Try to make healthy lifestyle choices.

Have backup. While it is important for the patient to start getting involved in their medical care, that does not mean they have to do everything alone. Think about how the patient can take the lead while still keeping their parents and caregivers involved and in the loop. It can be helpful to have a second pair of ears at appointments to help remember the conversation and explain things one might not have fully understood.

Keep a medical diary. In order to provide doctors with the complete and detailed information they need, the patient should keep a medical diary. Keep track of any medical symptoms experienced, questions to ask the doctor at the next appointment, and a schedule with all upcoming appointments and surveillance. Ask the doctors what information they need to ensure that the medical diary is a relevant and helpful tool for health management.

Having a medical diary can also help the patient to remember what health care professionals tell them. Most people can only remember 2 or 3 things they are told, unless they write the information down. The patient should take the medical diary with them and write down the information they need to remember.

It is all about the patient. Remember, their needs are the priority. One should tell their doctors what they are worried about or what they want to address. Sometimes health care professionals focus on something that they feel is important, even if the patient does not agree. Let them know. One can help redirect their doctors to see the big picture of their life and what they need.

Medical Communication: The GLADD Approach	
Give	Give information about how you are feeling and what you have done to stay healthy. Be honest. If you did not do something you were supposed to do or DID do something you were NOT supposed to do, tell your doctor. Also give your doctor information about how VHL is affecting your life and what your concerns are—now, and for the future.
Listen	Listen and Learn. Listen carefully to your health care providers and learn all you can from them about VHL and what you can do to be healthy.
Ask	Ask your doctors the questions you have about your health. If you do not understand what you are being told, tell them, and ask them to explain it in a different way. You can also ask for a pamphlet or printed copy of the information. VHLA (vhl.org) is a good resource for any information that you would like explained.
Decide	Decisions need to be made about what to do next at every heath care visit. Make sure you play an active role in decision making, since, starting age 18, you are the one who must agree to the plan of care.
Do	Do your part in following the plan!

Table 5. The GLADD Approach

SOCIAL AND PERSONAL LIFE

Having a strong network of friends and support can have a positive effect on emotional sense of self. It might be helpful to open up to friends and peers at school and talk about the condition. By sharing information about VHL and answering their questions, one can help friends understand what they are dealing with and why they may have certain limitations. It can also explain why the patient may have so many doctors' appointments. The more one's peers understand about VHL, the more likely they will be sensitive towards the condition, which may help the patient feel more socially accepted.

Those affected may also find support through advocacy groups like the VHL Alliance. Others with the same diagnosis can provide valuable insight into how they manage the challenges of having or dealing with VHL. Whether one chooses to share their story and experience or just listen to what others have to say, everyone is welcome.

How to Talk about VHL

The decision to share a diagnosis with different people in one's life is personal. It is up to the individual to decide whether or not they want to talk about VHL at all; it is OK to not talk about it. Some people are uncertain about what to say to their peers and they are nervous about how their relationships may be impacted. Those who do talk to friends often feel that it has been helpful to have people who understand their situation and can support them. The individual is in control of how they share information with others. Some people prefer to be honest and straightforward, while others prefer to joke and be funny. Regardless of the approach, here are some tips to help explain VHL and start the conversation with friends:

Keep it simple. Use one's own words and keep it basic, at least in the beginning. There is no need to explain everything at once; people can ask if they want more specific details.

Family members can help. It might be helpful to for one to talk to parents or another family member who also have VHL if one is feeling anxious about telling people about the diagnosis. One can practice the conversation with them to get comfortable with what they plan to say. You can also ask them for advice, since one of them has probably had conversations about VHL with their own friends.

Do not worry. It might be stressful to tell people and one might imagine that the news will change relationships, but it will not. It will probably not even be that surprising. Friends and classmates may have already guessed that something is going on.

Let friends help. It might be hard for friends to know what to do or say after learning about VHL. They will probably want to help but might not know how. Letting them know what helps the most will be a relief to everyone. This could include bringing homework to the patient and helping the patient catch up on schoolwork missed for medical appointments, going over to their house, or just being there if they want to talk.

Do what is comfortable. Maybe the patient wants to tell your close friends about VHL as soon as they find out about it; maybe they wait a while to tell them. Maybe the patient does not want to say anything at all. It is up to them; do whatever feels comfortable. It can be very helpful to have support from friends who know what is going on in their life, but the patient is the one who decides who and when to tell, if at all.

SECTION 5

VHL RESEARCH

The VHL Alliance is constantly striving to encourage and support VHL research. Once considered only an obscure medical curiosity, the *VHL* gene is one of the most important genes to study when it comes to finding a cure for cancer. This tumor suppressor gene controls the metabolic pathway of the cell and is involved in many other forms of sporadic cancer. For example, the *VHL* gene is responsible for 90% of all clear cell kidney cancer (ccRCC) cases. Kidney cancer is one of the fastest growing cancers in the world and 75% of these cases are ccRCC. While it is estimated that only 1 in 36,000 people in the U.S. has VHL, it is estimated that 60,000 people will develop kidney cancer each year.

VHL is also one of four major genetic causes of pheochromocytoma (pheos), accounting for approximately 20–35% of all pheos. Studying VHL and the other genetic causes of pheos gives researchers a much better understanding of the genetic pathway, or chain of events, that can lead to a pheo, as well as clues on how to prevent them.

Two types of research are needed to find a cure for VHL: basic science to understand exactly how a *VHL* mutation causes a tumor to form in a specific organ, and clinical research to learn which medications, surgeries, and lifestyle interventions prevent tumor formation, or slow, or even reverse tumor growth.

It is important to be part of both types of research efforts. Financial donations (vhl.org/donate) are needed to support research, and your participation is needed in clinical research. The VHL Alliance's website includes a list of all ongoing clinical trials at: (vhl.org/clinical-trials).

The MyVHL: Patient Natural History Study is an online patient registry open to everyone diagnosed with VHL, or with symptoms of VHL. Pay it forward to the community by contributing to research efforts to learn more about VHL, develop improved treatments and find a cure. Learn more about MyVHL at vhl.org/MyVHL.

GENETICS AND VHL

DNA (deoxyribonucleic acid) is the biochemical basis of life and of heredity. All of an individual's characteristics are written in their DNA. DNA (deoxyribonucleic acid) is the biochemical basis of life and of heredity. All of an individual's characteristics are written in their DNA. DNA is assembled into microscopic structures called chromosomes. In the human species, there are 46 chromosomes, 23 from the mother and 23 from the father. There are 22 autosomes, numbered 1 to 22, of which each person has a pair (two copies of

chromosome 1, two of chromosome 2, etc.). The 23rd pair are the sex chromosomes, XX is traditionally considered the female pair and XY is traditionally considered the male pair. On each chromosome are the genes that contain the specific information necessary to manufacture proteins. Each gene has two copies—one inherited from each parent.

Genes encode the formula for a protein. The first step is transcription, which is the process where DNA is transformed into ribonucleic acid (RNA). The RNA, , translates the DNA to form a genetically encoded protein. In the case of the *VHL* gene, the protein product is the VHL protein, or pVHL.

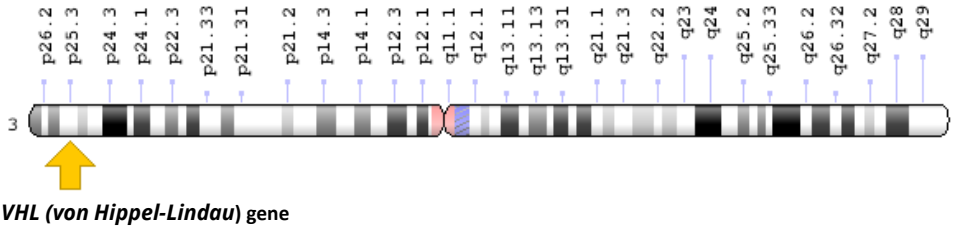


Figure 17. *VHL* gene location: The *VHL* gene is in the region 3p25-p26, near the tip of the short arm of chromosome 3. Illustration adapted from ghr.nlm.nih.gov/gene/VHL#location.

SECTION 5

VHL Gene

In 1993, an international research team identified the location of the *VHL* gene on the short arm of chromosome 3, at a site called 3p25-p26 (see Figure 17). The universal presence of the *VHL* gene in various species as small as fruit flies (Drosophila) demonstrates the importance of the gene. Despite the gene's small size, more than 15,000 different *VHL* mutations have been described, causing its 213 amino acid long protein product to be either dysfunctional or absent.

The *VHL* gene is in everyone. It normally acts as a tumor-suppressor gene whose function is to prevent the formation of tumors. In order for a tumor to form, both copies of the *VHL* gene must become inactivated. In an individual who does not have the inherited alteration in the *VHL gene*, it is necessary for each of these two normal copies of the gene to undergo some change resulting in a malfunctioning or non-existent pVHL, allowing a tumor to form. In the general population, this may take some time because multiple damaging "hits" to the genes in the cell are required in order to enable a tumor to form. This explains why tumors in the general public usually occur in a single organ at an older age. The average age of onset of symptomatic kidney cancer in the general population is age 62.

In the case of people who have inherited one copy of the gene that does not work correctly, like in VHL, it is only necessary to deactivate the one remaining copy before a tumor is likely to form. This is a much more probable occurrence, which means that tumors are more likely to develop more often, at younger ages, and in more organs than in the general population (see Figure 18).

Alterations (or mutations) of the *VHL* gene can now be identified in most people with VHL. The mutation is always the same in members of a single family. Conversely, the precise alteration in the gene will be different from one VHL family to another. Many individual mutations have already been described in the medical literature. Researchers are studying which specific mutations may be responsible for what different manifestations of VHL.

PROGRESS TOWARD A CURE

With advances in research, there is also increased hope for a cure, or at least for better management of VHL. Vast improvements in the survivability of prostate and breast cancer have been made without a cure, with the most important advances being in early detection and better treatment. Similarly, great strides have already been made in improving diagnosis and treatment of VHL.

Scientists are working to find a drug that will slow or halt tumor growth. If VHL tumors can be kept small, or made smaller, the frequency of surgical intervention required to manage the disease can be minimized. In the meantime, the best defenses are early detection and appropriate treatment. Knowledge and partnership with an experienced health care team offer the best prognosis.

VHL Protein and Hypoxia Inducible Factor

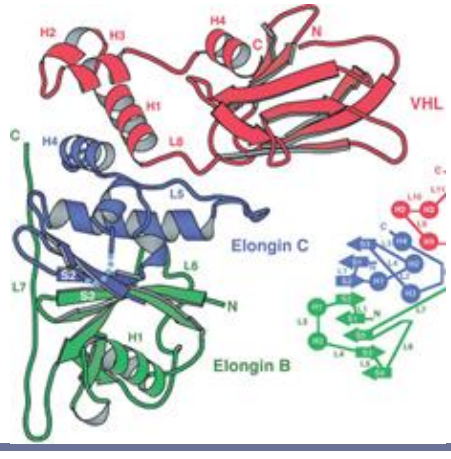


Figure 19. The "VBC complex": comprised of pVHL and Elongin C/B which under normal circumstances bind to HIF-2α. Modified from Stebbins CE, Kaelin WG, and Pavletich NP, Science 16 Apr 1999, Vol. 284, Issue 5413, pp. 455-461

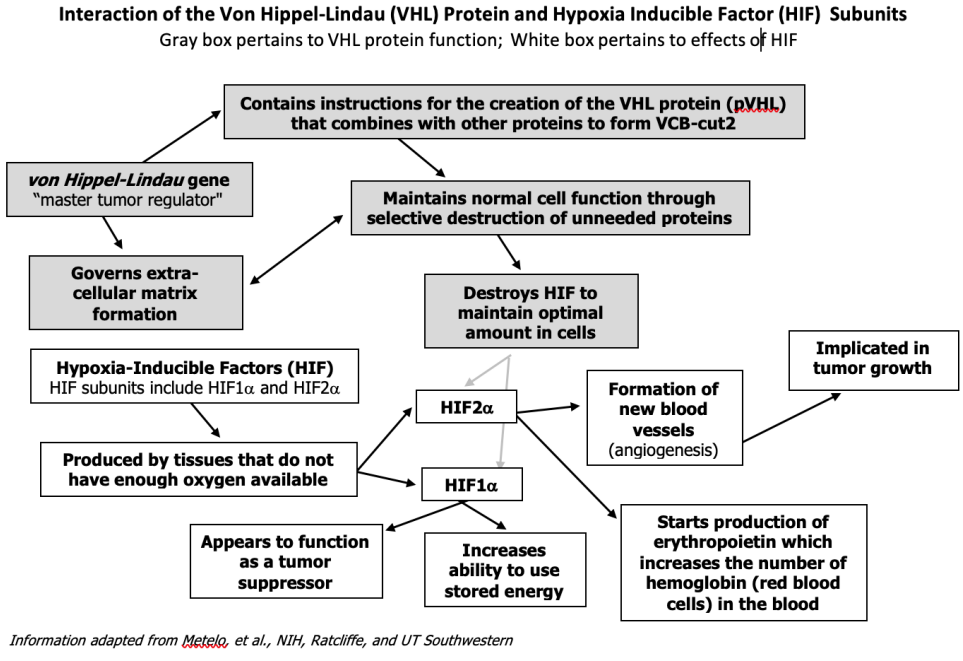


Figure 20. Interaction of von Hippel Lindau (VHL) protein and Hypoxia Inducible Factor (HIF) Subunits. Gray box pertains to VHL protein (pVHL) function; White box pertains to effects of HIF. Figure created by Alexa L. Werner, SPT. The views expressed here are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. Government.

Little by little, scientists have revealed more about the function of the VHL protein (pVHL) in the cell. They are learning about “drug targets” or places where a drug might be used to change the outcome.

The role of the pVHL is to bind to Elongin C/B and form the “VBC complex" (Figure 20). This complex targets other proteins to be degraded by the cell, including the hypoxia-inducible factor 2-alpha (HIF-2α). HIF-2α is one part (subunit) of a larger protein complex called HIF, which plays a critical role in the body's ability to adapt to changing oxygen levels. HIF controls several genes involved in multiple processes including cell division, the formation of new blood vessels (angiogenesis), and the production of red blood cells. It is the major regulator of erythropoietin (EPO) responsible for controlling red blood cell production in the liver and kidneys. HIF's function is particularly important when oxygen levels are

lower than normal (hypoxia). There are multiple subunits of this factor including HIF-1α and HIF-2α.

HIF-1α and HIF-2α appear to have slightly different roles in adapting the body to hypoxia. For instance, HIF-1α appears to be more tied to the pathways that increase the body's ability to convert energy from its storage form into energy that can be used by the body. It also works as a tumor suppressor for renal cell carcinoma. On the other hand, HIF-2α seems to play a larger role in the formation of new blood vessels (angiogenesis), which can promote tumor growth and acts as an oncogene for VHL-related renal cell carcinoma.

In the case of a missing or malfunction pVHL, such as in the case of VHL disease, the VBC complex is unable to bind HIF, protecting it from degradation. The overabundance of HIF causes the cell to perceive a hypoxic state. This in turn, induces angiogenesis, which can feed cancer growth. If this process can be stopped, it may cause the cancer to either die or, at least, stop growing and spreading through the body.

RESEARCH INTO MEDICATIONS

Understanding the mechanism behind VHL disease is essential for understanding possible therapeutic interventions. Gene therapy is the ultimate cure for VHL, but we are years away from applying this approach to a systemic disease, such as VHL.

Angiogenesis Inhibitors

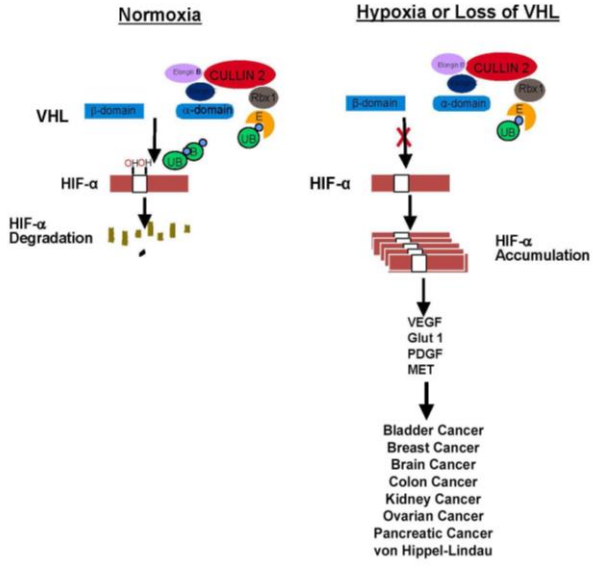


Figure 21. Comparison of normoxia and hypoxia on cellular function. Hypoxia leads to the development of tumors.

At the time of publishing this edition of the VHL Handbook, there are a number of drugs on the market approved for "advanced" (metastatic) kidney cancer, based in large part on research on the *VHL* gene and its protein product, pVHL. None of these drugs have been approved for treating VHL.

Anti-angiogenic drugs work to inhibit the abnormal angiogenesis response, thereby stopping the erroneous growth of new blood vessels. They include: Axitinib (Inlyta), Bevacizumab (Avastin), Cabozantinib (Cometriq), Everolimus (Afinitor), Pazopanib (Votrient), Sunitinib (Sutent), Sorafenib (Nexavar), and Temsirolimus (Torisel).

Small clinical trials have been performed to test each in their effectiveness for limiting VHL manifestations. For example, Sunitinib was found to have a significant response (33%) for RCC with no impact on hemangioblastomas. On the other, pazopanib demonstrated a 42% overall response rate (50% for kidney) with similar results in the pancreas. A small response was also seen in hemangioblastomas including retinal lesions.

HIF-2α Inhibitors

One promising class of drug that is currently being tested for use in VHL patients inhibits HIF-2α. This first of its kind is a drug that originated at Peloton Therapeutics (PT-2977) and was purchased by Merck (MK-6482). HIF-2α inhibitors work by blocking the signaling pathway that is incorrectly indicating cellular hypoxia, or lack of oxygen. Normally, the body would create new blood vessels in the hypoxic area in order to bring oxygenated blood to the area and fix the problem, which is a natural process known as angiogenesis. In a VHL patient, these newly formed blood vessels are what cause the tumors. By blocking this signaling pathway in a VHL patient, you can prevent angiogenesis from occurring.

At the time of publishing, a Phase 2 clinical trial is ongoing. The trial design includes eligibility criteria of a VHL diagnosis by a germline mutation, at least one measurable renal cell carcinomas (RCC) tumor, no prior systemic therapy, and no metastatic disease. Early results show shrinkage of the RCC tumors in 87% of patients with the decrease being at least 30% in approximately 28% of patients. The therapy also resulted in size reduction of hemangioblastomas in the brain and spine. The drug was found to be well tolerated with anemia being the primary side effect, as expected based on the mechanism of action of MK-6482. No potentially life-threatening side effects have yet to be reported.

GENE THERAPY

The research and application of gene editing therapeutic technologies is very much in its infancy. While there is hope that the technology can one day be used to cure systemic genetic diseases, like VHL, many years of research and development need to take place before it can be considered a reality.

News of the current state of VHL research and clinical trials is posted on the VHL Alliance website at vhl.org/clinical-trials.

BE PART OF FINDING A CURE

VHL Research Needs Your Support

Help researchers unravel the mysteries of VHL while learning more about how your VHL journey compares with others. Your information and input is needed to help researchers improve the quality of life for patients living with VHL and ultimately, lead to a cure.

MyVHL: Patient Natural History Study

MyVHL provides patients and researchers with more complete information about VHL, like how lifestyle, medications, and other factors impact the disease and quality of life. These insights help patients better understand the condition and help researchers know where to focus their efforts. Due to its rarity, there is less understanding of VHL and the factors that may have an impact. The data individuals provide in MyVHL helps researchers identify and uncover factors that may increase risk, inhibit or slow tumor growth, or lead to an effective cure.

Through MyVHL, patients can help researchers unravel the mysteries of VHL while learning more about how their VHL journey compares with others. Patient information and input is needed to help researchers improve the quality of life for patients living with VHL and ultimately, lead to a cure.

The success of MyVHL—and breakthroughs in treatments and ultimately a cure—require collaboration between researchers, doctors, and VHL patients! Please take the time to participate in the study if applicable. All of the information shared in this study will remain secure and confidential.

How Does MyVHL Work?

MyVHL is a patient registry, databank or natural history study consisting of surveys that provides researchers with the most up-to-date de-identified data available. These surveys ask about:

- Lifestyle, including nutrition, exercise, anxiety, and oral health
- VHL manifestations, including tumor size and locations
- Medications

All data entered needs to be authenticated before it can be used by a researcher. Therefore, participants will be asked to provide their medical records, such as scans and reports. They can be uploaded, mailed, or obtained by VHLA with a completed Medical Records Release Form (vhl.org/RecordsReleaseForm).

MyVHL is a longitudinal study, meaning that data are collected over time. The first entry around will take some time, but do not worry because updating data in the future will be much faster!

Every possible effort is being made to protect participants' data; MyVHL's security system has met stringent Institutional Review Board (IRB) approval. Participant privacy is the VHL Alliance's highest priority. **Only de-identified data (information from which no one can determine an identity) will ever be shared with researchers and no one will receive the full data set.** Researchers will not have direct access to the databank, and a committee will be responsible for reviewing and approving all researchers and their requests.

What Data Will Be Shared with VHL Researchers?

Only de-identified data will be shared with researchers, meaning NO identifying factors will be provided. Researchers are required to submit a data request form, which is thoroughly reviewed by VHLA's Research Council. ONLY data necessary for the defined study will be provided. Researchers do NOT have access to the database itself.

Current VHL Clinical Trials

Current clinical trials for people diagnosed with VHL are listed on the VHL Alliance website at vhl.org/clinical-trials. The list includes all trials that the VHL Alliance has been notified about, both in the US and worldwide. There are trials that may include experimental medications, imaging of lesions, and surgical procedures. Trials that include any VHL-associated lesions are listed. General details and a trial contact are included for all trials listed. Clinical trials receiving funding from the U.S. government are also listed at clinicaltrials.gov.

The VHL Alliance urges everyone who thinks that they may qualify to participate in one or more of the trials to contact the trials directly. Each clinical trial participant is an important part of VHL research.

SECTION 6

QUESTIONS TO ASK YOUR DOCTORS

With early detection and appropriate treatment, VHL has a better prognosis, or outcome, than many other tumor conditions and cancers. But any diagnosis of serious illness can be frightening. It is natural to have concerns about medical tests, treatments, insurance, and doctors' bills.

Patients have many important questions about VHL; their medical team is the best place to start to look for answers. Most people want to know exactly what kind of lesions they have, how they can be treated, and how successful the treatment is likely to be. It is wise to receive a second or even a third opinion.

GENERAL QUESTIONS

The following are some general questions that patients may want to ask their physician:

- Should I change my normal activities?
- How often are checkups needed?
- What other health professionals are needed on my medical team to ensure that we have checked for all the probable features of VHL?
- Who will be the main person responsible for looking after my medical interests and coordinating communication among my specialists?
- What is meant by "the cyst or tumor size is xx cm" (e.g. 2 cm)?
- At what point do I need to worry about this cyst or tumor?
- What symptoms should I watch for?
- Are there any critical symptoms of which I should be aware?
- What are the risks or side effects of these treatments?
- Is there a less invasive treatment to be considered?
- Is there a research project in which I can participate?
- Is there a clinical trial that would be appropriate for me?
- How experienced are you in dealing with VHL?
- Where can I consult with specialists who are experienced with VHL? (VHL Clinical Care Centers are listed at vhl.org/ccc)
- What can I do to assist doctors in learning more about VHL?
- If I were your family member, what would you want me to ask you?

QUESTION AFTER DIAGNOSIS

- What is VHL?
- How will this diagnosis impact my family?
- Did I inherit this from my parents?
- Do any of my family members need to be tested?
- How might this impact my children or future children?
- What are my options for family planning and who should I talk to?
- Is there anything that I can do to prevent VHL manifestations?
- What kind of doctors should I work with and where do I find them?
- What type of doctor should "quarterback" my care?
- Where can I find support resources?
- Do you offer any financial aid services?
- How will this impact my ability to get health, life, or long term care insurance?

QUESTIONS ABOUT TREATMENT

- What are my treatment options?
- If I was your relative, what would you have me do?
- How long will the treatment take?
- Will my insurance cover all or a portion of the cost of the treatment?
- What will my out of pocket expenses be?
- Is there a financial aid program?
- Which treatment is most common for my disease or condition?
- Are there any approved treatments that I have not tried and if so, why not?
- Is there a generic form of my treatment and is it as effective?
- What side effects can I expect?
- What risks and benefits are associated with the treatment?
- Are there other alternatives to treatments?
- What would happen if I didn't have any treatment?
- What would happen if I delay my treatment?
- Is there anything I should avoid during treatment?
- What should I do if I have side effects?
- How will I know if the medication is working?
- What should I do if I miss a dose of medication?
- Will my job or lifestyle be affected?

- If I take this treatment, how do you think it will impact my daily life in the short term and in the long term?

QUESTIONS ABOUT SURGERY

- Why do I need surgery?
- What surgical procedure are you recommending?
- Is there more than one way of performing this surgery?
- Will my insurance cover all or a portion of the cost of the surgery?
- What will my out of pocket expenses be?
- Is there a financial aid program?
- Can the surgery be done laparoscopically?
- Is robotic surgery an option?
- Are there alternatives to surgery?
- What are the benefits and risks of having surgery?
- What if I don't have this surgery?
- Where can I get a second opinion?
- What kind of anesthesia will I need?
- How long will it take me to recover?
- What are your qualifications?
- How much experience do you have performing this surgery?
- How long will I be in the hospital?

QUESTIONS ABOUT CLINICAL TRIALS

- If I take this treatment, does it make me ineligible for any other treatments/programs?
- Will I still be able to visit my current doctor if I take this treatment? If I cannot see my doctor, will my doctor be given information about my treatment?
- Will I need to travel anywhere to receive the treatment and if so, where to, how frequently, and for how long? Is support available for me to pay for this travel?
- Will I have to pay for the treatment, or will it be covered from another source such as my health care system, insurance plan, or the company making the investigational medicine?
- What will I be financially responsible to pay?
- If I have side effects and become hospitalized, who will pay for the treatment?

SECTION 7

VHL ALLIANCE AND SUPPORT RESOURCES

The VHL Alliance (VHLA) is a 501c3 non-profit organization founded in 1993 by three families with VHL to share experiences, learn from one another, support one another, help the doctors understand and treat VHL, and improve life for patients. Today, the VHL Alliance is the preeminent resource and clearinghouse of patients, caregivers, researchers, and the medical community.

VHL ALLIANCE'S VISION

Curing Cancer through VHL

VHL ALLIANCE'S MISSION

The VHL Alliance is dedicated to research, education, and support to improve awareness, diagnosis, treatment, and quality of life for those affected by VHL.

VHLA PATIENT AND CAREGIVER SUPPORT

It can help to talk with someone who is on the same journey. The VHL Alliance offers many ways to connect with others in the VHL community.

VHLA Annual Meeting: Held every fall, this is the best way to meet others with VHL face-to-face. In addition to meeting with others, there is an entire day of presentations from medical experts in VHL plus participation sessions. For more information, please visit: vhl.org/familyweekend.

Julie Flynn Hope Retreat for Young Adults: Held every June in Boston, MA, this retreat is open to all people with VHL between the ages of 18-32. It is an opportunity for young adults with VHL to network, learn more about VHL, and get involved with VHLA. For more information, please visit: vhl.org/yar.

VHLA Wellness Coaching Program: This is a practical and immediately applicable, science-based training program that provides patients, caregivers, and health care providers with practical tools and techniques to improve medical outcomes and overall wellbeing for themselves (and their patients). For more information, please visit: vhl.org/wellness-coaching.

VHLA Toll Free Hotline (800,767.4845 x1): The VHL Hotline is staffed by volunteers with years of experience dealing with VHL. The Hotline is available,

from 8 AM to 10 PM ET, 7 days a week. The Hotline volunteers rotate coverage to help you stay connected.

VHLA Quarterly Newsletter: The VHLA Newsletter is designed to educate and empower patients and all those impacted by VHL. It is a critical piece of VHLA's educational and support efforts and is the best way to stay up-to-date on the latest news in the VHL community. Sign up to receive the quarterly newsletter as well as read past editions at: vhl.org/newsletter.

VHLA Discussion Calls: These groups meet regularly for a supportive hour of moderated discussion. For a listing of all calls, visit vhl.org/calls.

- **VHL Patient/Caregiver Call:** Do you or a loved one have VHL? If so, please consider joining us for our VHL Patient/Caregiver Call. Learn more about this facilitated call at vhl.org/ptcgcall.
- **VHL Low/No Vision Call:** Do you suffer from low or no vision as a result of VHL? If so, please consider joining us for our VHL Low/No Vision Call. Learn more about this facilitated call at vhl.org/lownovisioncall.
- **Parents of VHLers Call:** Do you have a child with VHL? Please consider joining us for our Parents of VHLers Call. Learn more about this facilitated call at vhl.org/parentscall.

Better Together Peer Mentoring: Patients and caregivers of all ages are invited to participate in the VHL Alliance's "Better Together" peer mentoring program. This is a great way to share your experiences and learn from other people in the VHL community. Please email the VHL Alliance (info@vhl.org) if you are interested in participating or would like to learn more about the program. Since the VHL community is spread out across the world, peer-mentor pairs will likely use long distance communications (email, phone, video) instead of meeting in person. Caregivers will be paired with caregivers, and patients will be paired with patients. Minors must have permission from a parent/guardian to participate.

VHLA Online Support Groups

- **Private VHL Facebook Group:** facebook.com/groups/VHLawareness
- **Inspire:** Inspire.com/groups/vhl-alliance
- **VHL Alliance Public Page:** facebook.com/VHLAlliance
- **VHL Caregiver Connection Group:** facebook.com/groups/vhlcaregivers
- **VHL Low-No Vision Group:** facebook.com/groups/vhlvision
- **VHL Young Adult Group:** facebook.com/groups/VHLYoungAdults
- **VHL Parents to Parents Group:** facebook.com/groups/VHLparents2parents
- **VHL de Novo Connection Group:** facebook.com/groups/VHLDeNovo

Ambassadors

Ambassadors exist throughout the U.S. as a way of providing a local voice to the resources for the VHL Alliance's caregivers and patients. The VHLA Ambassador plays a crucial part in the work of the VHL Alliance, dedicated to those affected by VHL through education, support, and research. The work is essential in helping reach our overarching vision of **Curing Cancer through VHL!**

VHL Alliance Ambassadors represent the organization, its mission, its vision, and its policies. The role of the Ambassador falls into four main focus areas: Awareness, Engagement/Outreach, Fundraising, and VHL Clinical Care Center Liaison. Please note: all contacts are volunteers, who may sometimes be temporarily unavailable. Find out more information at: vhl.org/ambassadors.

International Affiliates

International affiliates are located in many countries around the world. Like Ambassadors, they can help provide a local voice to the resources available for VHL patients in that specific country. Find out more at vhl.org/international.

VHLA Clinical Care Centers

VHL Alliance recognized Clinical Care Centers (CCCs) are committed to providing outstanding holistic, coordinated care for VHL patients. Each CCC has a team that works together towards empowering VHL patients to find and receive the care they need.

The goals of the Clinical Care Center Initiative are:

- To improve diagnosis and treatment of VHL
- To provide coordination of care across medical specialties
- To provide resource centers for patients and physicians who are new to VHL
- To provide a ready channel for communicating advances to these centers of expertise
- To provide a model that can be replicated elsewhere

If you are interested in learning more about the VHL Clinical Care Centers, or want to find the one nearest you, please visit: vhl.org/ccc.

MYVHL: PATIENT NATURAL HISTORY STUDY

Please share what you have learned and pay it forward to the wonderful support community of which you are now a part. The best way to share your VHL experience is through the MyVHL: Patient Natural History Study. MyVHL is an online, longitudinal patient registry that helps researchers identify patterns across VHL patients. Learn more about von Hippel-Lindau and help researchers unravel the mysteries of the disease. MyVHL is available in English and Spanish.

The success of MyVHL—and breakthroughs in treatments and ultimately a cure —require collaboration between researchers, doctors, and VHL patients—YOU! Please take the time to participate. All of the information shared in this study will remain secure and confidential. **Find out more information and pay it forward at** vhl.org/MyVHL.

Please Contact the VHLA office at info@vhl.org or 617.277.5667 x4, or visit vhl.org/support to find out about these programs and more.

CONTACT US

Once you have learned how VHL affects you, you will need the latest information on how to manage your individual surveillance and treatments. If you need help understanding what you were told by your doctor, connection with psychosocial support individuals or groups, assistance in finding sources of second opinions, or would just like to be in touch with others living with VHL, please feel free to communicate with the VHL Alliance (info@vhl.org), the VHL Alliance affiliate in your country, or contact a VHL Clinical Care Center (vhl.org/ccc).

Phone: 617.277.5667 x4
Fax: 857.816.3649
Mail: VHL Alliance, 1208 VFW Parkway, Suite 303, Boston, MA 02132

HELP US, HELP YOU

How can the VHL Alliance better serve you? In what areas can we improve? Are there programs, processes, or information that you need or want? Let us know at vhl.org/HelpUsHelpYou.

Health care professionals are welcome to contact us to request input on a case. The VHL Alliance has also created listservs to ease the process of acquiring input from multiple sources.

Contributions to the VHL Alliance are essential to achieve our common vision of finding a cure! **Donate now at** vhl.org/donate.

SECTION 8

GLOSSARY AND MEDICAL TERMS

3 CM RULE: Best practice for dealing with VHL-related kidney tumors. It states that surgery for kidney tumors in VHL patients is only recommended when the largest tumor is larger than 3 cm. This is because research has shown there to be nearly no potential for metastatic disease before the tumor reaches 3 cm. Please note that this is more of a guideline, rather than a rule.

ADDISON'S DISEASE: Addison's disease is a disorder that occurs when your body produces insufficient amounts of certain hormones produced by your adrenal glands. In Addison's disease, the adrenal glands produce too little cortisol and often insufficient levels of aldosterone as well.

ADNEXAL PAPILLARY CYSTADENOMA: A cystadenoma that includes a lining of numerous small folds.

ADRENAL GLANDS: The pair of glands on top of each kidney which produce hormones that help the body control blood sugar, burn protein and fat, react to stressors like a major illness or injury, and regulate blood pressure. Two of the most important adrenal hormones are cortisol and aldosterone. The adrenal glands also produce epinephrine (adrenaline).

ADRENALECTOMY: Surgical removal of an adrenal gland. May be partial or total.

ADRENALINE (epinephrine): A hormone secreted by the adrenal medulla upon stimulation by the central nervous system in response to stress such as anger or fear. It acts to increase heart rate, blood pressure, cardiac output and carbohydrate metabolism.

ALDOSTERONE: A hormone that stimulates salt absorption in the kidneys to regulate salt and water balance in the body.

ALLELE: One of the two copies of each gene in an individual. In people with VHL, one copy of the *VHL* gene is altered and one has the normal sequence.

AMYLASE: Enzyme that is involved in the catalyses breakdown of carbohydrates and sugars.

ANESTHESIOLOGIST: A medical doctor specializing in the use of medications to safely support a patient's vital functions during the time of surgery.

ANGIOGENESIS: The physiological process involving the creation of new blood vessels from existing ones. This occurs in response to hypoxia, as a way to bring oxygenated blood to areas of the body that need it.

ANGIOGRAM (ANGIOGRAPHY): A picture or map of the blood vessels in a particular area of the body, usually produced by injecting a special dye into the blood vessels and taking an x-ray or MRI. See also Fluorescein angiogram.

ANGIOMA: An unusual growth made up of blood or lymphatic vessels forming a benign tumor; a hemangioma (blood vessels) or lymphangioma (lymphatic vessels). Angiomas are different from hemangioblastomas. Angiomas are found in the general population and they are not regarded VHL-specific lesions. In the past retinal hemangioblastomas have been referred to as retinal angiomas, creating some confusion. The overwhelming majority of the retinal lesions in VHL patients are retinal hemangioblastomas and not retinal angiomas.

ANTI-ANGIOGENIC DRUGS: Class of drugs that prevents blood vessels from forming and disrupts the growth process by preventing the formation and growth of blood vessels.

ANTIOXIDANT: A food or other chemical with properties which slow down cell oxidation, one source of cell damage and death.

ASYMPTOMATIC: Not experiencing discomfort or other symptoms.

AUDIOLOGY: The study of hearing. Often refers to a hearing test (audiogram), which determines hearing loss.

AUDIOGRAM (AUDIOMETRIC EXAM): An audiogram is an examination in which the hearing is measured and evaluated.

AUTOSOMAL DOMINANT: An autosomal dominant trait is one which occurs on one of the chromosomes which do not determine gender; it is dominant because it takes only one altered copy of the gene to cause the trait.

AUTOSOME: A non sex-determining chromosome. Humans have 22 pairs of autosomes.

BENIGN TUMOR: An abnormal growth does not spread to other parts of the body. Benign does not mean harmless, only that it does not spread.

BIOMARKER: Some trace chemical in the blood or urine that we can test for that will indicate the progress of a disease.

BIOPSY: Tissue removed from a living body for analysis to determine disease.

BRAINSTEM: Posterior part of the brain, continuous with the spinal cord. It contains the midbrain, pons and medulla oblongata. The brainstem plays a critical role in regulating cardiac and respiratory function, the central nervous system and the body's sleep cycle.

BROAD LIGAMENT: The broad ligament is a folded sheet of tissue that drapes over the uterus, fallopian tubes, and the ovaries.

CANCER: A general term for more than 100 diseases in which abnormal cells grow and multiply rapidly. Cancer is an abnormal growth of cells. Cancer cells rapidly reproduce despite restriction of space, nutrients shared by other cells, or signals sent from the body to stop reproduction and often form tumors. Because VHL can cause malignant tumors in the visceral organ systems, VHL is considered one of a group of familial cancer risk factors which are transmitted genetically.

CAPILLARY: The smallest type of blood vessels in the body, carrying nourishment to the cells.

CAROTENOIDS: A group of red-yellow fat-soluble antioxidants which includes beta carotene. All are a food source of vitamin A.

CATECHOLAMINES: Adrenaline by-products found in the urine or blood, where their measurement is used as a test for pheochromocytoma. Most important for VHL is measurement of fractionated metanephrines, especially normetanephrine.

CEREBELLUM: A large portion of the base of the brain which serves to coordinate voluntary movements, posture, and balance.

CEREBROSPINAL FLUID (CSF): A clear, colorless body fluid found in the brain and spinal cord. There is about 125 mL of CSF at any one time, and about 500 mL is generated every day. It functions as a cushion, providing protection to the brain inside the skull, as well as helps with autoregulation of cerebral blood flow.

CEREBRUM: The upper or main portion of the brain responsible for voluntary thought, speech, and initiation of voluntary movement; the cerebral cortex.

CERVICAL SPINE: The uppermost part of the spine that forms the neck. It contains seven vertebrae

CHROMOSOME: Sets of linear DNA from which the genes are arranged, carrying all the instructions for a species. Human beings have 23 pairs of chromosomes. In each pair, one chromosome containing one copy of each gene is inherited from the mother and one from the father.

CHRONIC KIDNEY DISEASE (CKD): Condition in which a person's kidneys are damaged and cannot effectively filter blood. This can cause waste buildup in the body leading to serious health problems.

CLEAR CELL RENAL CELL CARCINOMA (ccRCC): The most common type of Renal Cell Carcinoma (sometimes called conventional RCC) with characteristic clear appearance of cells in cross-section biopsies. Most cases of ccRCC are sporadic.

CLONIDINE TEST: A test for growth hormone deficiency.

COGNITIVE BEHAVIORAL THERAPY (CBT): A psycho-social intervention that aims to improve mental health. CBT focuses on challenging and changing unhelpful cognitive (perception/comprehension) distortions and behaviors, improving emotional regulation, and developing personal coping strategies that target solving current problems.

COMPUTED TOMOGRAPHY (CT) SCAN: A diagnostic procedure using a combina-tion of x-ray and computer, and optionally some contrast dye. A series of x-ray pictures are taken of the tissues being studied. The computer is then used to calculate the size and density of any tumors seen on the pictures.

CONTRAST AGENT: A chemical given by injection or orally that is used to enhance the visibility of various tissues and structures as seen in a medical image such as an x-ray, CT scan, or MRI.

CORTISOL: A glucocorticoid hormone produced in the adrenal glands. It helps the body respond to stress and change. It mobilizes nutrients and modifies the body's response to inflammation.

CCONTRAINDICATED: When a treatment or procedure is not recommended for the presenting situation.

CYBERKNIFE: A robotic radiosurgery system used for treating benign tumors, malignant tumors, and other medical conditions.

CRYOTHERAPY (CRYOSURGERY): A method of stunting the growth of tissues by freezing them. Used on VHL lesions in the retina and as part of laparoscopic surgery on VHL lesions in the kidney, pancreas, and adrenal glands.

CYSTADENOMA: Benign tumor from glandular tissue which retains secretions within a cyst.

CYSTS: Fluid-filled sacs that may occur normally in tissues from time to time or that may grow up around irritations in tissues.

DEEP VEIN THROMBOSIS (DVT): A blood clot in one of the veins deep inside the body, often a leg vein. The clot can break free and travel to the lungs or brain causing a medical emergency.

DE-IDENTIFIED: Removal of personal information from data that could be used to identify a study participant.

DE NOVO: New, for the first time. Also known as "first-in-family".

DENSITY: A quality of a tissue—soft or solid. Muscle is less dense than bone; a sac filled with fluid is less dense than a hard tumor.

DEOXYRIBONUCLEIC ACID (DNA): Four substances which make up chromosomes and their genes. As coding sequences, they determine the function of a gene—for instance the synthesis of a protein and the amino acid sequence of the protein.

DIETITIAN: An expert in human nutrition and the regulation of diet.

DIFFERENTIAL DIAGNOSIS: Many of the tumors of VHL occur in the general popula-tion or in other diseases as well. The doctor has to sort out whether the tumor is sporadic or whether it is part of VHL or another disease. To answer this question, a number of tests may be required, which may include DNA testing.

DILATED RETINAL EXAM (DILATION): Exam in which the doctor uses eye drops to expand the size of the pupils of the eye in order to see and evaluate the entire retina.

DOPAMINE: Hormone that functions as a neurotransmitter and plays a role in reward-motivated behavior.

DUODENUM: The first part of the small intestine below the stomach.

DURA MATER (DURA): Thick membrane made of dense irregular connective tissue that surrounds the brain and spinal cord.

-ECTOMY: A suffix which means removal. For example, adrenalectomy means removal of the adrenal gland.

EDEMA: Swelling of a tissue due to increased fluid, or increased fluid in the blood or lymphatic circulation.

ELECTROCHEMICAL DETECTION: An electrical current is used to identify and measure biological and environmental compounds.

ENDOCRINOLOGIST: A physician specializing in the treatment of the endocrine system, its hormones, and glands, which includes the adrenal glands, pancreas, and a number of other organs and glands.

ENDOLYMPHATIC SAC: The bulb-like end of the endolymphatic duct which connects to the semicircular canals of the inner ear.

ENUCLEATION: Referring to kidney or pancreas, removal of a tumor with only a small margin of healthy tissue to ensure that all the unhealthy tissue is out. This is sometimes referred to as a lumpectomy or removal of the tumor (lump) only. In ophthalmology, enucleation means removal of the eye. If the retina has detached, the blood supply to the eye is reduced and the eye may deteriorate, causing discomfort. If this occurs, enucleation of the eye may be recommended.

EPIDIDYMIS: A gland which lies behind the testicle, in the scrotum, on the path to the vas deferens, the vessel that carries the sperm from the testicle to the prostate gland, and is important for sperm maturation, mobility and storage.

EPINEPHRINE: See ADRENALINE.

EXON: The part of the gene that codes for amino acids.

FALLOPIAN TUBE: The channel carrying eggs from the ovary to the uterus.

FAMILIAL: Occurring in families, whether or not transmitted genetically.

FIBROUS TISSUE: In the retina, this is scar tissue that forms, connecting the vitreous humor (clear gel within the eye) to the top layer of the retina, pulling on the retina and causing it to detach. Unless the retina is quickly re-attached, vision will be lost.

FLUDROCORTISONE: Synthetic steroid used to replace aldosterone when the body does not produce enough of its own steroids, such as Addison's disease.

FLUORESCEIN ANGIOGRAM (ANGIOGRAPHY): An angiogram of the retina of the eye, named for the contrast dye that is used. This procedure produces an image of the blood vessels of the retina, sometimes in full motion video so that the ophthalmologist can see the health of the blood vessels and how the blood moves through them.

GADOLINIUM: A contrast agent injected into the patient's bloodstream prior to an MRI test to highlight the blood vessels and provide better contrast so the radiologist can see any abnormal structures more clearly.

GAMMA KNIFE: Radiosurgery; specialized equipment focuses close to 200 tiny beams of radiation on a tumor or other target.

GASTROENTEROLOGIST: A physician who specializes in the diagnosis and treatment of disorders of the gastrointestinal tract, including the esophagus, stomach, small intestine, pancreas, liver, gallbladder, and biliary system (liver).

GENE: The position on a chromosome where a specific DNA sequence, or allele, resides. Changes in the sequence from one allele to another can be transmitted to the next generation.

GENERALIZED ANXIETY DISORDER (GAD): Mood disorder characterized by generalized worry, chronic anxiety, and tension.

GENETIC COUNSELOR: A medical professional (not a physician) specializing in working with patients and families with genetically inherited conditions like VHL.

GENETICIST: A geneticist is a scientist specializing in the study of genes and the way they influence our health, and in treatment of genetic disorders.

GENOTYPE: The particular pair of alleles (copies of the gene) that an individual possesses at a given gene locus or site (two copies of each gene). The genotype describes the configuration of the altered gene pair, or can refer to all gene pairs.

GERMLINE: Any genetic alteration that occurs in every cell of the body, including the testes and the ovaries, that produce the sperm and eggs that may become children.

GLOMERULAR FILTRATION RATE (GFR): Calculated from a creatinine (waste product produced by muscles) test that determines the level of the kidney function. This test monitors kidney function in chronic kidney disease.

GLUCAGON: Hormone produced by the pancreas alpha cells that raises blood sugar (effect is opposite of insulin).

GLUCOCORTICOID: Released by the adrenal glands in response to stress; these steroid hormones signal the liver to release stored glucose and convert proteins and fats from the blood into glucose. Cortisol and aldosterone are glucocorticoid hormones.

GLYCEMIC INDEX: A ranking of foods on a scale of 1 to 100 in comparison to the effect of pure sugar (100) on blood sugar levels.

GLYCEMIC LOAD: A calculation of expected effect of a food on blood sugar. The food's carbohydrates in grams are multiplied by the glycemic index and divided by 100.

-GRAM: A suffix that indicates that a message or picture is being created. For example, an angiogram is a picture of the blood vessels (ANGIO-).

GRAM: Unit of weight. One ounce = 28.35 grams

HEMANGIOMA: An abnormal growth of blood vessels forming a tumor. There are two types: hemangioblastomas (benign), and hemangiopericytomas (can become malignant).

HEMANGIOBLASTOMA: An abnormal growth of blood vessels forming a benign tumor; a variety of hemangiomablastomas can be found, especially in VHL, in the eye, brain, or spinal cord.

HEMORRHAGE: Release of blood from a broken blood vessel. May occur internally (inside the body) or externally (outside the body).

HEREDITARY: Traits passed from parents to children through genetics that are not caused by environmental factors.

HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS) QUESTIONNAIRE: Tool used by doctors to determine levels of anxiety and depression that a person is experiencing.

HYDROCORTISONE: A glucocorticoid medication that contains the hormone cortisol and works as an anti-inflammatory and by immune suppression. In the context of VHL, it is typically given to treat adrenocortical insufficiency or around the time of surgery to prevent an adrenal crisis.

HYPOXIA: A state in which the cells of the body are deprived of oxygen.

HYPOXIA-INDUCIBLE FACTOR: Transcription that responds to decreases in available oxygen in the cellular environment, or hypoxia. It is part of the cell's oxygen sensing mechanism.

ICD-10 Code: International Classification of Diseases, 10th revision. The current ICD-10 code for VHL is Q85.8. Codes can be found at icd10data.com.

IMMUNOSUPPRESSION: The reduction of the body's immune system to function properly. This can be caused by certain treatments and conditions.

INSIGHT-ORIENTED THERAPY: Focuses on unconscious processes as they are manifested in a person's present behavior. The goals is to make the patient aware and understanding of the past on their present behavior.

INSTITUTIONAL REVIEW BOARD (IRB): An independent ethics committee required for approval and monitoring of all clinical research studies involving human subjects.

INSULIN: Hormone produced by beta cells in the pancreas that allows sugar to be metabolized and, thereby, lowers blood sugar.

INTERNAL AUDITORY CANAL (INTERNAL AUDITORY MEATUS): Canal within the petrous part of the temporal bone of the skull between the posterior cranial fossa and the inner ear.

INVASIVE: Describes medical procedures that require entering or "invading" your body.

IN VITRO FERTILIZATION (IVF): The process of fertilization by extracting eggs, retrieving a sperm sample, and then manually combining an egg and sperm in a laboratory dish. The embryo is then transferred to the uterus.

IODINE CONTRAST: A contrast agent used for x-ray-based imaging that contains iodine.

ISLET CELLS: Cells in the pancreas where hormones are produced and pancreatic neuroendocrine tumors (pNETs) develop.

JAUNDICE: A yellow appearance to the skin and eyes due to a high level of bilirubin in the blood.

KIDNEYS: A pair of organs located in the back of the abdominal cavity that filter waste materials out of the blood and pass them out of the body as urine.

KIDNEY-SPARING SURGERY: Surgery where kidney tumors are removed, while the maximum amount of functional kidney tissue is left intact. This is the best surgical strategy for VHL-related kidney tumors, when possible and appropriate.

KILOGRAM: Unit of weight equal to 1,000 grams or 2.2 pounds.

LAPAROSCOPY: A technique for performing a surgical procedure through slits in the skin using special surgical probes rather than making one large incision.

LASER THERAPY (LASER SURGERY): The surgical use of a minutely focused light to deliver a microscopic cauterization, or burn to seal off small blood vessels. Used to treat VHL lesions in the retina.

LESION: Any localized abnormal structural change, such as a hemangioblastoma.

LIPASE: Enzyme involved in the absorption of fats.

LIQUID CHROMATOGRAPHY (LC-MS/MS): Separation of ions or molecules in a solvent for purpose of measurement and identification from the bands of color produced.

LIVER: A large organ in the upper right side of the abdominal cavity that secretes bile and is active in regulating various parts of the process of digesting food and using it to best advantage in the body.

LOCALIZE: To find. Doctors use this term to mean finding on the scan exactly where a tumor is located. For a pheochromocytoma (pheo), for example, the tumor can occur anywhere from your groin to your earlobe, on either side of the body, so finding a pheo is not always easy.

LONGITUDINAL STUDY: Research design or survey in which the same subjects are observed repeatedly over a long period of time.

LUMBAR SPINE: The five vertebrae of the lower back. Most people have 5 lumbar levels (L1-L5), although it is not unusual to have 6. Each lumbar spinal level is numbered from top to bottom—L1 through L5, or L6.

LYMPHATIC: Small vessels similar to blood vessels that carry fluid from body tissues and empty the fluid back into the bloodstream.

MACROCYCLIC CONTRAST AGENT: Extremely stable type of contrast agent which decreases the risk of ion release into the bloodstream. This is especially important in patients with decreased renal function. Gadobutrol is one example.

MAGNETIC RESONANCE IMAGING (MRI): An imaging technique where magnetic energy is used to examine tissues in your body, and the information is used by a computer to create an image. MRI does not utilize radiation. The resulting images look very much like x-rays, but include images of soft tissues (like blood vessels) as well as hard tissues (like bones).

MALABSORPTION: The inability to absorb certain sugars, fats, proteins, or vitamins from food.

MALIGNANT: Cancer cells that have grown so that they can spread through the blood or lymphatic system to start new cancers in other parts of the body.

MASS EFFECT: The result of increased pressure in the skull, usually due to a mass such as a tumor.

MASS SPECTROMETRY (MASS SPECTROSCOPY): Chemical analysis of gas ions to measure and identify chemical components of a substance.

MENIÈRE'S DISEASE: Disorder of the inner ear that is characterized by episodes of feeling like the world is spinning (vertigo), ringing in the ears (tinnitus), hearing loss, and a fullness in the ear. VHL patients with Endolymphatic Sac Tumors (ELSTs) are often *misdiagnosed* with having Menière's disease.

MESONEPHRIC: Arising from the embryonic kidney structure; duct system is retained and incorporated into the male reproductive system.

METAIODOBENZYLGUANIDINE (MIBG) SCAN: A nuclear medicine procedure using a radioactive isotope or tracer, which is absorbed by pheochromocytoma tissue. MIBG is injected into the patient before the scan is performed, making the pheo stand out clearly on the diagnostic pictures.

METANEPHRINES: A group of adrenaline by-products found in the urine or blood where its measurement is used as a test for pheochromocytoma. A fractionated metanephrine assay breaks the group of metanephrines into its component parts (metanephrine and normetanephrine) and measures them separately.

METASTASIZE (METASTATIC TUMOR): To spread from one part of the body to another. When cancer cells metastasize and form secondary tumors, the cells in the metastatic tumor are like those in the original tumor.

METHOXYTYRAMINE: Measured in plasma, this metabolite of dopamine may be a new biomarker for metastatic pheochromocytomas.

MICROCYSTIC ADENOMA: Benign cyst-forming tumor of the pancreas.

MINERALOCORTICOID: Hormones which act in the kidneys, colon, and salivary glands to balance mineral levels (primarily sodium and potassium) to maintain water balance in and around cells. Aldosterone is a mineralocorticoid produced by the adrenal glands.

MONITORING: Monitoring is checking up on known issues to make sure that they are treated at the best time to ensure long-term health.

MOSAIC VHL (MOSAICISM): When a person with VHL has two different populations of cells that make up his body. One population contains two working copies of the *VHL* gene (these cells are normal) and a second population contains one working and one non-working *VHL* gene copy (these cells have a mutation). It is difficult to know which and how many cells of the body of a mosaic individual are affected. Only *de novo* (first-in-family) cases can be mosaic.

MULTIPLEX LIGATION-DEPENDENT PROBE AMPLIFICATION (MLPA): A newer, more efficient, and more accurate procedure for analyzing a DNA sample.

MUTATION: A change in the sequence of DNA coding in a gene.

NATUROPATH: A primary health care physician who emphasizes prevention and treatment using methods and substances to encourage self-healing.

NEOPLASIA: Literally, new growth, a lesion grown from a single cell, not transplanted from another place.

NEPHRECTOMY: Removal of all (total) or some (partial) of one kidney.

NEPHROLOGIST: A physician specializing in kidney disease and treatment.

NEUROAXIS: The axis of the central nervous system formed during development of the embryo. It consists of the spinal cord and all unpaired regions of the brain.

NEUROENDOCRINE: Having to do with the interactions between the nervous system and the endocrine system, which secretes (produces) hormones. Neuroendocrine describes certain cells that release hormones (neurohormone) into the blood in response to stimulation of the nervous system. In VHL these are found in pheochromocytomas and pancreatic neuroendocrine tumors.

NEUROLOGIST: A physician specializing in nonsurgical treatment of the nervous system, the brain, spinal cord, and peripheral nerves.

NEUROSURGEON: A physician specializing in the surgical treatment of the nervous system, the brain, spinal cord, and peripheral nerves.

NEUROTOLOGIST: A physician specializing in the structure and function of the internal ear, its neural connections with the brain, and the management of skull base diseases. A neurotologist is an ear, nose and throat surgeon (otolaryngologist) who has undergone additional training in this area and typically works in conjunction with a team of specialists including other otolaryngologists, neurologists and neurosurgeons.

NON-INVASIVE: Any treatment or procedure that does not break skin or physically enter the body.

NORADRENALINE (or NOREPINEPHRINE): The metabolite of adrenaline produced when adrenaline is metabolized or processed by the body.

NORMETANEPHRINE: The metabolite of metanephrine produced when metanephrine is broken down by the body.

OBSTETRICIAN: A medical doctor specializing in pregnancy, childbirth, and the postpartum period.

OCTREOTIDE SCAN: A scan using octreotide, a radioactive drug. The drug is injected into the bloodstream and attaches to tumor cells that have somatostatin (a small molecule associated with neural signaling) receptors. A specific device is used to detect where the radioactive drug has attached and creates images. Sometimes called somatostatin receptor scintigraphy (SRS).

ONCOLOGIST: A physician specializing in treatment of various forms of cancer.

OPHTHALMOLOGIST: A physician specializing in treatment of diseases and surgery of the eye.

OPHTHALMOSCOPE: An instrument used to examine the retina and other structures inside the eye.

OPTIC NERVE (CRANIAL NERVE II; CN II): The nerve that transmits visual information from the retina to the brain.

OPTOMETRIST: An optometrist, or doctor of optometry (OD), is a healthcare professional who diagnoses and treats eye health and vision problems.

PANCREAS: A gland near the stomach which secretes digestive enzymes into the intestine and also secretes the hormone insulin into the blood as needed to regulate the level of sugar in the blood.

PANCREATIC NET (pNET): Pancreatic Neuroendocrine Tumor, a solid tumor of the islet-cell portion of the pancreas which secretes hormones when it is “active”. The abbreviation pNET is also used to refer to two other tumors which are not related to VHL.

PANCREATITIS: Inflammation of the pancreas.

PAPILLARY: Finger-like projections of tissue.

PARAGANGLIOMA (para or PGL): A pheochromocytoma outside of the adrenal gland, which is also called an extra-adrenal pheochromocytoma (extra meaning "outside"). Paraganglioma is the term most frequently applied to pheochromocytoma of the head and neck.

PATHOLOGIST: A physician who identifies diseases and conditions through study of cell and tissue samples.

PERIPHERY: In the eye, the edges of the retina farthest from the optic nerve, form the retinal periphery. This is often the location of the earliest retinal hemangioblastomas.

PERITUMORAL: Cysts that grow around a tumor.

PETROUS TEMPORAL BONE: The very dense portion of the temporal bone that protects the inner ear from damage.

PHENOTYPE: The clinical appearance of a specific genotype, for example, the set of VHL symptoms one person may have.

PHEOCHROMOCYTOMA (pheo): A tumor (cytoma) of the adrenal gland which causes the adrenal gland to secrete too much adrenaline, potentially causing harm to the heart and blood vessels.

POLYCYSTIC KIDNEY DISEASE: Clusters of benign cysts develop in the kidneys and may lead to high blood pressure. Due to one of two possible genetic mutations.

POLYCYSTIC LIVER DISEASE: May be seen with polycystic kidney disease or may be a rarer genetic mutation causing cysts only in the liver.

POSITRON EMISSION TOMOGRAPHY (PET) SCAN: A specialized imaging tech-nique using short-lived radioactive substances to provide information about the body's chemistry. This technique produces three-dimensional color images showing the activity level of certain tumors. Some of the radioactive substances used are F-FDA, F-FDOPA, and F-FDG.

POSTERIOR FOSSA: Small space in the skull located near the brainstem and cerebellum.

PREIMPLANTATION GENETIC DIAGNOSIS (PIGD or PGD): Genetic testing on test-tube embryos and selection of healthy embryos prior to implantation in order to assure that the child born will be free of the tested disease.

PRENATAL DIAGNOSIS: Testing of the child before birth; includes genetic testing of an embryo prior to implantation (PIGD/PGD).

PRESYMPTOMATIC: Relating to, being, or occurring before symptoms appear.

PROTEASE: Enzyme involved in the breakdown of protein foods.

PULMONARY EMBOLISM: A sudden blockage in a lung artery usually caused by blood clot (deep vein thrombosis) that has traveled from a vein in the leg.

RADIO FREQUENCY ABLATION (RFA): A laparoscopic surgical procedure where a heat probe is inserted laparoscopically into the tumor and the tumor is heated to disable its growth potential.

RADIOLOGIST: A physician specializing in diagnostic techniques for viewing internal organs and tissues without surgery. Radiological methods include x-ray, MRI, computed tomography (CT) scan, ultrasound, angiography, and nuclear isotopes.

RENAL CELL CARCINOMA (RCC): The most common type of kidney cancer in adults; it begins in the lining of the kidney tubules. Clear cell renal cell carcinoma (ccRCC) is the type of RCC that is associated with VHL.

RESECTION: A term used to describe the removal of a tumor from an organ such as a kidney while retaining (sparing) the organ itself.

RETINA: The nerve tissue that lines the back of the eye, similar to the film in a camera, which takes the image you are looking at and transmits it to the brain through the optic nerve. This area is nourished by a web of very fine blood vessels.

RETINAL SPECIALIST: An ophthalmologist who specializes in treatment of diseases of the retina.

RIBONUCLEIC ACID (RNA): A nucleic acid that plays a role in gene expression and protein synthesis.

ROBOTIC SURGERY: Robot-assisted surgery which usually allows the doctor to perform the surgery through a small incision. The surgeon views the procedure through an endoscope (a tiny camera in a tube), and the robotic arm is controlled by the surgeon and uses tiny instruments.

SCANXIETY: Apprehension felt by people as they wait for their next scan, or the results of their previous scan.

SEROTONIN: An important chemical and neurotransmitter (signaling agent) in the human body. It is believed to help regulate mood and social behavior, appetite and digestion, sleep, memory, and sexual desire and function. There may be a link between serotonin and depression.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs): Class of medications used to treat anxiety and depression by blocking reabsorption of serotonin in the brain. This increases the amount of serotonin which improves positive mood.

SEROUS MICROCYSTIC ADENOMAS: Grapelike clusters of cysts which may occur in the pancreas. Cysts are composed of epithelium-lined collections of serous fluid that vary in size from several millimeters to over 10 cm (over 4 inches).

SEX CHROMOSOMES: The pair of chromosomes which determine sex. Males have one X and one Y chromosome while females have two X chromosomes. These chromosomes also code for other characteristics and mutations are the source of sex-linked diseases such as hemophilia.

SPORADIC: Occurring at random in the general population. Not due to heredity.

STEREOTACTIC RADIOSURGERY (SRS): Surgery using focused radiation to destroy tissue such as a tumor. The tissue is not removed as in standard surgery, but dies over time.

SURVEILLANCE: Testing before symptoms appear to make sure that any issues are found early.

SYMPATHETIC NERVOUS SYSTEM: A chain of small structures that transmit signals from the central nervous system to the organs. The adrenal gland is the major gland in this chain, in addition to small ganglia (structures containing a number of nerve cell bodies) that run from the groin to the ear lobe on both sides of the body. A pheochromocytoma can hide anywhere along this system.

SYMPTOM: A feeling or other subjective complaint suggestive of a medical condition.

SYMPTOMATIC: The patient is experiencing symptoms.

SYNDROME: A collection of signs and symptoms resulting from a single cause (disease, infection, or environment).

SYRINX: A fluid-filled sac, like a cyst, but occurring inside the spine where it has the shape of an elongated tube lying along or inside the spinal cord and inside the bony spinal column.

SYSTEMIC THERAPY: A therapy, or treatment, that affects the whole body, rather than just a specific region. For example, an oral medication would be considered a systemic therapy while a surgery would not.

THORACIC SPINE: The vertebrae between the neck and the lower back which are connected to the ribs in the back. The thoracic spine has 12 vertebrae stacked on top of each other, labeled from T1 down to T12. T-1 through T-5 nerves affect muscles, upper chest, mid-back and abdominal muscles. T-6 through T-12 nerves affect abdominal and back muscles.

TINNITUS: A ringing in one or both ears. It may also be a roaring or hissing sound.

TRANSCRIPTION: Process by which DNA information is copied into RNA; each section of DNA copied encodes at least one gene.

TRICYCLIC ANTIDEPRESSANT: Medications that treat depression by blocking reabsorption of serotonin and norepinephrine in the brain. Other chemical messengers in the brain are also affected, which may cause unwanted side effects.

TUMOR: An abnormal growth of tissue forming clusters of cells that are capable of growing and dividing uncontrollably. A tumor may be benign or malignant.

TUMOR SUPPRESSOR GENE: A gene which produces a protein that acts to prevent one step in the formation of tumors. The *VHL* gene is a tumor suppressor gene.

ULTRASOUND: A diagnostic technique that provides pictures of internal organs and structures. It works like the sonar used by submarines, bouncing sound waves off an object and using a computer to interpret the sound returned.

UROLOGIST: A physician specializing in surgical and non-surgical treatment of the kidney, bladder, and external genital organs, including the penis and scrotal structures.

VAS DEFERENS: Duct that moves sperm from the testicle to the urethra.

VERTIGO: A sensation of dizziness or loss of balance, inability to walk a straight line, or "walking into walls."

VHL PROTEIN (pVHL): A tumor suppressor protein produced by the normal function-ing *VHL* gene.

VISCERA: Any of a number of organs in the abdominal area, including the kidney, liver, pancreas, and adrenal glands.

VESTIBULONEURAL: Information related to the ability to balance and move based on the position of the head in relation to the body.

VITREORETINAL: The gel-like fluid filling most of the inside of the eye is the vitreous. It is attached to the retina and can pull on it, causing the retina to detach which can lead to loss of vision.

WAIST-HIP RATIO: A measurement to determine if a person is carrying too much abdominal weight, which is considered the greatest risk to health. It is calculated by measuring the waist and dividing by the measurement of the hips. Men should have a ratio of 1.0 or less, and women should have a ratio of 0.85 or less.

X-RAY: A diagnostic imaging technique where radiation passes through the body to create images of hard tissues (like bones and solid tumors) onto photographic film.

SECTION 9

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