What You Need to Know About VHL

THE VHL HANDBOOK

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

Edition 5
Revised 2015
Written by the VHL Alliance

What You Need to Know About VHL

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

Written by the VHL Alliance

Edition 5
Revised 2015

International edition (English) ISBN 978-151941-30-93

International edition (English) ISBN 1-519413-09-2

Arabic edition, ISBN 1-929539-16-9
Chinese edition ISBN 1-929539-09-6
Croatian ISBN 1-929539-13-4
Dutch edition ISBN 1-929539-10-X
French edition ISBN 1-929539-06-1
Greek edition
Hebrew edition ISBN 1-929539-15-0
Hindi edition, ISBN 1-929539-05-3
Italian edition ISBN 1-929539-11-8
Japanese edition ISBN 1-929539-08-8
Portuguese ISBN 1-929539-14-2
Spanish edition ISBN 1-929539-07-X
Turkish edition ISBN 1-929539-17-7
Ukrainian edition ISBN 1-929539-12-6

Available in additional languages on request.

DISCLAIMER

This book is intended to add to, not replace, conversations between a patient and a physician, as the specific details and the patient's total health situation need to be considered in making the final decisions about treatment. The content of the book should not be taken nor relied upon as medical advice on how to treat your specific manifestation of this condition. Rather, by providing context and understanding, we hope that this book will empower the patient to be a better partner in his or her own care, and will facilitate constructive conversations between patient and physician.

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

1208 VFW Parkway, Suite 303, Boston, MA 02132-4344 USA
1.617.277.5667, 1.800.767.4845
Fax: 1.858.712.8712; E-mail: info@vhl.org
vhl.org

VHL Alliance

The VHL Alliance was founded in 1993 as a partnership among people affected by von Hippel-Lindau disease, interested health care professionals and researchers in the field. The Alliance is supported by the generosity of its partners and supporters.

Caring . . .
an international network of family support groups

Sharing . . .
in person, on the telephone hotline, online forums, through the *VHL Alliance Newsletter*, *telephone discussion groups*, and *" VHL Partners" program*

Learning . . .
from each other and from our physicians and medical teams

Educating . . .
patients, families, the medical community, and the general public

Awareness . . .
raising awareness to reach those not yet diagnosed and their friends and family

Funding . . .
better ways of managing VHL and similar tumor conditions for everyone.

Research . . .
working for a cure through tissue banking, natural and medical history data collection, and awarding research grants.

Clinical Care Centers. Call 800-767-4845 x4 or see vhl.org/ccc for referral to an institution participating in the VHLA Clinical Care Center network. These medical centers have agreed to help patients coordinate the wide range of screening tests and variety of specialists needed to manage VHL.

Regional Support Chapters. Call or email (info@vhl.org) for the contact person in your area, or to start a new group. Support communities also exist on the internet in many languages, including English, Spanish, German, French, Italian, Greek and Japanese.

Website. Copies of this handbook as well as educational articles and information on VHL events are on the VHL Alliance website: vhl.org

Preface

This information has been compiled to help individuals with VHL, their families, and other interested people understand VHL. The information presented here is intended to add to conversations with physicians and other health care providers. This handbook can replace personal conversations and personal advice about questions on treatment.

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. Recent 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 physicians and medical professionals for their expert review of this handbook:

Dr. Ashok Asthagiri, University of Virginia (CNS / ELST)
Dr. Ignacio Blanco, Germans Trias Hospital (Genetics)
Dr. Gennady Bratslavsky, SUNY Upstate (Kidney)
Dr. Emily Y. Chew, National Eye Institute, Bethesda, Maryland (Retina)
Dr. Wendy Chung, Columbia University (Genetics)
Dr. Lorenzo Cohen, MD Anderson Cancer Center (Psychosocial)
Dr. Jean-Michael Corréas, Paris-Descartes University (Kidney)
Dr. Graeme Eisenhofer, Uniklinikum Dresden (Adrenal)
Dr. Charis Eng, Cleveland Clinic (Genetics)
Dr. Alain Gaudric, University of Paris (Retina)
Dr. Paul Gidley, MD Anderson Cancer Center (CNS / ELST)
Dr. Rachel Giles, University Medical Center, Utrecht (Genetics)
Dr. Sven Gläsker, University of Brussels (CNS / ELST)
Dr. Michael Gorin, University of California, Los Angeles (Retina)
Dr. Raymond Grogan, University of Chicago (Adrenal)
Dr. Pascal Hammel, Hôpital Beaujon (Pancreas)
Dr. Emily Hershenson, National Institute of Health (Psychosocial)
Dr. Thai Ho, Mayo Clinic, Scottsdale (Oncology)
Dr. Othon Iliopoulos, Massachusetts General Hospital (Oncology)
Dr. Eric Jonasch, MD Anderson Cancer Center (Oncology)
Dr. Eric Kauffman, Roswell Park Cancer Institute (Kidney)
Dr. Electron Kebebew, National Cancer Institute (Pancreas)
Dr. Jacques Lenders, Nijmegen Medical Center (Adrenal)

Dr. Steven Libutti, Einstein-Montefiore Medical Center (Pancreas)
Dr. W. Marston Linehan, National Cancer Institute (Kidney)
Dr. Russell Lonser, Ohio State University (CNS / ELST)
Dr. Rimas Lukas, University of Chicago (CNS / ELST)
Dr. Eamonn Maher, University of Cambridge (Genetics)
Dr. Surena Matin, MD Anderson Cancer Center (Kidney)
Dr. Ian McCutcheon, MD Anderson Cancer Center (CNS / ELST)
Sarah Nielsen, MS, CGC, University of Chicago (Genetics)
Dr. Karel Pacak, National Institutes of Health (Adrenal)
Dr. Nancy Perrier, MD Anderson Cancer Center (Adrenal)
Dr. Susan Peterson, MD Anderson Cancer Center (Psychosocial)
Dr. Kimryn Rathmell, Vanderbilt University (Oncology)
Dr. Stéphane Richard, Centres Expert Rare Cancers, Paris (Genetics)
Dr. Armand Rodriguez (Psychosocial)
Dr. Brian Shuch, Yale University (Kidney)
Dr. Catherine Stolle, Children's Hospital of Philadelphia (Genetics)
Dr. Martin Walz, Kliniken Essen-Mitte (Adrenal)

And the assistance of expert volunteers: Joyce Graff, MA, Tina Gruner, RD, CDE; Dan Kavanaugh, MS; Elizabeth Krieg, MS, CGC; and Mark Pallansch.

Revision 5, 2015, provides updates on screening standards and more in-depth information about Healthy Living. 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.

This book is available in print or electronic version from major book sellers worldwide.

This text is also available over the Internet, both as a Web service and for download as pdf or e-book. See vhl.org/handbook.

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.

Table of Contents

Tables and Figures

TABLES

FIGURES

SECTION 1

What is VHL?

Von Hippel-Lindau, abbreviated VHL, is one of more than 7,000 known inherited rare disorders. VHL is a *gene mutation* which frequently induces both nonmalignant *tumors* and malignant tumors or cancers which can spread and become *metastatic*. Tumors will develop in up to ten different parts of the body. Many of these tumors involve the abnormal growth of blood vessels in different organs of the body. Most of these tumors are *benign*, meaning that they stay in the same organ where they began. However, VHL tumors in the *kidney* and *pancreas* can grow to a stage where they become "malignant," meaning that the cancer can spread to other parts of the body. The VHL *screening guidelines* (vhl.org/screening-guidelines) were developed to prevent VHL tumors from becoming metastatic.

While blood vessels normally branch out like trees, in people with VHL little knots of blood *capillaries* sometimes occur in the brain, spinal cord, or *retina*. These little knots are called *hemangioblastomas* or *angiomas*. In other parts of the body, the tumors of VHL are called by other names.

These tumors themselves may cause problems, or problems may develop due to their size or location. For this reason they need to be carefully monitored by a medical team.

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

Dr. Eugen von Hippel, a German *ophthalmologist*, described the 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 the hemangioblastomas of the brain and spine in 1926. His 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 these physicians were describing different aspects of the same disease.

Von Hippel-Lindau (VHL) is different from most other conditions in that it has no single primary *symptom*, that it does not occur exclusively in one organ of the body, and that it does not always occur in a particular age group. The condition is *hereditary*, but the health problems of the involved families and the specialties of the attending physicians are so varied that the common cause may not be recognized for many years. In addition, the appearance and severity of the condition are so variable that many members of the family may have only some relatively harmless issue, while others may have a serious illness.

With careful *monitoring*, early detection, and appropriate treatment, the most harmful consequences of this gene can be greatly reduced, or in some cases even prevented entirely.

Researchers are also finding that a significant number of new cases are occurring. As many as 20% of the individuals seen at centers around the world are the first in their family to have VHL. 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 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; downloaded August, 2014

Cancer can be a frightening word. Cancer is not one disease; it is a group of more than 100 different diseases. While each cancer differs from the others in many ways, every cancer is a disease of some 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.

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, and tumors begin to form. **Tumors can be benign or malignant.**

Benign tumors do not spread. VHL 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.

Because VHL can cause malignant tumors in the *visceral* organ systems, it is considered one of a group of *familial* cancer risk factors, which are transmitted genetically. 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 cause loss of function. Since these tumors are inside the body, medical imaging techniques are needed to find and watch them.

Not all tumors require surgery when they are found. Research is ongoing to learn more about how to tell when a tumor is getting worrisome and 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 **Cancer in Our Genes International Patient (CGIP) Databank** at vhl.org/databank.

While VHL tumors are a form of cancer, with careful early monitoring and treatment, metastatic cancer may never occur.

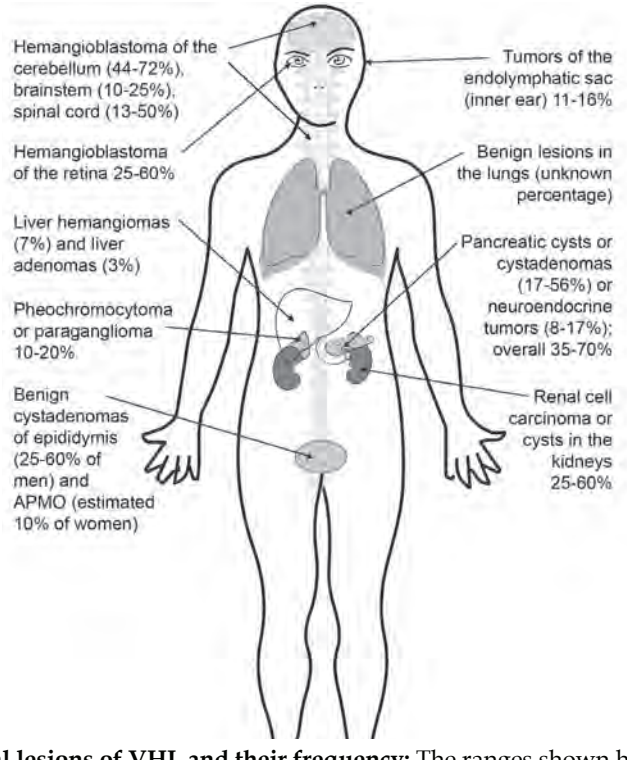


Figure 1. Principal lesions of VHL and their frequency: The ranges shown here were compiled by the US National Institutes of Health from a large international pool of patients.

Commonly Occurring VHL Manifestations

Age at onset varies from family to family and from individual to individual. The figures shown in Table 1 include age at *symptomatic* diagnosis, particularly in the early literature, and age at presymptomatic diagnosis because of a screening protocol. With better diagnostic techniques, diagnoses are being made earlier. This does not mean that action needs to be taken when early lesions are found, but care must be taken to watch the progression of these lesions and act at the appropriate moment.

Pheochromocytoma is very common in some families, while *renal cell carcinoma* is more common in other families. Individuals in a family may differ as to which of the family tumor types they express.

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

Rare manifestations include *cerebral* (upper brain) hemangioblastoma and rare occurrences of *hemangioma* in *liver*, spleen, and lung.

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.

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

Hemangioblastomas, Cysts and Tumors

Hemangioblastomas (also called angiomas and angioblastomas) are benign tumors occurring in the brain, spinal cord and retina in individuals with VHL and appear as knots formed by tiny blood vessels. (See Figure 1.)

When hemangioblastomas occur in the brain or spinal cord, the pressure they exert may in itself cause symptoms. Hemangioblastomas may press on nerve or brain tissue and cause symptoms such as headaches, problems with balance when walking, or weakness of arms and legs.

If the hemangioblastoma grows, the walls of the blood vessels may weaken and some blood leakage may occur causing damage to surrounding tissues. Blood or fluid leakage from hemangioblastomas in the retina (also called retinal capillary hemangioblastomas or retinal angiomas) can interfere with vision. Early detection, careful monitoring of the eye, and treatment when needed are very important to maintain healthy vision.

Cysts may grow around hemangioblastomas. Cysts are fluid-filled sacs which may themselves exert pressure or create blockages that can cause symptoms. Cysts and tumors may also occur in the *kidney*, *pancreas*, and *adrenal glands*. These cysts frequently cause no symptoms, but must be monitored for changes. Early *signs* of adrenal tumors may be high blood pressure, panic attacks, or heavy sweating. Early signs of pancreatic cysts and tumors may include digestive complaints like bloating, or disturbance of bowel

and bladder function. Some of these tumors are benign while others are cancerous. Early detection and careful monitoring are particularly important for these organ systems, usually with yearly *MRI*, assisted by *CT*, or *ultrasound* scanning.

How do people get VHL?

Von Hippel-Lindau is caused by an alteration in one of the two copies of a gene referred to as the VHL gene. This altered gene may be transmitted to children following an *autosomal dominant* pattern of inheritance, meaning that it is not limited to one sex, but may occur in both men and women. It also means that only one gene mutation is needed to produce the disease. Each child receives one gene of each pair from each parent. If one parent has an alteration (*mutation*) in a dominant gene, each child has a fifty-fifty chance of inheriting that gene and subsequently developing manifestations of the mutated gene.

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 child with VHL must have a parent with VHL. (See Figure 2.)

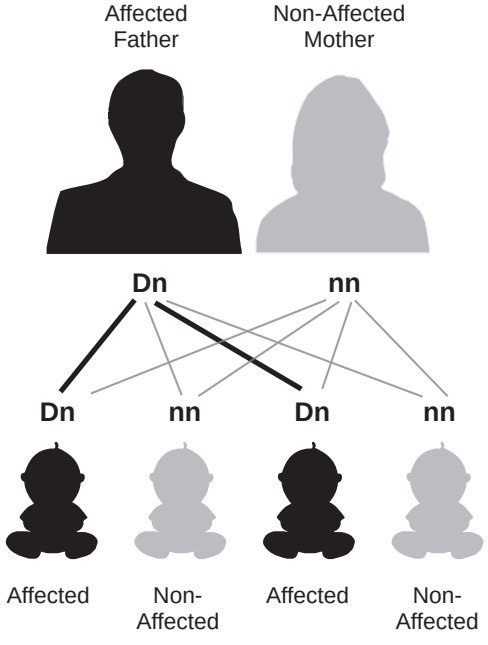


Figure 2. Inheritance of an autosomal dominant gene: A child receives one gene in each pair from each parent. If one parent has a Dominant gene (D), each child has a 50% chance of inheriting the condition.

Anyone with a parent with VHL and most people with a brother or sister with VHL are at a 50% chance of having VHL. Anyone with an aunt, uncle, cousin, or grandparent with VHL may also be at risk. The only way to determine for sure that someone does not have an altered VHL gene is through DNA testing. (See Obtaining DNA Testing.)

Even in people who have an alteration in the VHL gene, there is a wide variation in the age at which VHL tumors begin to grow, the organ system in which they grow, and the severity of the involvement. **VHL can cause different tumors in different people, even within the same family.**

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 in the Black Forest family in Germany and Pennsylvania has been documented back to the early 1600's. There are certain people, perhaps as many as 20%, who are the first in their family to have an alteration in the VHL gene. Neither parent is affected, but these people have a case of VHL. They are considered "de novo," for the first time. This "new mutation" is caused by a change in the gene in either one sperm from the father, in one egg from the mother, or in the copying of the gene during one of the first stages of division of the embryo. This alteration in the VHL gene can now be passed on to future children of this affected person. It necessitates medical screening of these children as well.

The handout and worksheet, *Your Family Health Tree*, published by the VHL Alliance, discusses the genetics of VHL in greater detail. It explains how you can compile family history information, which can be an important tool for your medical team. Family history information is important to understand your own condition and to assist researchers in learning more about VHL.

Obtaining DNA Testing

Anyone with a first or second-degree relative with VHL is "at risk" for VHL. First degree relatives are parents, children, sisters, and brothers. Second-degree relatives are aunts, uncles, grandparents, and grandchildren. Each child of a person with VHL is at 50% likelihood for VHL. The only way to determine for sure whether someone has VHL is through DNA testing. In any given family, it is best (most informative) to begin DNA testing of a person affected by VHL manifestations. This is a blood test that must be processed at a clinical testing laboratory (lab) that has the necessary equipment and reagents 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 at the VHL gene, the results are positive: this person has VHL. If the DNA testing finds that both copies of the VHL gene are unaltered, the test is negative or inconclusive: this person is unlikely to have VHL. There is always some margin for error and 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 to be as certain as it gets in nature. Anyone at risk for VHL who has not received a negative DNA test result should continue to follow a conscientious screening program to ensure early diagnosis of any VHL problems. In the United States, with the passage of the Affordable Care Act in 2010, health insurance companies can no longer deny coverage if there is a positive diagnosis of VHL, and the additional premium that may be charged is also capped by law. It is important to note, however, that this protection does not apply to other forms of insurance such as long-term disability insurance, long-term care policies, and life insurance.

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 screen of the VHL gene, sometimes including some additional testing to look for larger deletions. 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 this family. With this information, another person in the same family who does not have a clinical diagnosis of VHL can submit a blood sample and the lab can check for that same mutation in this second person's DNA. This first test in the family becomes a road map for subsequent tests in that family.

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 not to be correct.

For people who are the first in their families to be diagnosed with 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. For people in this situation, it is important to choose a lab with experience with research teams studying VHL that can provide a more thorough report.

It is best to initiate DNA testing through a geneticist or genetic counselor to ensure a thorough discussion of the personal impact of the results, whether they are positive or negative, and the possible insurance ramifications. To find a geneticist or genetic counselor, contact a VHL Clinical Care Center (vhl.org/ccc) or check the genetic counselors' website, nsgc.org. Large medical centers will usually have a department of cancer genetics. If so, this is the best place to assess your risk for VHL. 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.

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.

The list of clinical testing labs offering complete testing for VHL (including large deletions) is maintained on the internet at genetests.org. Every VHL Clinical Care Center can order DNA testing (vhl.org/ccc).

Researchers have identified five categories of VHL that may be useful in predicting the relative risk in a family for certain manifestations of VHL. These categories are not absolute, so it is important to undergo screening for all the features of VHL. (See Table 2.)

If your DNA diagnosis is unclear, please contact the VHL Alliance (info@vhl.org or 800-767-4845 x4) to discuss it further and to consider participating in a study to understand these situations.

Table 2. Genotype-phenotype classifications in families with von Hippel-Lindau disease: Sources: Hes F, Zewald R, Peeters T, et al. Genotype-phenotype correlations in families with deletions in the von Hippel-Lindau (VHL) gene. *Hum Genet*. 2000;106(4):425-431.; Maher ER, Webster AR, Richards FM, et al. Phenotypic expression in von Hippel-Lindau disease: correlations with germline VHL gene mutations. *Journal of medical genetics*. 1996;33(4):328-332.; Chen F, Slife L, Kishida T, Mulvihill J, Tisherman SE, Zbar B. Genotype-phenotype correlation in von Hippel-Lindau disease: identification of a mutation associated with VHL type 2A. *Journal of medical genetics*. 1996;33(8):716-717.

Note: Endolymphatic sac tumors and cystadenomas of the epididymis and broad ligament have not been assigned to specific VHL subtypes.

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	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	

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 screening early before any symptoms occur. Most VHL lesions are much easier to treat when they are small. Using the information provided in General Recommendations for Screening: Suggested Screening Guidelines (below and vhl.org/screening-guidelines), speak with your doctor about the best time to begin screening 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 for children at risk by age 1–3 years. 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"—you may not even have symptoms until

the problem has developed to a critical level. It is a little like not taking care of your house or car. You may get away with it for a while, but then it all catches up with you and it costs a great deal all at once. However, unlike your house or car, treatment may only be able to stop symptoms that have occurred; it is not always possible to reverse the changes and go back to normal. **There is clear, documented evidence that you will stay healthier longer if you follow recommended screening tests and are watchful.**

"I explain what's going on, how it works and what we're trying to fix, what could happen if it isn't fixed. I'm educating my patient in a way, but I'm also dispelling uncertainty. Uncertainty is the worst illness. The fear of the unknown can really be disabling."

—Dr. Thomas Delbanco, Beth Israel Hospital, Boston, Massachusetts, as quoted in Bill Moyers, Healing and the Mind, Doubleday Books, New York, 1993, p. 18.

Detection of affected individuals by DNA analysis of a blood sample is now possible for nearly all VHL families. The accuracy of the testing and its usefulness in most families is increasing rapidly. DNA testing can be used to determine which members of the family need to be followed closely. It can also determine which members may be reassured that they do not carry the altered VHL gene. **If family members do not have the altered VHL gene previously identified in the family, they will not need further testing or annual screening. They also do not have an altered gene to pass to their children**.

If you are positive for VHL or if genetic testing does not yet work for your suspected VHL mutation, but you have been clinically diagnosed, you will need to continue regular medical screening tests. One normal screening examination does not necessarily mean there is no VHL present, since the first evidence of VHL may occur later in life. Occasionally a person may be so mildly affected that VHL may seem to skip a generation. VHL has been diagnosed for the first time in people as old as 80, often because their children or grandchildren developed VHL tumors.

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. It is quite possible for someone to be the first in the family to have VHL. In some studies, 20% of the patients were 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 alteration in their DNA. In some cases, the VHL mutation is present only in certain cells, but not in all cells, making the person "mosaic" for VHL.

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

Once VHL has been diagnosed in any one part of the body, it is important to undergo screening for possible evidence of the disease in other parts of the body too, and to return for additional screening on the schedule recommended by your medical team.

"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

General Recommendations for Screening

Your medical team will work with you to develop the right screening and monitoring program for you and your family.

Screening is testing before symptoms appear to make sure that any issues are found early. See Suggested Screening Guidelines below (and vhl.org/screening-guidelines).

Monitoring is checking up on known issues to make sure that they are treated at the best time to insure long-term health. You and your medical team will work out the right interval for checkups, depending on your particular situation.

It is important to begin screening children who are at risk as early as possible. Using DNA testing, it is possible to identify which children have VHL and need screening, and which children do not carry the VHL mutation and will not need to be screened.

The VHL Alliance and its Clinical Advisory Council recommend that you begin screening children as early as age 1. **Make sure that the pediatrician knows that the child is at risk for VHL**. Complete eye examinations including a *retinal* examination at this young age are particularly recommended.

Screening can be done using techniques that are not painful and do not involve radiation or contrast dyes: a thorough medical eye examination by a *retinal specialist*; a complete physical examination, including blood pressure and neurological examination; a hearing testing by an audiologist; imaging of the brain; ultrasound of the abdomen; and a 24-hour urine collection usually begin about age 5–15, or sooner if symptoms or signs occur.

Participation in VHLA's **Cancer in Our Genes International Patient (CGIP) Databank**, vhl.org/databank, allows participants to generate screening reminders.

Suggested Screening Guidelines

The guidelines are current at the time of publication (2015). Please see the VHL Alliance website for the latest guidelines: vhl.org/screening-guidelines.

Screening is the testing of individuals at risk for von Hippel-Lindau disease (VHL) who do not yet have symptoms or who are known to have VHL but do not yet have symptoms in a particular area. Even without these symptoms, the unaffected organs should still be screened.

Modifications of screening schedules may sometimes be done by physicians familiar with individual patients and with their family history. **Once a person has a known manifestation of VHL or develops a symptom, the follow-up plan should be determined with the medical team. More frequent testing may be needed to track the growth of known lesions.**

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 need the screening testing. Even with

the VHL gene, once an individual has reached the age of 60 and still has no evidence of VHL on these screening tests, imaging tests may be cut back to every two years for MRI.

Revisions in the 2014 screening guidelines include a change in recommendations from CT to MRI in order to reduce exposure to radiation for all people. CT should be avoided for all pre-symptomatic people and should be reserved for occasions when it is truly needed to answer a diagnostic question.

In order 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*, and attention to inner ear/*petrous temporal bone* to rule out both *endolymphatic sac tumors (ELSTs)* and hemangioblastomas of *neuraxis*.

Eye examinations are important from age 1 onward in order to find any lesions on the retina (inside, at the back of the eye). When found early, most of these lesions can be treated with a laser and result in no functional loss of vision. However, if the eye is not examined until a change in vision is noticed, the vision in that eye may not be able to be saved.

Regular *audiometric* tests are included in the screening protocol to provide a reference point in case of signs or symptoms of hearing loss, *tinnitus* (ringing in the ears), and/or *vertigo* (dizziness, loss of balance). If hearing drops, swift action may be required to save hearing. A study of audiometric information is being conducted to determine whether early signs of ELST might be detected with audiometric testing alone.

MRI is the preferred screening method for the abdomen. Quality ultrasound may be substituted for MRI of the abdomen no more than once every two years. "Quality" is defined as a machine that produces good quality pictures, with an operator experienced in imaging the organs being studied. The objective is to find even small tumors, which are difficult to identify on ultrasound.

Any age

- Inform families that, if they choose, they and their geneticist may contact one of the clinical DNA testing laboratories familiar with VHL for DNA testing. If the family marker is detectable, DNA testing can identify those family members who are not at risk and may discontinue screening. Testing may also be useful in calculating risks for family members who do carry the altered gene and require periodic screening tests. Risk factors are not definitive indicators of what will happen, but only highlight areas at higher or lower risk probability. Early detection and appropriate treatment are the best defenses.

From conception

- Inform the obstetrician of any family history of VHL. If the mother has VHL, see also the discussion of pregnancy in this handbook and in the screening protocol. A mother-to-be who is having any genetic testing done may request a VHL test be included in that series of tests.

From birth

- Inform the pediatrician of any family history of VHL. The pediatrician can look for signs of neurological disturbance, *nystagmus*, *strabismus*, white pupil, and other signs which might indicate a referral to a retinal specialist. Include a routine newborn hearing screening.

Ages 1–4

Annually:

- Eye/retinal examination with indirect *ophthalmoscope* by an ophthalmologist skilled in diagnosis and management of retinal disease, especially for children known to carry the VHL mutation.
- Pediatrician's exam to look for signs of neurological disturbance, nystagmus, strabismus, white pupil, and abnormalities in blood pressure, vision, or hearing.

Ages 5–15

Annually:

- Physical examination and neurological assessment by pediatrician informed about VHL, with particular attention to blood pressure, both while lying and standing, hearing issues, neurological disturbance, nystagmus, strabismus, white pupil, and other signs which might indicate a referral to a retinal specialist.
- Eye/retinal examination with indirect ophthalmoscope by an ophthalmologist or optometrist informed about VHL, using a dilated exam.
- Test for fractionated *metanephrines*, especially *normetanephrine* in a "plasma free normetanephrine" blood test or in a 24-hour urine test. Abdominal ultrasonography annually from 8 years or earlier if indicated. Abdominal *MRI* or *MIBG* scan only if biochemical abnormalities found.

Every two to three years:

- Complete *audiology* assessment by an audiologist. Annually if any hearing loss, *tinnitus*, or *vertigo* is found.
- In the case of repeated ear infections, MRI with contrast of the internal auditory canal using thin slices, to check for a possible ELST.

Ages 16 and beyond

Annually:

- Eye/retinal examination with indirect ophthalmoscope by ophthalmologist informed about VHL, using a dilated exam.
- Quality ultrasound and at least every other year MRI scan of abdomen with and without contrast to assess kidneys, pancreas, adrenals, but not during pregnancy. Physical examination by physician informed about VHL.
- Test for fractionated metanephrines, especially normetanephrine in "plasma free metanephrines" blood test or 24-hour urine test. Abdominal MRI or MIBG scan if biochemical abnormalities found. (Please see the VHL in the Adrenal Glands (Pheochromocytoma) section for details about testing for pheochromocytomas.)

Every two years:

- MRI scans should be ordered as no less than a 1.5T MRI with and without contrast of brain, cervical, thoracic, and lumbar spine, with thin cuts through the posterior fossa, and attention to inner ear/petrous temporal bone to rule out both ELST and hemangioblastomas of the neuraxis.
- Audiology assessment by an audiologist.

During pregnancy

- Regular retinal checkup to anticipate potentially more rapid progression of lesions
- Test for pheochromocytomas early, mid, and again late pregnancy to ensure no active pheochromocytoma during pregnancy or especially labor and delivery.
- During the 4th month of pregnancy, MRI—without contrast—to check on any known lesions of the brain and spine. If known retinal, brain, or spinal lesions, consider C-section.

Diagnosis and Treatment

Your medical team will advise you on the best diagnostic tests to use and the best course of treatment for the VHL involvement identified through your screening. There are a number of very effective treatments and more are being discovered.

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, cyst, or tumor.

Treatments usually involve some kind of surgery to remove potentially malignant tumors before they become harmful to other tissues. Evaluation of a surgical alternative is always a matter of choosing the lesser of two evils. Surgery always has some level of risk, but keeping the hemangioblastoma or tumor also has risks. You may want to ask your doctor about the odds for a poor outcome. Finding out it is a list of things, all of which add up to less than 4%, as opposed to a single risk level of 50%, helps to put the risk into perspective. 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.

Diagnostic Imaging in VHL

The imaging most commonly used to screen and manage VHL lesions includes:

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). The use of linear contrast agents in patients with kidney failure was halted in 2011. Recent data has shown accumulation of *gadolinium* in neural tissue of patients undergoing repeated contrast-enhanced MRI scans. The clinical significance is unclear at this time.

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 (only need to take one scan). Newer CTs also need less contrast agent. Keep in mind that data available on radiation and cancer is from Hiroshima survivors, so there is little data on the low exposure from CT scans. Therefore, try to avoid CT scans under age 18; use MRIs. Low dose CT scanners reduce radiation by 2/3rds.

Other options and considerations include ultrasound. Ultrasound is safe and non-invasive, but it is very operator dependent. Ultrasound can be used to detect *paraganglioma* (PGL) in the neck. These are also very uncommon in VHL. A whole body MRI is also an option for VHL. Pulmonary (lung) cysts are an uncommon feature of VHL. These look similar to multiple cysts seen in the pancreas. These are not tumors.

Common Treatment Recommendations

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. The following are offered as general guidelines for possible treatment therapies. Doctors are asked to read Lonser et al., (*Lancet*, 2003; 361:2059-67) for a more detailed explanation.

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. Symptomatic lesions grow more rapidly than *asymptomatic* lesions. Cysts often cause more symptoms than the tumor itself. Once the lesion has been removed, the cyst will collapse. If any portion of the tumor is left in place, the cyst will re-fill. Small hemangioblastomas (under 3 cubic cm, or 1.7 cm measured diagonally), which are not symptomatic and are not associated with a cyst have sometimes been treated with *stereotactic radiosurgery*, but this is more a preventive than a treatment, and long-term results seem to show only marginal benefit.

Pancreatic Neuroendocrine Tumors

Careful analysis is required to differentiate between serous *cystadenomas* and *pancreatic neuroendocrine tumors (Pancreatic NET)*. Cysts and cystadenomas generally do not require treatment. Pancreatic NET should be rated on size, behavior, and DNA type. Tumors greater than 3 cm or with a doubling rate of fewer than 500 days should be considered for surgery. In patients with an alteration in exon 3, tumors greater than 2 cm should be considered for surgery.

Renal Cell Carcinoma

With improved imaging techniques, kidney tumors are often found at very small sizes and at very early stages of development. A strategy for ensuring that an individual will have a sufficient functioning kidney throughout his or her lifetime begins with careful monitoring and choosing to operate only when tumor size or rapid growth rate suggest the tumor may gain metastatic potential (approximately 3 cm). The technique of kidney-sparing surgery is widely used in this setting. *Radio Frequency Ablation* (RFA)

or *cryosurgery (cryotherapy)* may be considered, especially for smaller tumors at earlier stages. However, only removal of the tumor "resets" the clock. Care must be taken not to injure adjacent structures and to limit scarring which may complicate subsequent surgeries. Robotic surgery can be used to limit scarring.

Retinal Hemangioblastomas

In the periphery, consider treatment of small lesions with laser and larger lesions with *cryotherapy*. If the hemangioblastoma is on the optic disc, follow the growth pattern as there are few treatment options for tumors of the optic disc. The optimal treatment would be a drug, but to date none has proven successful. Check with one of the expert centers for the latest treatment options for hemangioblastomas on or near the optic nerve.

Pheochromocytoma

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 delivery. Even pheos that do not appear to be active or causing symptoms should be removed.

Endolymphatic Sac Tumors

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. Perhaps the 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 (in bed or on a plane) 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.* A blood clot that travels to the brain can cause a stroke.

There are a number of things your doctor may prescribe to reduce the risk of DVT. In the hospital, you will be required to wear mechanical compression devices on your legs to help pump blood back up to your heart. In some circumstances, blood thinners may 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 or stroke, either of 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. Stroke symptoms may be more difficult to notice at first, but include face drooping, sudden trouble seeing, sudden severe headache, sudden weakness of arm, leg, or face, speech difficulty, sudden confusion or trouble understanding, or sudden problem with walking or balance. Any of these symptoms 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.

Questions to Ask Your Doctors

With early detection and appropriate treatment, von Hippel-Lindau disease 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 get a second or even a third opinion. The following are some questions that patients may want to ask their physician:

1) **Should I change my normal activities?**
2) **How often are checkups needed?**
3) **What other health professionals are needed on my medical team to ensure that we have checked for all the probable features of VHL?**
4) **Who will be the main person responsible for looking after my medical interests and coordinating communication among my specialists?**
5) **What is meant by a term, the cyst or tumor size is xx cm (e.g. 2 cm)?**
6) **At what point do I need to worry about this cyst or tumor?**
7) **What symptoms should I watch for?**
8) **Are there any critical symptoms of which I should be aware?**
9) **What kinds of treatment are available?**
10) **What are the risks or side effects of these treatments?**
11) **What are the odds of those risks happening?**
12) **What are the risks of no treatment?**
13) **Is there a less *invasive* treatment to be considered?**
14) **Can the surgery be done laparoscopically?**
15) **Is robotic surgery an option?**
16) **Is there a research project in which I can participate?**
17) **Is there a clinical trial that would be appropriate for me?**

18) How experienced are you in dealing with VHL?

19) Where can I consult with specialists who are experienced with VHL? (VHL Clinical Care Centers are listed at vhl.org/ccc)

20) What can I do to assist doctors in learning more about VHL?

References

The American Society of Human Genetics (ASHG) has information on policy and ethics on their website. See http://genetics.faseb.org/genetics/ashg/ashgmenu.htm

Asher KP, et al., Robot-assisted laparoscopic partial adrenalectomy for pheochromocytomas: the National Cancer Institute technique, *Eur Urol*, 2011 Jul; 60(1):118-24

Asthagiri AR, et al., Prospective evaluation of radiosurgery for hemangioblastomas in von Hippel-Lindau disease, *Neuro Oncol*. 2010 Jan;12(1):80-6. Epub 2009 Dec 23. PMID: 20150370

Blansfield JA, et al., *Surgery*, 2007 (See Table 1.)

Choyke P. Imaging in VHL: What You Need to Know!, Presentation at VHLA annual meeting, October 2014

Collins, D., Information for Genetic Professionals: http://www.kumc.edu/gec/prof/kugenes.html

Dayal M, et al., Preimplantation Genetic Diagnosis, *Medscape*, November 4, 2013 http://emedicine.medscape.com/article/273415-overview

Giles R; University of the Netherlands, Utrecht; correspondence with the VHL Alliance May 2015

Gupta GN, et al., Robot-assisted laparoscopic partial nephrectomy for tumors greater than 4 cm and high nephrotomy score: feasibility, renal function, and oncological outcomes with minimum 1 year follow-up, *Urol Oncol*, 2013 Jan; 31(1):51-6

Hoeffel C. Radiofrequency ablation of renal tumors, *European Radiology*, 2010, 20(8): 1812-21

Maher ER, et al., von Hippel-Lindau disease: a clinical and scientific review. *Eur J Hum Genet*. 2011 Jun;19(6):617-23. Epub 2011 Mar 9. PMID: 21386872

Lindau RS, et al., von Hippel-Lindau disease. *Lancet*. 2004, 363:1231-4. PMID: 15081659

Lonser RR, et al., von Hippel-Lindau disease. *Lancet*. 2003 Jun 14;361(9374):2059-67. PMID: 12814730

Lonser RR, et al., The vestibular aqueduct: site of origin of endolymphatic sac tumors, *J Neurosurgery*, April 2008, Vol. 108, no. 4: 751-756)

Maher ER, et al., von Hippel-Lindau disease: a clinical and scientific review. *Eur J Hum Genet*. 2011 Jun;19(6):617-23. Epub 2011 Mar 9. PMID: 21386872

Matin SF, et al., Patterns of intervention for renal lesions in von Hippel-Lindau disease, *BJU International*, October 2008, Vol 102, issue 8:940-45

Phuah C. The Danger of Blood Clots after Surgery, VHL Alliance Ask the Experts: Blood Clots, vhl.org

Richard S. von Hippel Lindau, *Atlas Genet Cytongenet Oncol Haem* 20001; 5(21): 145 -149

Seeger A, et al., Comparison between a linear versus a macrocyclic contrast agent for whole body MR angiography in a clinical routine setting, *J Cardiovasc Magn Reson* 2008; 10(1):63

Stroke Warning Signs, Together to End Stroke, Strokeorg, http://www.strokeassociation.org/STROKEORG/WarningSigns/Learn-More-Stroke-Warning-Signs-and-Symptoms_UCM_451207_Article.jsp

See additional articles cited in topic sections for each organ system.

Online Resources

National Library of Medicine has a list of labs that meet the standards set by CLIA: http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab

National Society of Genetic Counselors has a website where you can find a genetic counselor near you. http://nsgc.org

The US government offers a tool for preparing a Family Health History document to help you and your family assess their health risks and learn to manage them. http://familyhistory.hhs.gov

The Office of Biotechnology Activities maintains a website that contains information on the work of the Advisory Committee to the Secretary of Health and Human Services on "Genetic Testing." http://www4.od.nih.gov/oba/

The Human Genome Institute has a section on Policy and Ethics that deals with the Ethical, Legal, and Social Implications of the Human Genome Project and genetic testing. See http://www.genome.gov/PolicyEthics

SECTION 2

Possible VHL Manifestations

Presented in order of decreasing average frequency of incidence

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 location of these tumors in the brain is the *cerebellum*, and in the spine is the *cervical spine*. 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. With regular visits to a *neurosurgeon* on the schedule recommended by your medical team, early signs may be found that may require further testing, usually with MRI. Early signs and symptoms may include back pain, headaches, numbness, dizziness, bowel/bladder incontinence, increased reflexes, incoordination and/or weakness or pain in the arms and legs.

In general, it is the pressure on the adjacent brain tissue or nearby nerves by the hemangioblastoma and/or associated cyst/*syrinx* that causes symptoms. Although treatment may be deferred even in the setting of a growing tumor, treatment should be initiated before symptoms become severe. The timing of intervention, therefore, is currently a delicate balance. Rarely can severe or longstanding symptoms/signs be reversed or diminished by tumor removal. Judicious surgical resection of tumors is critical because there is risk associated with surgical removal of hemangioblastomas of the brain or spinal cord, and asymptomatic tumors may never require removal. Thus, it is important to carefully consider both the benefits and risks.

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

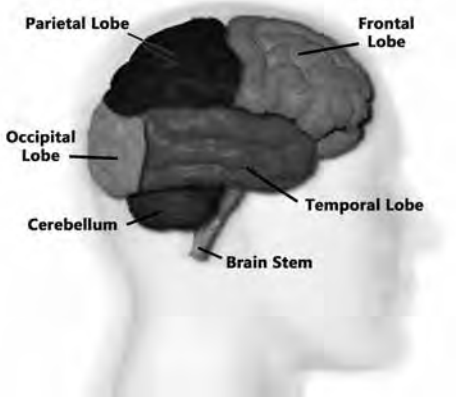
Stereotactic *radiosurgery*, sometimes called by the name of the machine such as *gamma knife* or *cyberknife*, is a non-invasive treatment which does not require open surgery. Radiation is delivered to a very specific internal area where the multiple beams of radiation meet and deliver a therapeutic dose. You should discuss stereotactic radiosurgery with your medical team, but it, like many other techniques, is not appropriate in every case, as it may cause post-treatment swelling or scarring that could make open surgery more difficult in the future. Stereotactic radiosurgery for any brain or spinal hemangioblastoma needs to be discussed carefully with a neurosurgeon knowledgeable about VHL. (See next section, Considering Stereotactic Radiosurgery.)

The goal of all open surgical treatments is the complete resection (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 the most critical decision to make. No approach is always the right one. 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 to you and to your neurosurgeon to have multiple opinions on the best approach to your problem.

Table 3. Regions of the brain and associated functions: Source: rah.sa.gov.au/birs/bi_brain.php

The charts below show the regions of the brain and list possible symptoms for lesions in these locations. There is overlap of function among some regions and the brain is "plastic," meaning that if one region is affected, another region can often take over some of the functions.



Frontal Lobes

Function	Observed dysfunction
• Conscious thought • Concentration • Perseverance • Judgment • Attention span • Impulse control—self monitoring and supervision • Problem solving • Organization • Critical thinking • Forward thinking • Ability to feel and express emotion • Empathy • Memory for habits and motor activities	• Paralysis • Difficulty in sequencing (Inability to plan a sequence of complex movements need to complete multi-stepped tasks) • Loss of spontaneity in interacting with others • Loss of flexibility in thinking • Perseveration (persistence of a single thought) • Difficulty attending (inability to focus on task) • Emotionally labile (mood changes)

Parietal Lobes

Function	Observed dysfunction
• Visual attention • Touch perception • Monitors sensation and body position • Control reading • Face recognition • Understanding time • Goal directed voluntary movements • Manipulation of objects	• Inability to attend to more than one object at a time • Anomia (Inability to name an object) • Agraphia (Inability to locate the words for writing) • Alexia (Reading difficulties) • Difficulty drawing • Difficulty in distinguishing left from right • Dyscalculia (difficulty with mathematics • Apraxia (Lack of awareness of certain body parts and/or surrounding space) • Inability to focus visual attention • Difficulties with hand-eye coordination

Occipital Lobes

Function	Observed dysfunction
• Receives visual information • Interprets color, shape, distance	• Visual field deficits • Difficulty locating objects • Color Agnosia (difficulty identifying color) • Production of hallucinations • Visual illusions • Inability to recognize words (word blindness) • Difficulty recognizing drawn objects • Movement Agnosia (inability to recognize movement of an object) • Difficulty reading and writing

Temporal Lobes

Function	Observed dysfunction
• Memory and new learning • Receives auditory messages • Understands spoken language and rhythm • Controls how things are ordered and categorized • Some visual perception	• Prosopagnosia (difficulty in recognizing faces) • Wernicke's Aphasia (difficulty in understanding spoken words) • Disturbance with selective attention to what we see and hear • Difficulty with identification of and verbalization about objects • Short-term memory loss • Interference with long term memory • Increased or decreased interest in sexual behavior • Inability to categorize objects • Persistent talking (right lobe damage) • Increased aggressive behavior

Brain Stem

Function	Observed dysfunction
• Breathing • Heart rate • Swallowing • Startle response (reflexes to seeing and hearing) • Autonomic nervous system (sweating, blood pressure, digestion, temperature) • Affects level of alertness • Ability to sleep • Vestibular function (sense of balance)	• Decreased vital capacity • Dysphagia (swallowing) • Difficulty with balance and movement • Vertigo (dizziness and nausea) • Insomnia, sleep apnea (sleeping difficulties) • Persistent cough • Hiccups • Weight loss or inability to gain weight

Cerebellum

Function	Observed dysfunction
• Coordination • Balance and equilibrium	• Asynergia (Loss of coordination of motor movements) • Dysmetria (inability to judge distance and when to stop) • Adiadochokinesia (inability to perform rapid alternating movements) • Intention tremor • Abnormal/ataxic gait (staggering wide based walking) • Tendency to fall • Hypotonia (weak muscles) • Dysphonia (slurred speech) • Nystagmus (abnormal eye movements) • Loss of ability to coordinate fine movements

Special Imaging Considerations for the Brain and Spinal Cord

T1-weighted contrast-enhanced MRI remains the imaging modality 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. T-2 weighted and FLAIR MRI sequences are useful for determining the extent of swelling or cysts around a tumor as well as monitoring their progression over time.

Considering Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) is a non-invasive surgical technique similar to laser surgery, but using beams of radiation instead of light. As with all other forms of

radiation treatment, the tumor or lesion is not removed, but the DNA is damaged. In addition, radiosurgery can also cause direct blood vessel damage, especially in vascular tumors such as hemangioblastomas, thickening and closing off of the blood vessels over a period of a few months, up to two years. Therefore, stereotactic radiosurgery is not effective "instantaneously' like surgery. Though the beneficial effects may be delayed, initial side effects may occur and include swelling of the treated lesion due to the loss of the cells' ability to regulate fluids as well as swelling in the brain tissue that is adjacent to the treated tumor.

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

After over 20 years of experience with SRS and hemangioblastoma, the VHL Alliance's Clinical Advisory Council recommends:

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

The best candidate tumor for SRS is a brain tumor 1 cubic 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 resection.

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 effects of SRS are not yet known, but doctors have seen scarring following SRS treatment that may make some subsequent surgeries more difficult.**

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

(1) 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, interventional radiologist, or someone who practices only SRS. Be sure to talk with surgeons who are experts in each method and get both perspectives. In many cases, it is safer to approach a tumor with conventional surgery. If it is removed, the tissue can be examined under a microscope and the recovery period is better defined. Of course, conventional surgery has its own set of risks and drawbacks. 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.

(2) How big is the tumor? Recommendations are NOT to treat a hemangioblastoma larger than 1.7 cm. Size is not the only issue, but it is a very important issue. Dr. Haring Nauta of the University of Louisville Hospital states, "It is a matter of how finely you can focus the beams of radiation. It is rather like trying to burn a hole with a magnifying

glass and sunlight. To make a small hole, you can focus the beam to a small point and use less radiation. To make a bigger hole, you have to cover a larger field; the beam is more weakly concentrated, and you have to use a lot more radiation to do the job. The tumor absorbs more energy and will swell more after the treatment."

(3) Is there a cyst or other source of mass effect? *Mass effect* is the effect of having some additional mass in your skull. This could be from a cyst, swelling, or from the tumor itself. If there already is extra pressure inside your skull, SRS is probably not a good idea since the additional swelling caused by the procedure would compound the mass effect and make the symptoms worse.

(4) 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 it to expand, 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.

(5) 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, then 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.

(6) 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.

(7) What experience does this team have with treating hemangioblastomas, as opposed to solid tumors? Hemangioblastomas react differently to radiation treatment. 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.

References

Ammerman JM, et al., Long-term natural history of hemangioblastomas in patients with von Hippel-Lindau disease: implications for treatment, *J Neurosurg*, 2006 Aug;105(2):248–55. PMID: 17219830

Asthagiri AR, et al., Prospective evaluation of radiosurgery for hemangioblastomas in von Hippel-Lindau disease, *Neuro Oncol*, 2010 Jan;12(1):80–6. Epub 2009 Dec 23. PMID: 20150370

Dictionary for Brain Tumor Patients and A Primer of Brain Tumors, *American Brain Tumor Association*, ABTA, 2720 River Road, Suite 146, Des Plaines, IL 60018. (800) 886-2282 or 1 708 827-9910; Fax: 1 708 827-9918. http://hope.abta.org info@abta.org

Lonser RR, et al., Surgical Management of CNS tumors in VHL. Series of articles concerning the specific sites of VHL tumors of the CNS, *J Neurosurgery*, 2003–2008,

PMIDs: 12546358 (spinal), 12546357 (brain stem), 12859062 (nerve root), 18240914 (cerebellar)
Peyre M, et al., Natural history of supratentorial hemangioblastomas in von Hippel-Lindau disease, *Neurosurgery*, 2010, 67: 577-87. PMID: 20647972
Simone CB 2nd, et al., Infratentorial craniospinal irradiation for von Hippel-Lindau: a retrospective study supporting a new treatment for patients with CNS hemangioblastomas, *Neuro Oncol*, 2011 Sep;13(9):1030-6. PMID: 21798886
Stereotactic Radiosurgery Overview, *International Radiosurgery Association*, http://www.irsa.org/radiosurgery.html
Wind JJ, et al., Management of von Hippel-Lindau disease-associated CNS lesions, *Expert Rev Neurother*, 2011 Oct;11(10):1433-41. PMID: 21955200

VHL in the Pancreas

What is the Pancreas and What Does It Do?

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, lying directly behind and against the stomach and the small intestine. (See Figure 3.) It is about 5–7 inches long. 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. The pancreatic 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*).

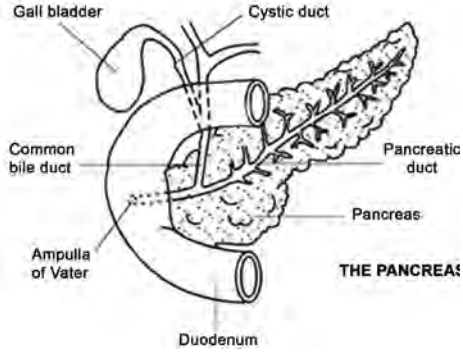


Figure 3. Diagram of the pancreas: Source: patient.co.uk

The pancreas consists of two glandular parts; one produces secretions that are essential in digestion. This secretion flows by way of the large pancreatic duct together with bile produced by the *liver* into the upper part of the digestive tract. The other part of the pancreas is formed by the islet cells, in which hormones such as *insulin* are formed. Insulin is the hormone that regulates the blood sugar level.

Functions of the Pancreas

The pancreas regulates how the body's cells are fed 24 hours a day. The pancreas is 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.

These three digestive enzymes are:

1. *protease* to break down protein foods
2. *amylase* to break down carbohydrates and sugars
3. *lipase* to help us absorb fats

Producing hormones that regulate blood sugar.

The other important job of the pancreas is to make hormones (insulin and *glucagon*) that help balance blood sugar and regulate the body's ability to feed every cell 24 hours a day.

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 too low (between meals or during sleep), the pancreas makes a hormone called glucagon which tells the liver to release stored sugar, or to make sugar from fat and muscle cells.

Pancreatic lesions are generally considered to be the least symptomatic among the lesions of von Hippel-Lindau disease. However, patients report a number of subtle symptoms which may be caused by pancreatic cysts.

Lesions in the Pancreas

Three types of lesions may be found commonly in the pancreas:

1. Cysts
2. *Serous microcystic adenomas*, or "cystadenomas"
3. Islet cell tumors, or pancreatic neuroendocrine tumors (NET)

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 the stomach and cause discomfort. Surgical drainage of a large cyst may provide relief.

Pancreatic tumors are found in about 12% of people with VHL. *Serous microcystic adenomas* (benign tumors) are the most common. 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.

Depending on their size, type, and location, VHL 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. The job of the pancreas is to create hormones and enzymes that are important to the digestion of the food, making the nutrients in the food available to the body's cells. Cysts and tumors may block one or more of the ducts that carry essential fluids from the pancreas to the digestive tract, causing diarrhea, constipation, fatty stools, other digestive complaints, and weight loss. 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.

If lesions obstruct the bile ducts, there may be *jaundice*, pain, inflammation or infection. Jaundice is when the skin and urine become yellow, and the stools become quite pale. Pain is the body's signal that there is something wrong and requires attention. Seek medical help immediately, as *pancreatitis* is a serious condition requiring medical attention.

The most worrisome pancreatic issue is solid tumors, not cysts, arising within the islet cells of the pancreas. These may be pancreatic neuroendocrine tumors (*Pancreatic NET* or *pNETs*), which can cause bile duct obstructions and can even metastasize or spread to the liver, bone, or other organs.

Some of the "hard tumors" turn out to be *microcystic adenomas*, honeycombed clusters of small cysts that look solid on the scans but, in fact, are not a problem.

Careful evaluation of pNETs is critical because it would be best not to operate on the pancreas unless it is important to do so. PNETs are not "functional" in VHL, meaning they do not emit hormones, so chemical tests will not help to determine their nature.

Although MRI is the preferred screening method for the abdomen, a CT may be needed to answer a specific diagnostic question, especially if there are symptoms. There are several advantages when evaluating pNETs. CT provides a superior anatomic study to MRI and helps to plan an operation as relationships of the tumor to other structures are more easily discerned. The most sensitive and specific study for diagnosing pNETs is an early arterial phase CT scan. CTs are also less subject to motion artifact variability between different machines, allowing more accurate monitoring of changes in the size of the lesion. The recommended CT is a three phase contrast (early arterial, portal, delayed) scan. A 12-year study at the US National Institutes of Health identified three variables that are important in deciding whether intervention is required—size, behavior, and the nature of the DNA alteration.

> **DNA:** Research has shown a higher correlation of dangerous pNETs among people who have an alteration in *exon* 3 of the VHL gene. The VHL gene has three distinct parts, called exons. Each family has a particular mutation, like a misspelling of one word in the book of instructions that make up the VHL protein. That family mutation is passed intact from parent to child, so each family member has the same alteration in their VHL gene. People with a mutation in exon 3 seem to have a more aggressive type of pancreatic tumor.
>
> **Behavior:** Researchers also looked for signs of aggressive behavior. To measure aggressiveness, they took a series of images and compared the size of the largest tumor in each of these scans, then calculated its rate of growth, or "doubling rate."

If the tumor doubled in size in less than 500 days, it was deemed to be high risk. If it took longer than 500 days for the tumor to double, it was at a more moderate risk level.

Size: In the past, recommendations for when to operate have been based entirely on size. But now, with the addition of these new measures, Dr. Steven Libutti at Einstein-Montefiore Medical Center, has divided tumors into three categories—low risk tumors can be watched every 2–3 years; medium risk tumors should be followed more closely, and high-risk tumors should be evaluated for surgery. (See Table 4.)

Table 4. Assessing the risk level of a pancreatic neuroendocrine tumor: Source: "Clinical, genetic and radiographic analysis of 108 patients with von Hippel-Lindau disease (VHL) manifested by pancreatic neuroendocrine neoplasms (pNETs)." by Blansfield JA et al., *Surgery*, 2007 Dec;142(6): 814-8; discussion 818.e1-2.

High risk— evaluate for surgery	**Medium risk—follow until a second criterion is present**	**Low risk— follow every 2–3 years**
Size >= 3 cm Mutation in exon 3 Doubling in <500 days	Size 2–3 cm Mutation in exon 1 or 2	Size < 2 cm Mutation in exon 1 or 2

Possible effects on pancreatic function

While cysts are *benign* (they do not become cancerous), they may block one or more of the tiny tubules in the pancreas that deliver insulin, glucagon, or pancreatic enzymes to the gut. It is somewhat like stepping on the garden hose. Even though the pancreas is still making these hormones and enzymes, they are unable to get to where they need to go to aid digestion.

Diabetes is the condition that occurs when the pancreas does not make enough insulin to keep blood sugar within the normal range. This can be treated with pills that can help the pancreas make more insulin, or pills that tell the liver to make less sugar, or injections of insulin to replace what is not getting 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.

Tumors 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.

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 clearly 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 on 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 loss of weight. 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 and the strength of your immune system.

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, even if when they are taking a prescription oral enzyme. 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.

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 are the ones with 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.

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.

All dairy products can contain as much as 10 grams of fat per serving. Reduce portion size or choose nonfat or 1% fat alternatives.

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.

Eating out is tricky because it is harder to determine exactly how much fat is in the meal. One VHL patient, who has lived without a pancreas for nearly 40 years, worked as a travel agent and traveled internationally eating local food. "I estimated how much Creon I would need and kept some Imodium in my suitcase for emergencies, but I learned to manage pretty well. Eating the local fare is part of the fun of traveling."

—Jackie H., PA

CAUTION: ALCOHOL AND DEHYDRATION

If you have pancreatic disease, it is important to never drink alcohol. Research has shown that dehydration causes 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. Drinking sports drinks is a good way to keep from being dehydrated, but it is important to be aware that many have added sugar or other sweeteners.

DIET: MEDICAL CARE

The dietitians with the most experience dealing with pancreatic insufficiency are those who work with people with cystic fibrosis (CF). VHL has no connection with CF, but 75% of people with CF to have pancreatic insufficiency for a different reason. On the cff.org website, there is a list of Care Centers for CF. Call the CF Care Center nearest you and ask to speak with the dietitian who works with adults with CF.

Because fats are not being digested, the fat-soluble vitamins are not being absorbed. Ask the 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.

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.

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 first thing you say to new patients with pancreatitis when you see them?

A: I would explain to them that my goal is to adjust their diet to help their body absorb nutrients better.

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

A: Their body 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, because this will decrease the amount of enzymes needed to digest meals. If significant symptoms are still present after making these diet changes, I would encourage the patient to speak with the doctor because there may be a 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. Also, 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.

References

Addona K. Pancreas and Nutrition: Your Diet for Pancreatitis, *Columbia University Department of Surgery Blog RSS.* Columbia University Medical Center, 14 Nov. 2012, 05 May 2014, http://www.columbiasurgery.net/2012/11/14/pancreas-and-nutrition-your-diet-for-pancreatitis/

Blansfield JA, et al., Clinical, genetic and radiographic analysis of 108 patients with von Hippel-Lindau disease (VHL) manifested by pancreatic neuroendocrine neoplasms (pNets), *Surgery*, 2007 Dec;142(6):814-8; discussion 818.e1-2, PMID: 18063061

Corcos O, et al., Endocrine pancreatic tumors in von Hippel-Lindau disease: clinical, histological and genetic features, *Pancreas*, 2008, 37:85-93, PMID: 18580449

Cunningham JC, et al., An Introduction to Cystic Fibrosis for Patients and Their Families, 6th ed., *Cystic Fibrosis Foundation*, 2013. http://www.cff.org/UploadedFiles/LivingWithCF/StayingHealthy/Intro-to-CF.pdf.

Find a CF Care Center, *Cystic Fibrosis Foundation, n.d.*, http://www.cff.org/LivingWithCF/CareCenterNetwork/CFFoundation-accreditedCareCenters/.

Hammel P, et al., Pancreatic involvement in von Hippel-Lindau disease: prevalence, course and impact in the management of patients, *Gastroenterology*, 2000, 119: 1087-1095. PMID: 11040195

Nutrition Advice & Recipes, *National Pancreas Foundation*, 2014, http://www.pancreasfoundation.org/patient-information/patientfamily-information/nutrition-advice-recipes/.

Staying Healthy, *Cystic Fibrosis Foundation n.d.*, 05 May 2014, http://www.cff.org/LivingWithCF/StayingHealthy/.

Toouli J, et al., Management of pancreatic exocrine insufficiency: Australasian Pancreatic Club recommendations, *Med J Aust*, 2010; 193(8): 461-467.

VHL in the Kidneys

The kidneys are organs located in the back of the abdominal cavity which are about 12 cm (4 inches) long, or about the size of the fist. (See Figure 4.) VHL in the kidney may cause cysts or tumors to form. It is common for any adult in the general population to have an occasional kidney cyst. VHL cysts are usually multiple. The presence of one or more simple cysts is not a problem in itself. However, each cyst may contain a small tumor, and it is possible for these tumors to become *renal cell carcinomas (RCC)*, one kind of kidney cancer, formerly known as *hypernephroma*.

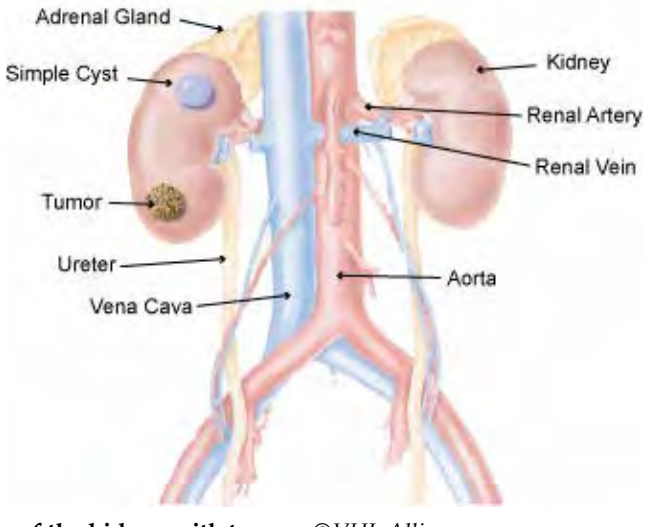


Figure 4. Diagram of the kidney with tumor: ©*VHL Alliance*

There are generally no specific physical signs to indicate the presence of kidney cysts and tumors early, so it is critically important to begin monitoring the kidneys long before any obvious physical symptoms or signs occur. The kidneys continue to function while these structural changes are occurring without physical symptoms, and with normal blood and urine tests.

Think of it as having a mole on your skin, except that you cannot see that it is growing. When it is very small there may be no cause for alarm. When the mole begins to grow or change in suspicious ways, your doctor would recommend that it be removed.

Similarly, when a kidney tumor is quite large when discovered, if it changes shape, size, 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 surgical resection (removal of the tumor). Once VHL kidney tumors appear, they act like *Clear Cell Renal Cell Carcinoma (ccRCC)* which represents 75%–80% of *sporadic* RCC occurring in the general population. The biggest difference is that in VHL there is the opportunity to find them earlier than people who have sporadic kidney cancer. That provides better options for dealing with the tumor early and allowing the kidney to function as long as possible while avoiding the worst consequences of cancer—metastasis. Knowing that someone with VHL is at risk for RCC, the tumors can be found at much earlier stages. If you wait for symptoms, the tumor will usually be at a much later and more dangerous stage when it is found.

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. Clearly, one cannot remove every little tumor, since that would be too many surgeries for the person, and this small organ, to endure. The goal is to maintain the patient's own kidney function throughout his or her lifetime, to minimize the number of surgeries, and remove tumors before they metastasize and cause the cancer to grow in other organs. The tricky part is to choose the right moment to operate—not too early and not too late.

The objective is to track the progression of the cells from harmless (benign) to the point before they become capable of spreading (metastatic). 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.

Figure 5. 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.

There is a similar transition in cancer. Cancer researchers have identified a series of distinct steps that the cells go through before they are even capable of metastasizing.

It would be ideal if there were some easy blood or urine test—some biomarker—to check on the cell progression. There is no such test at this time though there is a great deal of research effort to find one. Meanwhile, clinical research has shown that the size of a solid tumor is one relatively crude but fairly reliable sign of its progress.

Biopsies are usually not called for in this case, since with a diagnosis of VHL one is pretty certain what the structure will contain. There will be cancer cells even in very small tumors. The question is: what is their level of progression? This is not a question that can be answered accurately through a biopsy.

Cysts are generally not considered sufficient cause for to operate. In the rare event a tumor is present in the wall of a cyst, it will be important to watch the size of that tumor, not of the cyst. MRI imaging of the kidneys both with and without contrast agents as detailed in the VHL Screening Guidelines (Section 1; vhl.org/screening-guidelines) is a reliable way to follow these tumors.

The consensus from the VHL International Medical Symposium meeting in 1994 (Freiburg, Germany) was to recommend surgery only when the largest tumor is larger than 3 cm. This recommendation was verified by a multi-center study led by the late Dr. Andrew Novick. All the VHL study teams, worldwide, now concur with this guideline. After nearly 20 years of experience using these guidelines, there are only three verified reports of metastasis from tumors smaller than 4 cm; all of which were at or greater than 3 cm.

In summary, 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. In addition to the 3 cm guideline for the longest tumor diameter, your doctor will look at the size of the tumor 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.

In watching the kidneys, your medical team is working to evaluate whether there are cysts or solid tumors. Magnetic resonance imaging (MRI) or computed tomography (CT) are the best methods of medical screening. The doctors will watch the tissue density, the position of the tumors, their size, and the rate of growth. MRI is preferred in most cases as it does not use radiation and can detect even those tumors located within a cyst.

It is important that you understand in as much detail as you can 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 compact discs (CDs) can easily be sent to a consulting physician far away, even in another country. Contact a VHL Clinical Care Center or the VHL Alliance for assistance in locating an expert who can assist you.

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

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 kidney, itself. Since the new kidney has the donor's genetic structure and two healthy copies of the VHL gene, it is not at risk for VHL tumors. Immune suppression for transplantation has not been seen to increase the growth of VHL tumors in other organs.

Imaging Considerations with Reduced Kidney Function

People with low creatinine clearance (due to reduced kidney function) need to be protected from any side effects of the *contrast dyes* used in contrast-enhanced CT scans and MRIs. 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. Typically, for patients with an estimated *glomerular filtration rate* (GFR) of less than 60 and greater than 45 undergoing CT scans, fluids are given to flush the kidneys. CT scans require *iodine contrast* which can harm kidneys when the estimated GFR is less than 40–45, so iodine contrast is not given to those patients. For MRI, the *gadolinium* contrast does not harm the kidneys, but in those with much reduced kidney function can cause skin side effects. Therefore for 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.

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 affects overall kidney function, you may develop reduced kidney function (also called Chronic Kidney Disease or CKD).

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 Center's (nationalkidneycenter.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 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 3, 5, 7 years in 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 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 fluid 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. Your dietitian can help you create a diet to fit your needs. 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.

The National Kidney Foundation (kidney.org) has chapters in most states. It is an excellent resource for programs and educational materials to help people with kidney disease and their families.

Carbohydrates

If you are overweight or have diabetes, you may need to limit the amount of carbohydrates you eat. 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.

Hard candies, sugar, honey, and jelly. If needed, you can even eat high-calorie desserts such as pies, cakes, or cookies, as long as you limit desserts made with dairy, chocolate, nuts, or bananas.

Fats

Fats can be a good source of calories. Make sure to use monounsaturated and polyunsaturated fats (olive oil, canola oil, safflower oil) 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.

Calcium and phosphorus

Calcium and phosphorus, two other 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 foods you eat because they contain large amounts of phosphorus. This includes milk, yogurt, and cheese. Some dairy foods are lower in phosphorus, including tub margarine, butter, cream cheese, heavy cream, ricotta cheese, brie cheese, sherbet, and nondairy whipped toppings.

Fruits and vegetables contain only small amounts of phosphorus, but may contain large amounts of potassium.

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.**

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. Ask your doctor, nurse, or dietitian.

If diet changes to lower phosphorus 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 is 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 much food that contains a lot of water, such as soups, gelatin desserts, popsicles, ice cream, grapes, melons, lettuce, tomatoes, and celery.

Use smaller cups or glasses and turn over your cup after you have finished it.

Tips to keep from becoming thirsty include:

- Avoid salty foods
- Freeze some 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

Salt or sodium

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 per serving. Also, avoid foods that list salt near the beginning of the ingredients. Look for products with less than 100 mg of salt per serving.

HEALTHY TIP: **Salt is not the only way to make your food flavorful.**

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

Do not use salt when cooking and take the salt shaker 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.

References

Cho E, et al., Epidemiology of Renal Cell Cancer, *Hematol Oncol Clin N Am*, 2011 (25): 651-665

Duffey BG, et al., The Relationship Between Renal Tumor Size and Metastases in Patients with von Hippel-Lindau Disease, *J Urol*, 172: 63-65, 2004. PMID: 15201738

Goldfarb DA, et al., Results of renal transplantation in patients with renal cell carcinoma and von Hippel-Lindau disease, *Transplantation*, 1997 Dec 27;64(12):1726-9. PMID: 9422410

Joly D, et al., Progress in nephron-sparing therapy of renal cell carcinoma and von Hippel-Lindau disease. *J Urol*. 2011, 185:2056-60, PMID: 21496837

Kidney Disease Nutrition and Diet, *The National Kidney Foundation: A to Z Health Guide*, The National Kidney Foundation, n.d., https://www.kidney.org/atoz/atozTopic_Nutrition-Diet.cfm.

Lin H. Diet - Chronic Kidney Disease, *MedlinePlus Medical Encyclopedia*, U.S. National Library of Medicine, 21 Sept. 2011, http://www.nlm.nih.gov/medlineplus/ency/article/002442.htm.

Living with Kidney Disease, *National Kidney Center*, National Kidney Center.org, Inc., http://www.nationalkidneycenter.org/chronic-kidney-disease/living-with-kidney-disease/

Matin SF, et al., Patterns of intervention for renal lesions in von Hippel-Lindau disease, *BJU Int*, 2008 Sep; 102(8):940-5, Epub 2008 May 15, PMID: 18485044

Nutrition and Chronic Kidney Disease, *National Kidney Foundation, Council on Renal Nutrition*, National Kidney Foundation, New York: National Kidney Foundation, 2006, http://www.kidney.org/atoz/pdf/nutri_chronic.pdf

Shuch B, et al., Repeat partial nephrectomy: surgical, functional, and oncological outcomes, *Curr Opin Urol*, 2011, Sep; 21(5):368-75, doi: 10.1097/MOU.0b013e32834964ea. PMID: 21788903

Steinbach F, et al., Treatment of renal cell carcinoma in von Hippel-Lindau disease: a multicenter study, *JUrol*, 1995 153:1812-1816

Srinivasan R. "Tumor Growth Rate and VHL," vhl.org/Ask the Expert

VHL in the Eye

When capillaries form hemangioblastomas (also called retinal capillary hemangioblastomas or retinal angiomas) in the back of the eye, they start out extremely small and difficult to see. The capillaries themselves are less than the diameter of a red blood corpuscle, one of the cells that make up the blood.

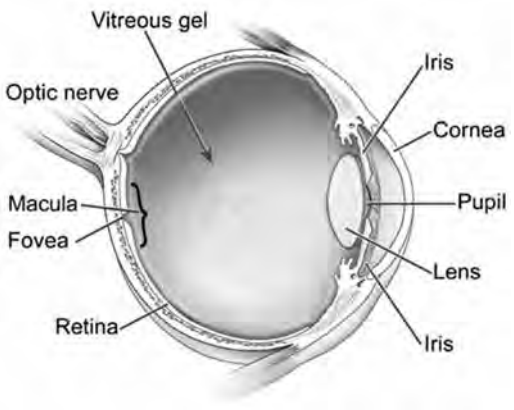


Figure 6. Diagram of the eye: Source: *National Eye Institute*: nei.nih.gov/health/eyediagram

When hemangioblastomas begin, they often grow around the equator or periphery of the retina, far away from the area of central vision. Unlike the equator drawn around the globe of the world, the equator of the eye is vertical. As you stand, draw a circle around your eye from eyebrow to nose and around—this is the equator.

To see this area, your *ophthalmologist* or *optometrist* must dilate your eye, use high-powered magnifying lenses, and look from side angles. It is more than the usual eye examination. Tell your doctor if there is VHL in your family so that he or she will be sure to do this thorough examination and find any small hemangioblastomas. Treating them in the early stages is important. A referral to a retinal specialist will be required for treatment of these tumors.

Not all ophthalmologists and optometrists are familiar with VHL; it is better to use a specialist familiar with VHL who is qualified to perform a thorough dilated examination of the *fundus* and *periphery* with an indirect *ophthalmoscope*.

The objective of treatment is to stop growth of the hemangioblastoma while it is still so small that it does not affect your vision. Treatments generally include laser treatment (light surgery) or *cryotherapy* (freezing). If the retina is detached from the back of the eye as a result of leakage from the hemangioblastoma or as a result of *fibrous* tissue that has grown in the eye and pulling on the retina, then *vitreoretinal* surgery may be necessary. Leaflets on these treatments are produced by the American Academy of Ophthalmology and other professional associations, which are usually available from your ophthalmologist or retinal specialist.

Sixty percent of people with VHL have retinal lesions. People as young as 3 and sometimes even younger can be affected, making screening children very important. Children who have a positive DNA diagnosis of VHL should be screened for eye lesions beginning at age 1.

New hemangioblastomas can occur throughout life, so regular eye exams in affected individuals are important. Generally, smaller lesions can be treated more successfully and with fewer complications than larger ones. Leakage or bleeding from larger hemangioblastomas can lead to serious vision damage or retinal detachment, so early treatment and careful management is very important to preserve vision. Untreated or partially-treated hemangioblastomas that are not actively bleeding or leaking can stimulate the growth of fibrous tissue in the eye that can endanger vision and need to be regularly assessed.

Lesions on or near the optic nerve are very difficult to treat successfully, and there is no consensus among doctors on the best treatment approach. Fortunately, they tend to grow slowly. Contact the VHL Alliance for the latest recommendations.

References

Gorin, MB, et al., von Hippel-Lindau disease: clinical considerations and the use of fluorescein-potentiated argon laser therapy for treatment of retinal angiomas. *Seminars in Ophthalmology*, 1992 Sep 7(3):182-91

Dollfus H, et al., Ocular manifestations in von Hippel-Lindau disease: a clinical and molecular study, *Invest. Ophthalmol Vis Sci* 2002, 43: 3067-74. PMID: 12202531

Gaudric A, et al., Vitreoretinal surgery for severe retinal capillary hemangioglastomas in von Hippel-Lindau disease, *Ophthalmology*, 2011, 118: 142-9, PMID: 20801520

Laser Surgery in Ophthalmology and Cryotherapy, *American Academy of Ophthalmology*, online brochures, AAO, P.O. Box 7424, San Francisco, CA 94120-7424. 1 415 561-8500. http://www.aao.org

Wong WT, et al., Ocular von Hippel-Lindau disease: clinical update and emerging treatments, *Curr Opin Ophthalmol*, 2008 May;19(3):213-7, Review, PMID: 18408496

The National Eye Institute (nei.nih.gov) and the National Library of Medicine (www.nlm.nih.gov) are both excellent resources for new terms and treatments.

VHL in the Adrenal Glands (Pheochromocytomas)

VHL may be associated with a kind of tumor of the adrenal glands called a *pheochromocytoma*, *("pheo")*. Pheos are usually noncancerous and most commonly occur in the adrenal glands. Pheos located outside the adrenal glands are called *paragangliomas*; these tumors are very rare, even in VHL patients.

The adrenal glands are approximately 3 x 2 x 2 cm (1 inch long) perched on top of each of the kidneys. (See Figure 7.) The adrenal glands make hormones in the body, 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 and 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).

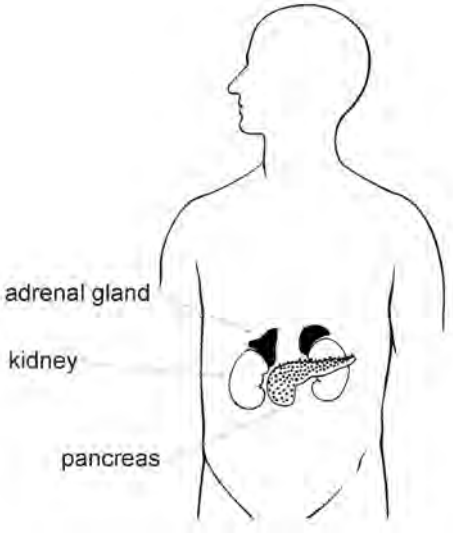


Figure 7. Kidney, pancreas, and adrenal glands: The figure shows the relative positions of these organs. Illustration by Gerhard Spirzer, from Kahle et al., *Color Atlas*, 2:141.

Pheos occur more frequently in some families than in others. They are rarely malignant (<7%) among people with VHL. Detected early, pheos are not difficult to deal with, but they are potentially lethal if not treated. This is especially true during times of stress, such as surgery, accidents, or childbirth. It is particularly important for patients with VHL with or without symptoms to be checked for a pheo prior to any surgery, pregnancy, or childbirth. If a pheo is present, complications may be avoided by blocking off the effects of stress hormones with drugs beginning at least 7–14 days before the procedure.

Pheos secrete excessive amounts of catecholamines, norepinephrine and epinephrine, also known as "stress hormones." However, pheos in VHL only produce norepinephrine (also known as noradrenaline). The primary clinical sign is usually high blood pressure, especially spiking blood pressure, that puts strain on the heart and vascular system, which can cause a heart attack or stroke. In some patients, though, blood pressure 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 heavy sweating for no good reason. Sometimes people have hot flashes (or cold flashes). There may be abdominal pain or unexplained weight loss. It is recommended that all people with VHL be screened for pheos. New 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 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.

If surgery is required, the standard of care in VHL patients is 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.

In recent years, the "key hole" operating technique (*laparoscopy*) is being 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.

For more information on pheochromocytomas, visit science.nichd.nih.gov/confluence/display/pheo/Home.

Testing for a Pheochromocytoma

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 "plasma-free metanephrines" test involves measurement in a sample of blood of both metanephrine, the metabolite of adrenaline, and normetanephrine, the metabolite of noradrenaline. More widely available is the 24-hour urine collection, analyzed for fractionated metanephrines, normetanephrine, and metanephrine. If additional information is required or if there are symptoms of a pheo, but the blood and urine tests are negative, anatomical imaging scans may be used.

In patients with VHL, it is the measurement of normetanephrine that is most important since associated pheos do not produce adrenaline or its metabolite, metanephrine, in significant amounts. *Methoxytyramine* is a new *biomarker* for the diagnosis of pheos and was introduced in 2011 as a measurement tool. However, only about 17% of VHL patients with pheos produce methoxytyramine. An increase in methoxytyramine can be useful to assess malignancy.

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. Even if no instructions are provided, you should avoid tobacco, alcohol, and caffeine for at least four hours before the test. Be sure to tell your doctor and the technician if you are taking any antidepressant or mood-altering medication. You might want to prepare a list of all the medications

you are taking, discuss this list with the doctor before the test, and even send it along to the lab with the blood or urine sample, to assist in interpreting the results.

Where other instructions are given, they may differ from center to center, sometimes due to different methods of analysis. Follow any instructions carefully to avoid a false reading. See Preparing for Pheo Testing.

2014 Testing Standards for Pheochromocytoma and Paraganglioma

New clinical guidelines were recently approved by the Endocrine Society (June 2014) for testing for the presence of pheochromocytomas and paragangliomas, together known as PPGLs.

> **Screening for PPGLs** should always include measurements of plasma-free metanephrines (obtained from a blood sample) or urinary fractionated metanephrines (obtained from a urine sample).
>
> **For a blood sample**, it is now recommended that patients be supine (lying down) for a minimum of 20 (ideally 30) minutes between the time the needle is inserted and the time the blood is drawn.
>
> **For blood sample analysis**, upper reference intervals (the test result above which a pheo is determined to be possible) should be established from supine tests, not seated tests, to minimize the chance of a false negative result (missing a PPGL that is present).

The decision was made based on the finding that seated blood testing results increased false positives, meaning that these patients must be retested. The reason for this is that the release of catecholamines by peripheral nerves and the adrenal gland is stimulated by an upright posture resulting in increased blood levels of metanephrines in seated compared to supine positions of blood sampling.

The VHLA guidelines for pheo testing are based on the Endocrine Society clinical guidelines:

Measurement of plasma free metanephrines (with blood drawn following 20–30 minutes in a supine position following needle insertion) or urinary fractionated metanephrines (with patient adherence to recommended collection and refrigerated storage). Analysis is performed using *liquid chromatography* 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 *localize*, or locate, a pheo, even if it is outside the adrenal glands. Pheos located outside the adrenal glands are called paragangliomas. These very rare tumors may occur anywhere

on the *sympathetic nervous system*, meaning anywhere along a line drawn from your groin to your ear lobe on either side of the body. Multiple tests may be needed to find them. According to research at the US 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 your 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, in fact, there but cannot be detected by that particular test. You may need to seek a second opinion from a VHL or pheochromocytoma expert.

Preparing for Pheochromocytoma Testing

It is most important to test for pheochromocytomas before undergoing surgery for any reason and before going through childbirth. Undergoing either of these stressful experiences with an unknown 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 any unborn child.

Testing of blood and urine are the best tests to determine whether an active pheo is present and whether additional scanning is needed to localize or find the tumor. The urine and blood tests for a pheo are most reliable when care is taken in two areas—diet prior to the testing and preservation of the urine sample from the start of the test until the lab processing is complete.

Medications are often recommended or self-prescribed. It is important to note that all medications may interfere with the accurate analysis of tests for pheo. If at all possible, testing for pheo should be done BEFORE beginning any medication. If this is not possible, then it is critically important that you disclose ALL medications you are taking—prescription, herbal, over-the-counter, and even illegal—in order to get an accurate reading from the tests. Such medications can interfere with the results, depending on the method of measurement used by the laboratory. Please adhere to any recommendations about medication indicated to you by the laboratory or your physician.

To get the best information from a 24–hour urine test, it is critically important that the patient carefully follow the pheo test instructions that go with the test. Not all hospitals provide these instructions to the patient and not all patients follow them conscientiously. Differences in instructions may reflect different methods of analysis.

Follow the instructions provided to you by your hospital lab staff. If instructions have not been provided, ask them if the instructions that follow would be good to ensure that the sample is fresh and that the chemical levels for which they are testing are not artificially influenced by things in your diet. It is also very important that the urine be carefully refrigerated and preserved throughout the 24–hour urine collection period and delivered fresh to the lab for immediate processing. Some people carry the jug in an insulated bag or backpack, with one or more plastic cold packs alongside the jug.

PREPARATION FOR BLOOD TESTING

Do not take any medications, including aspirin and acetaminophen, without the knowledge and agreement of the doctor ordering the test. In particular, be sure to discuss theophylline, anti-hypertensives (blood pressure medicines), methyldopa, L-dopa, or any diuretic, birth control pills, birth control patches, smoking cessation products, or any antidepressants or other mood-altering drugs. Theophylline is found in tea and some other herbal supplements as well as medications.

Refrain from eating or drinking anything except water from 10 PM the evening prior to your blood test; do not take any medications the morning of the test unless specifically approved by the doctor ordering the test. If you are instructed not to take your morning medications, take them with you to the test so that you can take them right after the completion of the test.

If you smoke, you should not smoke on the day of the test. Contact your physician if you have questions regarding your diet.

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.

Pheos in VHL-related tumors do not produce epinephrine (adrenaline) or its metabolite metanephrine. VHL-related tumors only produce norepinephrine and its metabolite, normetanephrine. Therefore, it is the value for plasma normetanephrine that one must watch carefully in patients screened because of VHL mutations. The chemical profiles for other genetic mutation types are different.

Upper limits for reference intervals of plasma concentrations of metanephrines in children (from samples collected lying down with an indwelling i.v.) are published:

For boys 5 to 18 years, the upper limit for normetanephrine is 97 picograms/milliliter (0.53 nanomoles/liter) and for metanephrine 102 pg/mL (0.52 nmol/L).

For girls 5 to 18 years, the upper limit for normetanephrine is 77 pg/mL (0.42 nmol/L) and for metanephrine 68 pg/mL (0.37 nmol/L).

The reference intervals for your 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, to achieve the highest sensitivity and selectivity in checking fractionated metanephrines, especially normetanephrine.

PREPARATION FOR 24-HOUR URINE TESTING

Vanillyl Mandelic Acid testing (VMA): This test should no longer be used because the diagnostic accuracy of *VMA* is insufficient.

For catecholamines, metanephrines, epinephrine, norepinephrine: On the day of the test, avoid tobacco, medications, chocolate, fruits (especially bananas), and caffeine. Be sure to tell your doctor and the technician what medications you are taking, including any antidepressants.

Collection instructions: 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 this 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 paper work 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).

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.

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 electrolytes) levels in the body. Aldosterone is produced by the adrenal glands, and if someone does not have 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 levels or no aldosterone are often categorized as "salt-wasters;" they cannot maintain salt (sodium) levels. These individuals must take supplements to replace the aldosterone hormone. 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. Some good liquid options include water (always the best liquid), 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, 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.

Please note that if you have had both of your adrenal glands completely removed, it is important to follow your prescribed daily dosages 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.

References

Adrenal Disorders, *LifeExtension.com*. Life Extension, n.d. http://www.lef.org/protocols/metabolic_health/adrenal_disorders_07.htm#dietary.

Asher KP, et al., Robot-assisted laparoscopic partial adrenalectomy for pheochromocytoma: the National Cancer Institute technique, *Eur Urol*, 2011 Jul;60(1):118-24. Epub 2011 Apr 9. PMID: 21507561

Eisenhofer G, et al., Measurements of plasma methoxytyramine, normetanephrine, and metanephrine as discriminators of different hereditary forms of pheochromocytoma, *Clin Chem*, 2011 Mar;57(3):411-20. Epub 2011 Jan 24. PMID: 21262951

Germain A, et al., Surgical management of adrenal tumors, *J Visc Surg*, 2011 Sep;148(4):e250-61. Epub 2011 Aug 5. PMID: 21820984

Grouzmann E, et al., Diagnostic accuracy of free and total metanephrines in plasma and fractionated metanephrines in urine of patients with pheochromocytoma, *Eur J Endocrinol*, 2010 May;162(5):951-60. Epub 2010 Feb 8. PMID: 20142367

Guidelines on Pheochromocytoma and Paraganglioma, *J Clin Endocrinol Metab*, June 2014, 99(6) 1916-1917

Hydration, "Salt Wasters" And Dehydration, *News Articles & Research – NADF*, National Adrenal Diseases Foundation (NADF), Aug. 2005, http://www.nadf.us/news-articles-research/

Kantorovich V, et al., Pheochromocytoma: an endocrine stress mimicking disorder, Ann *NY Acad Sci*, 2008 Dec;1148:462-8, PMID: 19120142

Loechner K, ed. *Adrenal Insufficiency and Addison's Disease*. NIH Publication no. 14–3054. National Endocrine and Metabolic Diseases Information Service (NEMDIS), Jan. 2014. http://endocrine.niddk.nih.gov/pubs/addison/addison.aspx.

Pacak K, et al., Pheochromocytoma, in Jameson, JL et al., (eds) *Textbook of Endocrinology*. 6th edition. Elsevier Science Inc., Philadelphia, 2010

Patient Education: Pheochromocytoma, *National Institutes of Health Clinical Center*, June 2007. http://www.cc.nih.gov/ccc/patient_education/pepubs/pheo.pdf.

Stéphane R. Presentation at the 4th International Symposium on Pheochromocytoma, Paris 2011

Yousef HB, et al., Laparoscopic vs open adrenalectomy: experience at King Faisal Specialist Hospital and Research Centre, Riyadh, *Ann Saudi Med*, 2003 Jan-Mar; 23(1-2):36-8. PMID: 17146220

Weise M, et al., Utility of plasma free metanephrines for detecting childhood pheochromocytoma, *J Clin Endocrinol Metab*, 2002 May;87(5):1955-60, PMID: 11994324

VHL and Reproductive Health

VHL lesions in the reproductive tract are classified as *cystadenomas*. In males, *epididymal* cystadenomas may occur in as many as 50% of men with VHL. Similarly, women with VHL may have cystadenomas of the *broad ligament* near the *fallopian tube*, the *embryological* counterpart to the *epididymis*. Both lesions are benign although they may sometimes cause pain.

For Men

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 of the testicle. It is a complex tubular system that gathers the sperm and stores them until needed. (See Figure 8.) After having been stored in the epididymis, sperm then moves through the vas deferens to the prostate where they are mixed with seminal fluid from the seminal vesicles and move through the prostate into the urethra during ejaculation.

A small number of cysts are found in the epididymis of about 25% of men in the general population. By themselves, cysts are not an occasion for concern and are not even particularly noteworthy. However, one specific type of cyst is significant in VHL A cystadenoma is a benign tumor with one or more cysts inside it, having more *density* than a simple cyst. *Papillary* cystadenomas of the epididymis are a rare occurrence in the general population. In VHL, these cysts can occur on one or both testes. When they occur on both sides, they almost always mean a definite diagnosis of VHL. They range in size from 1 to 5 cm (0.3 to 1.7 inches). The man may feel a "pebble" in the scrotum. They are usually not painful and do not continue to enlarge.

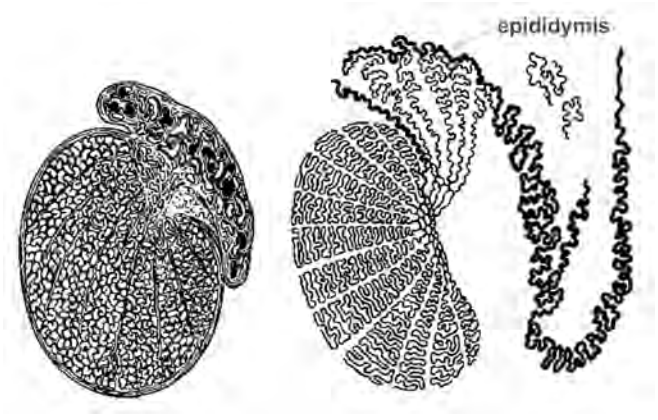


Figure 8. Epididymis: On the left, a cross-section through the testis and epididymis. On the right, the system of tubules of the testis and epididymis (see pointer). Illustration by Gerhard Spitzer, after Rauber-Kopsch, from Kahle et al., Color Atlas, 2:261.

Papillary cystadenomas of the epididymis may arise during the teenage years or later in life. It is not unusual for them to occur for the first time in men in their forties. The cysts can be removed if they are annoying. Removal is much the same operation as a vasectomy and may result in the disabling of the delivery of sperm from the operated side.

These cysts do not interfere with sexual function. In most cases, the only "problem" associated with cystadenomas is the minor annoyance of knowing it is there. Occasionally, depending on their position, cystadenomas may block the delivery of sperm and cause infertility. If a cystadenoma is painful, check with a doctor, since on rare occasions they can become inflamed and even rupture.

In some cases, they may cause atrophy of the vas deferens, which will also cause infertility. Men who wish to keep their childbearing options open may want to bank some sperm in their teens or twenties for possible later use.

Testicular Self-Exam

The best way to keep track of epididymal cysts is to do a Testicular Self-Exam (TSE) monthly, as recommended for all men in the general population. VHL does not increase the risk of testicular cancer. 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.

If there are lumps or swellings, it does not necessarily mean that you have testicular cancer, but you must be checked by your healthcare provider.

For Women

A corresponding tumor occurs in women, called an *Adnexal Papillary Cystadenoma* of Probable Mesonephric Origin (APMO). A cystadenoma is a benign tumor with one or more cysts inside it making it denser than a simple cyst. *Papillary* cystadenoma of the broad ligament are a rare occurrence in the general population.

The broad ligament is a folded sheet of tissue that drapes over the uterus, fallopian tubes and the ovaries. (See Figure 9.) Cells in this area are from the same origin in the development of the embryo as the epididymis in males.

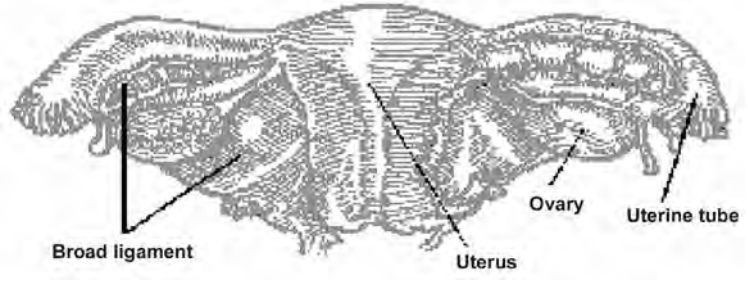


Figure 9. Broad ligament: The broad ligament is a large area of tissue that lies on top of the reproductive organs in women. Illustration by Frank James.

Cysts in this area are very common in the general population. However, 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. Ask the doctor to do a careful differential diagnosis to prevent over-treatment of benign tumors, which are sometimes confused with ovarian cancer.

Many physicians recommend that a woman with VHL limit her 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.

Pregnancy and VHL

Women with VHL should consider pregnancy carefully. There is no clear answer as to whether pregnancy promotes additional tumor growth, making it important for women to discuss a possible pregnancy with their doctor and medical team. Discuss 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 if testing in advance be performed. In addition, women should know what their risk factors are.

It is also important to discuss possible risk factors with your partner before making the decision to get pregnant. This is a joint decision. You might be willing to risk it, but is your partner willing to put you and possibly the baby at risk?

If you are already pregnant, tell your obstetrician and connect him or her with other members of your VHL medical team. Watch for symptoms and report any symptoms 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 women, since these can also be signs of brain and spinal tumors. Do not ignore them 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. You should always check with your medical team if there is cause for concern.

Doubling of blood volume: If you have a hemangioblastoma in the brain, spinal cord or retina, this increased blood flow may expand the tumor at least for a period of time during the pregnancy. Some women 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)* (See section, VHL in the Adrenal Glands: Pheochromocytomas)**:** It is important to get a thorough test for a pheo before planning a pregnancy, or as soon as you are pregnant, and especially before going through the birthing process. An active pheo can be life-threatening to you and your baby. Be sure to get checked—and re-checked—for a pheo during the pregnancy to avoid these complications. The issue is that pheo symptoms can be overlooked during pregnancy, assuming that high blood pressure is due to preeclampsia or another cause. Undiagnosed pheos can increase risk of maternal death from 2–4% for pheos diagnosed prior to pregnancy to 14–25%. This higher maternal mortality arises from difficulties in controlling blood pressure due to a pheo during pregnancy. For example, the blood pressure elevation can result in the premature separation of the placenta from the uterus, posing a life-threatening problem for the mother 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: You need to make sure that your kidney function is normal so that your kidneys will serve you and your baby well.

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, and to monitor progress during the pregnancy, including an MRI without contrast in the fourth month of pregnancy. The recommendations for special care during pregnancy include:

Having an MRI—without contrast—during the fourth month of pregnancy, especially if you have known tumors of the brain or spinal cord, to check on any change in these lesions.

If you have eye, brain, or spinal lesions, a C-section should be considered in order to avoid pushing during labor which might aggravate these lesions. If a hemangioblastoma exists and a woman experiences pain during labor, there is an unknown effect of pain on the hemangioblastomas. Thus, having hemangioblastomas or noting changes in them during pregnancy may be a reason for recommendation of a C-section. This recommendation should occur based on a consultation with the neurosurgeon, anesthesiologist, and maternal-fetal medicine specialist.

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 can occur postpartum and thus the woman with VHL should be examined carefully, especially if any new symptoms arise.

A frequent question asked is "Does pregnancy have any effects on the growth of tumors or cysts associated with VHL?" What is known about VHL-associated hemangioblastomas during pregnancy is derived from a few small studies. One study included 30 women with 56 pregnancies. These women were all very healthy; only one had VHL symptoms before pregnancy and only one had an increase in CNS pressure. Another study was comprised of only 9 pregnant patients and 26 non-pregnant patients. This study reported no change in the hemangioblastomas during pregnancy, but the sample size on which this conclusion is based is very small. Another study describing 29 patients with VHL who became pregnant reported that 17% of pregnancies had various complications due to VHL:

1) cerebellar hemangioblastomas may progress and cause problems
2) pheos can increase risk for both mother and baby
3) pancreatic cysts can rupture
4) there are no studies that report the effects on kidney lesions

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 participation in the VHL Alliance's online clinical study, the **Cancer in our Genes International Patient (CGIP) Databank: vhl.org/databank.**

Pre-Implantation Genetic Diagnosis

Pre-implantation genetic diagnosis (PGD) was developed in the United Kingdom in the 1980s as an alternative to *prenatal diagnosis*, and the first baby conceived using this method was born in London in 1989. 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 woman's 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, DNA testing must be done from embryos, not from banked eggs or sperm.

It takes pre-planning to accomplish this, since the DNA testing must be accomplished in a very short time. Before the IVF process can be started, a test must be prepared for analyzing the VHL status of the embryonic sample. This will require sending DNA samples to the testing lab. Samples from the VHL parent and sometimes also from other close relatives are needed if the parent with VHL has not had previous DNA testing 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, not all, VHL mutation types. Each embryo to be implanted must have DNA testing for the VHL mutation present in the affected parent. IVF-PGD can be costly: check with your health insurance about coverage specifically for VHL—**ICD-10 code Q85.8**. Countries outside of the US may use a different code, or may cover this procedure as part of national health insurance.

It is important to make sure that insurance will cover both the fertility treatment required to obtain the embryos for testing and the genetic testing fee. It is also important to know that the process may take several cycles before it succeeds.

Some studies have demonstrated that for couples the experience of 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.

If you would like to explore this option, contact a certified Fertility Clinic offering In-Vitro Fertilization with Pre-implantation Genetic Diagnosis (PGD).

The VHL Alliance knows of multiple healthy children born to couples with VHL using this method. Please share your experiences with pre-implantation genetic diagnosis by participating in the Databank (vhl.org/databank).

References

Abadie C, et al., The role of pregnancy on hemangioblastomas in von Hippel-Lindau disease: a retrospective French study, *9th International Symposium on VHL*, Rio de Janeiro (Brazil). 2010 Oct 21–24

Aydin H, et al., Clear cell papillary cystadenoma of the epididymis and mesosalpinx: immunohistochemical differentiation from metastatic clear cell renal cell carcinoma, *Am J Surg Pathol*, 2005 Apr;29(4):520-3. PMID: 15767808T

El-Sayed Y, Pregnancy and VHL, VHL *Alliance News*, 2001, www.vhl.org/newsletter/vhl2001/01eapreg.htm

Frantzen C, et al., Letter to the Editor, *J. Neurosurg*, 2013 March, calling for a larger global study.
Frantzen C, et al., Pregnancy-related hemangioblastoma progression and complications in von Hippel-Lindau disease, *Neurology*, 2012 Aug 21; 79(8):793-6. PMID: 22875085
Fugueroa E. How to Perform a Testicular Self-Examination, *kidshealth.org*, Alfred I. DuPont Hospital, Wilmington, DE, and Jefferson Medical Center, Philadelphia
James GP. Hastening the Road to Diagnosis: the Role of the Broad Ligament Cystadenoma in Early Detection of VHL. *VHL Alliance News*, 1998, www.vhl.org/newsletter/vhl1998/98ccapmo.php or search for "James and APMO"
Janovski NA, et al., Serous Papillary Cystadenoma arising in Paramesonephric rest of the mesosalpinx, *Obstet Gynecol*, 1963 Nov;22:684-7, PMID: 14082297
Lenders J. Endocrine disorders in pregnancy: Phaeochromocytoma and pregnancy: a deceptive connection, *Eur J Endocrinol*, 2011 Sep 2, PMID: 21890650
Odrzywolski KJ, et al., Papillary cystadenoma of the epididymis, *Arch Pathol Lab Med*, 2010 Apr;134(4):630-3, PMID: 20367315
Stratton P. Gynecology and Reproductive Health Issues in VHL, 2014 VHLA Annual Meeting presentation
Ye B, et al., Effect of pregnancy on hemangioblastoma development and progression in von Hippel-Lindau disease, *J Neurosurg*, 2012 Nov; 117(5):818-24, PMID: 22937928
Zanotelli DB, et al., Bilateral papillary cystadenoma of the mesosalpinx: a rare manifestation of von Hippel-Lindau disease, *Arch Gynecol Obstet*, 2010 Sep, 282(3):343-6, Epub 2010 Feb 16, PMID: 20157715

Hearing Changes and VHL

The screening protocol includes a recommendation that you go regularly for an audiometric hearing examination. You should have a "baseline" study to document the state of your hearing soon after the diagnosis of VHL is made and periodically thereafter to verify that it has not changed.

If you sense changes in your hearing or other indications of inner ear problems, you should follow up with a *neurotologist*. MRI of the Internal Auditory Canal should be used to check for an *Endolymphatic Sac Tumor (ELST)*, which may occur in about 15% of people with VHL. The combined MRI recommended in the screening protocol is designed to monitor this area as well. (See Section 1, Suggested Screening Guidelines.)

An ELST forms in the endolymphatic sac behind the inner ear. The endolymphatic duct runs from the inner ear to the back surface of the *petrous bone* and ends beneath the dura as a flattened expansion, the endolymphatic sac. (See Figure 10.) This tiny structure is filled with fluid (called endolymph) and has a delicate system of pressure regulation

that is responsible for balance and equilibrium. Menière's disease is another condition that is caused by a disturbance in this area. With similar symptoms, ELSTs are often misdiagnosed as Menière's disease.

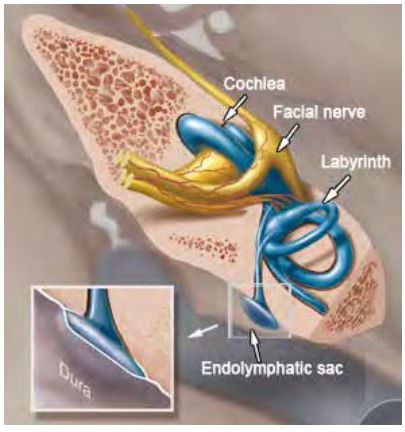


Figure 10. The inner ear, showing the endolymphatic sac (ELS): Illustration courtesy of Dr. Lonser, then at US NIH. As published in The *VHL Alliance News*, 12:2, September 2004.

People report hearing changes which range 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. Other symptoms may include *tinnitus* (ringing in the ears), dizziness, fullness in an ear, or facial weakness.

Once hearing is lost, it is very difficult to regain, making it is very important to watch for early symptoms and address the problem carefully in order to try to preserve hearing. If there is a loss of hearing, swift action is needed if there is to be any hope of preserving it. If your local team is not familiar with ELST, please check with the nearest VHL Clinical Care Center (vhl.org/ccc), or with the VHL Alliance office.

When an ELST is visible on an MRI, surgery should be considered to prevent disease progression and hearing loss. Careful surgical removal of the ELST 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.

There is one case reported where chronic ear infections were the first sign of an ELST in a 6-year-old. For this reason, a child with known VHL requires tubes for middle ear infections. An MRI of the internal auditory canal should be performed to evaluate for possible ELST and to prevent disease progression and hearing loss.

References

Butman JA, et al., Neurologic manifestations of von Hippel-Lindau disease, *JAMA*, 2008 Sep 17;300(11):1334-42, PMID: 18799446

Choo, DI, et al., Endolymphatic Sac Tumors in von Hippel-Lindau Disease, *J Neurosurg*, 2004; 100:480-487, PMID: 15035284

Kim HJ, et al., Tumors of the endolymphatic sac in patients with von Hippel-Lindau disease: implications for their natural history, diagnosis, and treatment. *J Neurosurg*, 2005 Mar;102(3):503-12, PMID: 15796386

Kim M, et al., Hemorrhage in the endolymphatic sac: a cause of hearing fluctuation in enlarged vestibular aqueduct, *Int J Pediatr Otorhinolaryngol*, 2011 Dec;75(12):1538-44, PMID: 21963424

Lonser RR, et al., Tumors of the Endolymphatic Sac in von Hippel-Lindau Disease, *NE J Med*, 2004, 350:2481-2486, PMID: 15190140

Megerian CA, et al., Evaluation and management of endolymphatic sac and duct tumors, *Otolaryngol Clin North Am*, 2007 Jun;40(3):463-78, viii. Review, PMID: 17544692
Poulsen ML, et al., von Hippel-Lindau disease: Surveillance strategy for endolymphatic sac tumors, *Genet Med*, 2011 Dec;13(12):1032-41, PMID: 21912262

VHL and the Liver

VHL is associated with multiple cysts in the liver called simple hepatic cysts. These relatively common lesions do not become malignant. They are present in 2–7% of the general population and can be seen using MRI, CT, or ultrasound imaging. Multiple cysts are more common in patients with certain diseases:

VHL
Polycystic liver disease
Polycystic kidney disease

One study found that 17% of VHL patients had liver cysts. None of these had been symptomatic.

This study also found other benign asymptomatic VHL lesions in the liver; liver adenomas in 3% and liver hemangiomas in 7% of VHL patients.

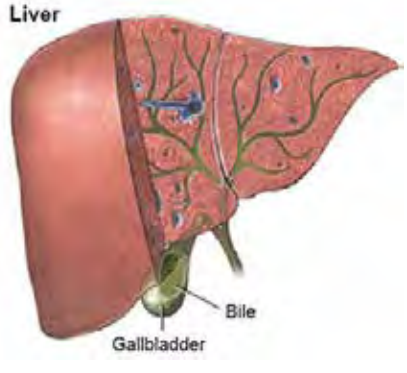


Figure 11. Diagram of the liver: Source: Courtesy of the *National Institutes of Health*: nlm.nih.gov/medlineplus/ency/imagepages/9104.htm

References

Rodrigeuz Gomez M, Neurocutaneous Diseases: A Practical Approach, *Butterworth-Heinemann* 1987, p. 60

VHL and the Lungs

VHL has been 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. At this point, the percentage of VHL patients who have these benign cysts is unknown as there have been just a few case reports in medical literature. Please add to the knowledge about these lesions by participating in the VHL Alliance Databank (vhl.org/databank). You can let us know whether or not you have been diagnosed with benign cysts or any other lesions in your lungs.

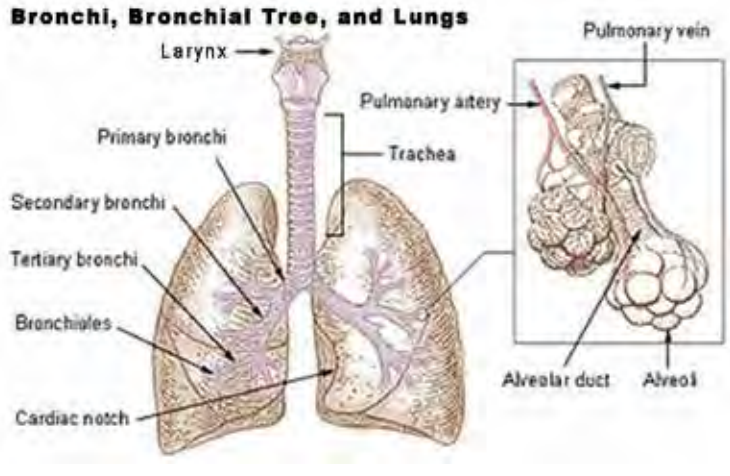


Figure 12. Diagram of the lungs: en.wikibooks.org/wiki/Human_Physiology/The_respiratory_system

References

Klein J, et al., Multifocal microcysts and papillary cystadenoma of the lung in von Hippel Lindau Disease, *Am J Surg Pathol*, 2007 Aug 31 (8): 1292-6

SECTION 3

Healthy Living for the VHL Family

Whether you are currently a patient, a caregiver, or a family member, there are many factors that affect your health; some you cannot control such as your genetic makeup or your age. But you can make changes to your lifestyle based on factors that are in your control.

There are three factors that are in our control that have a lot to do with our health:

1. How much we move
2. What we eat
3. How we feel emotionally

The choices you make every day affect your health and wellness. Choosing to be active, eat healthy foods, and improve your emotional wellbeing are the most important investments you can make in your life. Strive for the best health you can have in all areas of your life by making mindful, healthy choices. Take charge of your life and feel good about the choices you make!

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

Strive for balance in both your personal and work life

Make time for important relationships in your life

Ask for help whenever you need support from others

Find ways to relieve stress, such as physical activity and relaxation techniques

Be open-minded to try something new, like a hobby or activity

Talk to your family doctor, who can provide resources and advice when needed

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 your daily life and that you can take charge of and accomplish.

VHL puts you at greater risk for cancer, particularly *renal cell carcinoma (RCC)*. An individual affected with VHL will have a higher baseline risk for RCC 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—these factors could make the risk for RCC higher or lower than the baseline genetic risk. 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, you can reduce your cancer risk as much as possible.

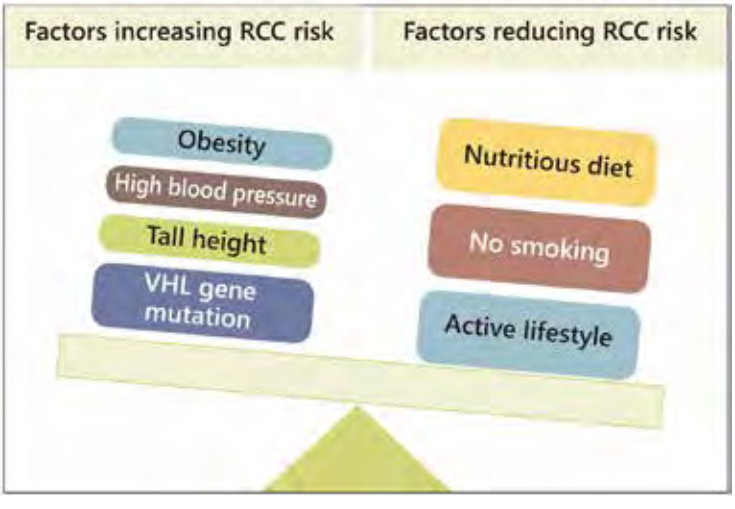


Figure 13. Factors increasing/decreasing RCC risk: Diagram by the VHL Alliance ©2015

You should 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 who have adrenal or kidney function problems, and someone with physical limitations may be limited to moderate exercise. Meet with your doctor or health care provider before making significant changes to your lifestyle or if you are concerned about your 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 600 thousand 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—over 4,000 chemicals, 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 you have stopped smoking for more than 10 years, the elevated risk from smoking is reduced.

E-cigarettes should not be considered a risk-free alternative to smoking. There is currently no FDA regulation, however studies show wide variability in nicotine levels. The FDA has found detectable levels of carcinogens both in the e-cigarettes and in second-hand emissions.

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 you 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 your house and out of your life is important to your health and to the health of your entire family.

References

Aberg A. *Socialstyrelsen*. Rep. no. 53. Sweden National Board of Health and Welfare, 9 Dec. 2011. http://www.socialstyrelsen.se.

Bjørge T, et al., Relation of height and body mass index to renal cell carcinoma in two million Norwegian men and women, *Am J Epidemiol*, 2004 Dec 15; 160(12): 168-76.

Cho E, et al., Epidemiology of Renal Cell Cancer, *Hematol Oncol Clin N Am*, 2011 (25): 651-665

Harmful Chemicals in Cigarettes, *Stop Smoking Programs.* N.p., 2012. http://www.stop-smoking-programs.org/chemicals-in-cigarettes.html.

Health Guides: Health Is a State of Mind and Body, *Health Education*. FamilyDoctor, Dec. 2010. http://familydoctor.org/familydoctor/en/prevention-wellness/staying-healthy/healthy-living/health-guides-health-is-a-state-of-mind-and-body.printerview.html.

Hu J, et al., Diet and vitamin or mineral supplements and risk of renal cell carcinoma in Canada, *Cancer Causes Control*, 2003 Oct 14(8):705-14

Lipworth L, et al., The epidemiology of renal cell carcinoma. *The Journal of Urology*, 2006, 176: 2353-2358.

Mann D. U.S. Has 7th Highest Cancer Rate in the World, *WebMD*. WebMD, 24 Jan. 2011. http://www.webmd.com/cancer/news/20110123/us-has-7th-highest-cancer-rate-in-the-world.

Rini BI, et al., Renal cell carcinoma. *The Lancet*, 2009; 373: 1119-32.

Sedghi A. Cancer Rates: See How Countries Compare Worldwide, *Theguardian.com*. Guardian News and Media, 24 Jan. 2011. http://www.theguardian.com/news/datablog/2011/jan/24/worldwide-cancer-rates-uk-rate-drops.

Statement on E-cigarettes, American Lung Association, March 2015. http://www.lung.org/our-initiatives/tobacco/oversight-and-regulation/statement-on-e-cigarettes

Tobacco, *World Health Organization (WHO)*. WHO International, July 2013. http://www.who.int/mediacentre/factsheets/fs339/en/.

Where to Get Help When You Decide To Quit Smoking, *National Cancer Institute*. National Cancer Institute at the National Institute of Health, 28 Oct. 2010. 27 Apr. 2014. http://www.cancer.gov/cancertopics/tobacco/smoking.

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. More specifically, 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 your health care team, it is best not to use supplements, but to rely 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 yourself of the foods you love. Rather, it is about feeling great, having more energy, stabilizing your mood, and keeping yourself as healthy as possible—all of which can be achieved by learning some nutrition basics and using them in a way that works for you. You can expand your range of healthy food choices and learn how to plan ahead to create and maintain a tasty, healthy diet. To set yourself up for success, think about planning a healthy diet as a number of small manageable steps rather than one big drastic change. If you approach the changes gradually and with commitment, you will have a healthy diet sooner than you think.

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 you can maintain for life, not just a few weeks or months, or until you have hit your ideal weight. So 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 your plate—it is also about how you think 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 yourself or others. It is time for a healthy relationship with food.

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

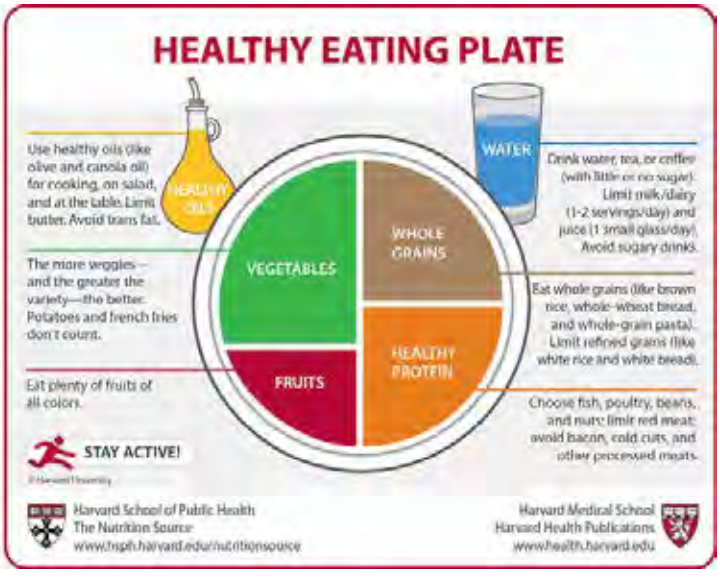


Figure 14. Healthy Eating Plate: Source: Willett et al., *Harvard School of Public Health*, 2011.

"One of the most important fields of medical science over the past 50 years is the research that shows just how powerfully our health is affected by what we eat. Knowing what foods to eat and in what proportions is crucial for health. The evidence-based Healthy Eating Plate shows this in a way that is very simple to understand."

—Anthony Komaroff, Professor of Medicine at Harvard Medical School and Editor in Chief of Harvard Health Publications, 2011.

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

Here are some additional tips for eating right and feeling good:

Whole Grain Foods (at most meals):

The body needs carbohydrates mainly for energy. The best sources of carbohydrates are whole grains such as oatmeal, whole-wheat bread, and brown rice. They deliver the outer (bran) and inner (germ) layers along with energy-rich starch. Seeds such as quinoa, buckwheat, spelt, flax, and amaranth are becoming more popular as grain substitutes. The body cannot digest whole grains and seeds as quickly as it can digest highly processed carbohydrates such as white flour. This keeps blood sugar and insulin levels from rising and then falling too quickly. Better control of blood sugar and insulin can keep hunger at bay, will decrease inflammation, and may prevent the development of Type 2 diabetes.

Foods containing fiber are linked to a reduced risk of cancer. These foods include whole-grain bread and pasta, oats, vegetables, and fruits. Fiber is thought to have many benefits, including helping to speed up how long it takes food to move through the digestive system.

Healthy Fats:

The importance of healthy fats is shown by the bottle of oil next to the Healthy Eating Plate (see Figure 14). Note that it specifically mentions plant oils, not all types of fat. Good sources of healthy unsaturated fats include extra-virgin olive oil, canola, and other plant oils, as well as fatty fish (salmon, trout, mackerel, sardines, anchovies, and herring). These healthy fats not only improve cholesterol levels (when eaten instead of highly processed carbohydrates), but can also protect the heart from sudden and potentially deadly rhythm problems. **Limit consumption of butter and try to avoid trans-fat.**

Healthy fats contain omega-3 fatty acids. They have been shown to reduce inflammation and may help lower the risk of chronic diseases. Inflammation is a process triggered by the immune system in which the body's white blood cells and chemicals help protect against infection and foreign substances such as bacteria and viruses. Sometimes the immune system triggers an inflammatory response when there are no foreign substances present. There is growing evidence that prolonged inflammation may have some influence on the course of diseases such as cancer, Alzheimer's, and heart disease. This is why omega-3 fatty acids may lower the risk of these diseases by reducing inflammation. Good dietary sources of omega-3 fatty acids include extra-virgin olive oil, expeller-pressed canola oil, nuts, hemp seeds, freshly ground flaxseed, and oily fishes.

HEALTHY TIP: **Eat nuts, but don't go nuts!**

Nuts, which contain unsaturated fatty acids and other nutrients, can be a great snack choice and part of a healthy diet. They are inexpensive, easy to store and easy to pack when you are on the go. Eating small portions of nuts could even reduce your risk of heart disease. This is because, along with other healthy nutrients, nuts contain unsaturated fats that help lower LDL (bad) cholesterol and raise HDL (good) cholesterol. Eating nuts may also help with blood flow by keeping the lining of the arteries healthy and reducing the risk of developing blood clots.

Nuts contain healthy fats, but too much of any fat is not good. As much as 80% of a nut is fat and even though most of this fat is healthy fat, it is still a lot of calories. Remember, for a heart-healthy diet, just adding nuts to your diet is not enough, it is also important to cut back on saturated fats found in many dairy and meat products.

To add nuts to your healthy diet, select raw or dry-roasted nuts rather than those cooked in oil and stay away from nuts covered with chocolate, sugar, or salt. The American Heart Association recommends eating four servings of unsalted nuts a week. A serving is a small handful (1.5 ounces) of whole nuts or 2 tablespoons of nut butter. These amounts can be increased if you are a vegetarian or vegan and most of your protein comes from plants.

NUTTY NUTRITION

Most nuts appear to be generally healthy, though some more so than others. Walnuts are one of the best-studied nuts; it has been shown they contain high amounts of omega-3 fatty acids. Almonds, macadamia nuts, hazelnuts, and pecans are other nuts that appear to be quite heart healthy. Peanuts, though technically a legume and not a nut, also seem to be relatively healthy.

Table 5. Nutrition information for a 1 ounce (or 28.4 grams) serving of different unsalted nuts: The protein, fat, and fiber content are given in grams.

	Amount in 1 oz.	Calories	Protein	Fat	Saturated Fat	Fiber
Almonds	23	165	6	14	1	3.5
Brazil Nuts	3	185	4	19	4	2
Cashews	18	155	5	12.5	2	1
Hazelnuts	21	180	4	17	1	2.5
Macadamia Nuts	10–12	205	2	21.5	3.5	2.5
Pecans	19 halves	195	2.5	20.5	2	2.5
Pine Nuts	167	190	4	19.5	1.5	1
Pistachios	49	160	6	13	1.5	3
Walnuts	14 halves	185	4.5	18.5	2	2
Peanuts	28	170	8	14.9	2.5	3

Adapted from Erwin, Jessie. "Nutty Nutrition and Kitchen Challenges." Stone Soup. Food & Nutrition Magazine, 21 Jan. 2013. 06 June 2014. foodandnutrition.org/Stone-Soup/January-2013/Nutty-Nutrition-and-Kitchen-Challenges/.

Lozicki S. "What's Inside That Nut?" E2dietitians Blog. E2dietitian, 3 Aug. 2011. 06 June 2014. e2dietitian.com/2011/08/03/933/.

Fruits and vegetables (and lots of them!)

A diet rich in fruits and especially in vegetables can decrease the chances of having a heart attack or stroke, protect against a variety of cancers, lower blood pressure, help avoid the painful intestinal ailment called *diverticulitis* (formation of pouches in the colon walls), guard against cataracts and macular degeneration, and add variety to your diet and wake up your palate.

Research shows that vegetables and fruits probably protect against a range of cancers, including mouth, pharynx, larynx, esophagus, stomach, lung, pancreas, breast, and prostate. There are many reasons why vegetables and fruits may protect against cancer. As well as containing vitamins and minerals, which help keep the body healthy and strengthen the immune system. They are also good sources of substances like phytochemicals. These are biologically active compounds, which can help to protect cells in the body from damage that can lead to cancer. Plant foods can also help maintain a healthy weight because many of them are lower in energy density (calories).

HEALTHY TIP: **Potatoes count as starches.**

Potatoes are currently the most common vegetable in the American diet but should be counted as starches, not vegetables. Both white and sweet potatoes are classified as starchy root vegetables along with yams, cassava, pumpkin, butternut squash, and other winter squashes. Although these starchy vegetables may provide excellent sources of certain nutrients such as beta-carotene from sweet potatoes, consumption should count as a starch in your diet. The skins of both white and sweet potatoes are good sources of additional fiber.

If you are going to include potatoes in your diet, it is important to remember that the preparation method is key. Fried potatoes, scalloped potatoes, and toppings such as butter, cheese, bacon, sour cream, and gravy should be an occasional treat. Keep in mind when planning meals that either bread or potatoes may be included, but routine meals need not include both.

The American Cancer Society recommends that you eat a combined 2½ cups of fruits and vegetables each day. This may sound like a lot, but it is easier than you think.

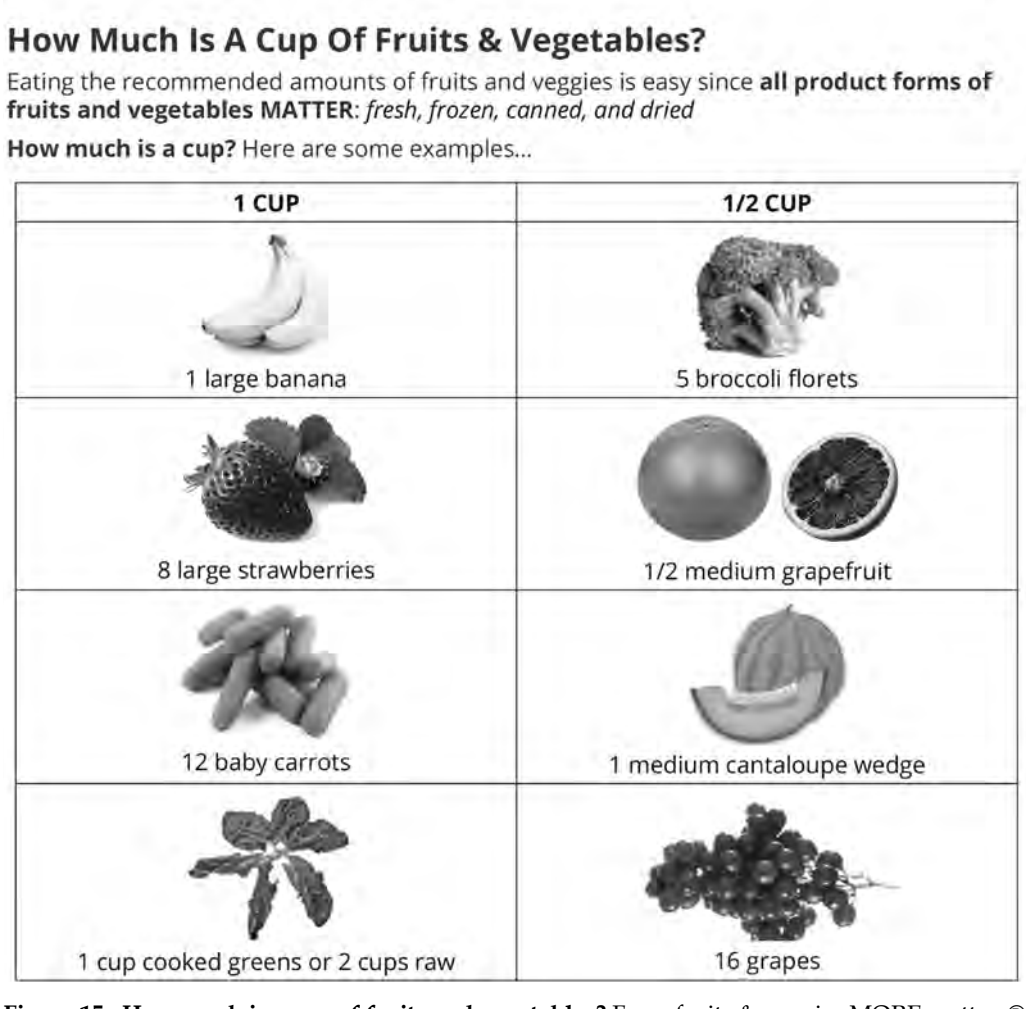


Figure 15. How much is a cup of fruits and vegetables? From fruits & veggies MORE matters®

Healthy Proteins

Choose healthy sources of protein like fish, poultry, beans, or nuts. A wealth of research suggests that eating fish can reduce the risk of heart disease. Chicken and

turkey are also good sources of protein and can be low in saturated fat. Eggs, which have long been demonized because they contain fairly high levels of cholesterol, are not as bad as they had been cracked up to be. In fact, an egg is a much better breakfast than a doughnut cooked in an oil rich in trans fats or a bagel made from refined flour.

Legumes, which include black beans, navy beans, garbanzos, lentils, and other beans, are excellent sources of protein, fiber, vitamins, and minerals. These can be purchased dried or in cans—just make sure to rinse the canned product to remove added salt. Tofu, made from soybeans, is also a healthy meat substitute. Try to substitute plant protein for animal sources at least once a week.

HEALTHY TIP: **Limit consumption of red meats and avoid processed meat.**

Red meat refers to beef, pork, and lamb—foods like hamburgers, steak, pork chops, and roast lamb. The term processed meat refers to meats preserved by smoking, curing or salting, or by the addition of preservatives. Examples include ham, bacon, pastrami, and salami, as well as hot dogs and sausages. Eat no more than 18 oz. (cooked weight) per week of red and processed meats. Eating these meats on a regular basis raises the risk of heart disease, Type 2 diabetes, colon cancer, and may result in weight gain.

When meat is preserved by smoking, curing or salting, or by the addition of preservatives, cancer-causing substances (carcinogens) can be formed. These substances can damage cells in the body, leading to the development of cancer. Additionally, there is convincing evidence linking red meat to cancer, as well as possibly heart disease. For example, red meat contains substances that are linked to colon cancer specifically. Heme iron, the compound that gives red meat its color, has been shown to damage the lining of the colon. Studies also show that people who eat a lot of red meat tend to eat fewer plant-based foods, so they benefit less from their cancer-protective properties.

The way meat, poultry, and fish are cooked can also result in creation of chemicals (heterocyclic amines) which may increase cancer risk. These chemicals occur when meat is cooked to the point of being charred or well-done at high temperatures. Grilled, barbequed, broiled, and pan-fried methods can all produce these potential carcinogens.

Beverages

Drink water; adding lemon to water is especially healthy

Drink tea or coffee with little or no sugar

Limit milk and dairy (1–2 servings per day)

Limit juice (1 small glass a day)

Use alcohol in moderation

Avoid sugary drinks (such as soft drinks)

Your choice of beverages is important especially since some beverages, such as sodas (pop, soft drinks) and sweetened fruit juices, can be sources of added or empty calories.

Milk (and other dairy products) is only one source of calcium, a necessary factor for building strong bones. Other sources include fortified soy milk, collards, bok choy, and supplements combining calcium with vitamin D. There is a lot of fat in whole milk (and other dairy products). Three glasses of whole milk, for example, contains as much

saturated fat as 13 strips of cooked bacon. If you choose milk, then try to stick with no fat or low fat products. (If you do not drink milk or consume other dairy products then you should consider a calcium supplement.)

Many studies suggest that having an alcoholic drink a day lowers the risk of heart disease. Moderation is clearly important, since alcohol has risks as well as benefits. For men, a good balance point is 1–2 drinks a day. For women, it is at most 1 drink per day.

***HEALTHY TIP:* Water is the best choice of beverage.**

Staying hydrated is important to good health. Believe it or not, two-thirds of the human body is made up of water. Every cell and organ depends on water to function properly. Water is critical to the balance of all the body's systems, including the brain, heart, lungs, kidneys, and muscles.

Remove waste and toxins
Transport nutrients and oxygen
Control heart rate and blood pressure
Regulate body temperature
Lubricate joints
Protects organs and tissue, including the eyes, ears, and heart
Creates saliva (important for the health of teeth and gums)

Note for those with reduced kidney function: Please see the Kidney section for specific dietary recommendations, including reduced intake of water and other fluids.

***HEALTHY TIP:* Check your vitamin D—vitamin D deficiency is common.**

Research shows that more than one-third of the population in the United States and other developed countries is deficient in vitamin D. Vitamin D is important for bone health and to keep the immune systems strong. While the body normally makes vitamin D when exposed to sun, we are living more of our lives indoors than ever before, limiting this source of vitamin D. People with reduced kidney function are particularly prone to vitamin D deficiency. Kidney and pancreas issues can interfere with vitamin D absorption. There is a simple blood test for vitamin D, which many doctors have already added to their routine blood testing. Ask what your levels are, and take vitamin D3 supplements to get your levels to at least 50 nanograms/milliliter (60–70 ng/ml preferred).

***HEALTHY TIP:* Nutrition supplements cannot replace healthy eating.**

It is better to choose a balanced diet with a variety of foods rather than take supplements, but in certain instances, your doctor may recommend a daily multivitamin. A standard, store-brand, RDA-level vitamin is fine. Look for one that meets the requirements of the USP (US Pharmacopeia) or another organization that sets standards for drugs and supplements.

***HEALTHY TIP:* Consider limiting salt intake.**

On a population level, consuming too much salt can be harmful to our health leading to poor vascular health, including high blood pressure, heart attacks and strokes. However, the effect on a particular individual can be difficult to predict. An *epidemiologist* and former president of the International Society of Hypertension explains that there are large individual differences in response to salt intake based upon kidney function. Certain people (elderly and some African Americans) appear to be hypersensitive to salt and will greatly benefit from reducing salt in their diets, while for others, a low-salt diet may result in a compensation mechanism that increases blood pressure.

The daily intake of salt should be less than 2,400 mg, but much less is needed, possibly as little as 200 mg. Most of the sodium in our diets comes from processed foods rather than salt added as a seasoning. We are not always aware that these foods are high in salt because they may not taste "salty," so make sure to read the sodium content on the Nutrition Facts label. Watch out for breakfast cereals, bread, frozen meals, pizza, chips, and salted nuts. Also, check the amount of sodium in canned products, such as soups and sauces, and avoid processed meats. Even sweet foods like cookies can contain high levels of salt. Reducing consumption of processed foods may be the best benefit of limiting your salt intake.

Other benefits of a small reduction in salt intake include improved vascular health which protects the kidneys and the heart. Salt restriction also lowers the risk of kidney stones by reducing the amount of calcium in the urine and appears to protect against diabetes, at least in Caucasians.

Those who have had their adrenal glands removed due to pheochromocytomas or who have *adrenal insufficiency (Addison's Disease)* generally need more salt in the diet. Please see the VHL in the Adrenal Glands (Pheochromocytoma) section for specific diet tips.

***HEALTHY TIP:* Limit sugar intake.**

Sugar is a source of calories with no benefit beyond being a source of energy. Eating too much sugar will cause weight gain not just from the excess calories, but because of how sugar affects appetite and eating habits. Sugar causes higher levels of the hormone *ghrelin*, which is responsible for sending signals to the brain indicating hunger. In addition, sugar interferes with levels of the hormone *leptin*, which sends signals to indicate satiety (feeling full). By affecting these hormones, sugar causes the feeling of being less full, making you more likely to eat more food than needed. Sugar also reduces *dopamine* (a hormone or neurotransmitter that plays a number of important roles in the human brain and body), signaling in the reward center of the brain, thereby decreasing the amount of pleasure received from food so that we want to eat more to achieve the typical level of pleasure gained from eating.

Do you know how much sugar you consume on a daily basis? The American Heart Association recommends that women have no more than six teaspoons of sugar per day (25 g), and men have no more than nine teaspoons per day (37 g). This equals to

about 100 calories for women and 150 for men. Most Americans eat more than double that much sugar in a day—about 22 teaspoons. That's 260 cups or 130 pounds (59 kg) of sugar each year.

It is common knowledge that soda (pop, soft drinks), candy, ice cream, and other similar foods are loaded with sugar. But there are many other foods and drinks with high sugar content that are not as well-known sources of sugar, including:

Tomato-based pasta sauces—Some brands contain about 15 g of sugar per ½ cup serving. In reality, most people consume about 1 full cup of sauce.

Beverages—Many beverages contain added sugar. For example, an average bottle of cola contains over 60 g of sugar, an 8 oz juice drink contains up to 23 g of sugar, and a 16 oz iced coffee with chocolate syrup, milk and whipped cream contains over 40 g of sugar.

Fat-free salad dressings—In order to preserve good taste but also eliminate fat, salad dressings often contain fairly high amounts of sugar. There could be as much as 8 g of sugar per 2 tablespoons of dressing.

Barbecue Sauce—Many brands are high in sugar and can contain close to 12 g of sugar in just 2 tablespoons of barbecue sauce.

Some sugary foods do not include "sugar" on the ingredient list. That is because sugar is often disguised under different names. Here are some hidden "sugar" words to look out for:

fructose	(natural sugar from fruits)
lactose	(natural sugar from milk)
sucrose	(made from fructose and glucose)
maltose	(sugar made from grain)
glucose	(simple sugar, product of photosynthesis)
dextrose	(form of glucose)
brown rice syrup	(rice malt)

Consider replacing regular sugar with natural sweeteners that contain antioxidants like molasses, agave nectar, honey, and maple syrup. But these sweet options still have about the same amount of calories as regular sugar, so be careful not to use too much.

Sugar, when eaten in small amounts, can fit into a balanced diet. If you have a sweet tooth, it is better to get your sugar fix from naturally sweet fruits than processed foods or artificial sweeteners. That way, you will satisfy your craving and get more of the nutrients your body needs.

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 a lot of 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 for development of type 2 diabetes.

Table 6. Glycemic index (relative to glucose) and glycemic load values for selected foods

Food	Glycemic Index (Glucose=100)	Serving Size	Carbohydrate per serving (g)	Glycemic Load per serving
Dates, dried	103	2 oz	40	42
Corn flakes	81	1 cup	26	21
Jelly beans	78	1 oz	28	22
Puffed rice cakes	78	3 cakes	21	17
Russet potato (baked)	76	1 medium	30	23
Doughnut	76	1 medium	23	17
Soda crackers	74	4 crackers	17	12
White bread	73	1 large slice	14	10
Table sugar (sucrose)	68	2 tsp	10	7
Pancake	67	6″ diameter	58	39
White rice (boiled)	64	1 cup	36	23
Brown rice (boiled)	55	1 cup	33	18
Spaghetti, white; boiled 10–15 min	44	1 cup	48	21
Spaghetti, white; boiled 5 min	38	1 cup	48	18
Spaghetti, whole wheat; boiled	37	1 cup	42	16
Rye, pumpernickel bread	41	1 large slice	12	5
Oranges, raw	42	1 medium	11	5
Pears, raw	38	1 small	11	4
Apples, raw	38	1 small	15	6
Skim milk	32	8 fluid oz	13	4
Lentils, dried; boiled	29	1 cup	18	5
Kidney beans, dried; boiled	28	1 cup	25	7
Pearled barley; boiled	25	1 cup	42	11
Cashew nuts	22	1 oz	13	3
Peanuts	14	1 oz	6	1

Source: Oregon State University Micronutrient Information Center, reviewed February, 2009

REFERENCES

A Backyard Chef's Guide to Healthier Grilling, *American Cancer Society*, May 20, 2013. www.cancer.org.

AICR video summary of this report: http://www.vimeo.com/21464219

Alcohol and Cancer Risk, *Fact Sheets: Diet and Nutrition*. National Cancer Institute, 24 June. 2013.

Campbell T, et al., The China Study, *Ben Bella Books*, 2005

Diet and Cancer Prevention: It's All About Eating Right, *Academy of Nutrition and Dietetics*, Dec. 2012. 28 Apr. 2014. www.eatright.org/Public/content.aspx?id=9904

Don't Use Supplements to Protect against Cancer, R*ecommendations for Cancer Prevention*. American Institute for Cancer Research (AICR), 29 June 2011. http://www.aicr.org/reduce-your-cancer-risk/recommendations-for-cancer-prevention/recommendations_08_supplements.html.

Diet, Nutrition, and Cancer Prevention: The Good News, *U.S. National Institutes of Health*, various publications are available from 1-800-4CANCER.

Do root vegetables like sweet potatoes count as vegetables or starches, and is it true that all of the nutrition is in the skins?, *boston.com*, May 2, 2011

Dyck, et al., The anticancer effects of Vitamin D and Omega-3 PUFAs in combination via cod-liver oil: One plus one may equal more than two. *Med Hypotheses*, 2011 May 30. PMID: 21632182

Ehrlich SD. "Omega-3 Fatty Acids." University of Maryland Medical Center. University of Maryland School of Medicine, 10 May 2011. http://umm.edu/health/medical/altmed/supplement/omega3-fatty-acids.

Espat A. Does Cancer Love Sugar?, *MD Anderson Cancer Center*. The University of Texas MD Anderson Cancer Center, Nov. 2012. http://www.mdanderson.org/publications/focused-on-health/issues/2012-november/cancersugar.html.

Food, Nutrition, Physical Activity and the Prevention of Cancer: a global perspective, 1997, 2007. http://www.dietandcancerreport.org/

Gnagnarella, P., et al, Glycemic index, glycemic load, and cancer risk: a meta-analysis, *Am J Clin Nutr*, 2008 Jun; 87(6): 1793-801

Harvard Healthy Eating Plate and discussion, *adapted from Willett, Eat, Drink, and Be Healthy, Harvard School of Public Health*, 2001, 2008, 2011.

Hydration 'Salt Wasters' and Dehydration, *News Articles & Research – NADF*. National Adrenal Diseases Foundation (NADF), Aug. 2005. http://www.nadf.us/news-articles-research/.

The Importance of Hydration, *Cancer.Net*. American Society of Clinical Oncology (ASCO), http://www.cancer.net/navigating-cancer-care/cancernet-feature-articles/importance-hydration.

Lipton B. Why You Should Start Your Day with Lemon Water, *Health Magazine*, Feb 24, 2015.

Lustig RH, et al., Public health: the toxic truth about sugar. *Nature*, 2012; 282: 27-29

Mantovani A, et al., Cancer-related inflammation. *Nature*, 2008; 454(7203):436-444.

Moyer MW. It's Time to End the War on Salt, *Scientific American*, July 8, 2011

Paul M, et al., Healthy Eating, *HelpGuide.org*, HelpGuide, Feb. 2014. http://www.helpguide.org/life/healthy_eating_diet.htm.

Nuts and Your Heart: Eating Nuts for Heart Health, *Mayo Clinic*, MayoClinic.org, 19 Feb. 2014. http://www.mayoclinic.org/diseases-conditions/heart-disease/in-depth/nuts/art-20046635?pg=1.

Nuts for the Heart, *The Nutrition Source*, Harvard School of Public Health, http://www.hsph.harvard.edu/nutritionsource/nuts-for-the-heart/.

Salt and your health, Part I: the sodium connection, *Harvard Men's Health Watch*, October 2010

The problem with potatoes, *The Nutrition Source*, Harvard School of Public Health, January 24, 2014

Wu S, et al., Vitamin D, Vitamin D receptor, and macroautophagy in inflammation and infection. *Discov Med*, 2011 Apr;11(59):325-35. PMID: 21524386

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. Check with your doctor to determine your own exercise tolerance. Moderate exercise, however, is good for everyone. So grab your athletic shoes and head out the door!

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 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 the 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. Similar guidelines from the American Cancer Society recommend a total of 150 minutes per week of moderate activity or 75 minutes per week of intense activity, preferably spread out into several sessions. Children and teens should have one hour per day, and at least 3 days with vigorous activity.

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 stay sharp as you age. It can also reduce your risk of depression and may help you sleep better. 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 give you these mental health benefits. Some scientific evidence has also shown that even lower levels of physical activity can 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. You may already exercise while you watch television; now you may want to try standing while working on your computer, or having a meeting while walking. It is recommended that you get up and move for 1–3 minutes every half hour.

Exercise Examples

Moderate Activity

Moderate activity is anything that gets your heart beating a bit faster and makes you breathe more deeply—like brisk walking, climbing stairs, or even housework. Moderate activity does not require leaving home.

Examples of moderate physical activity:

A 154-pound man (5′ 10″; 70 kg, 1.8 m) will use up about the number of calories listed doing each activity below (those who weigh more will use more calories, and those who weigh less will use fewer).

Table 7. "Reduce your cancer risk: physical activity" American Institute for Cancer Research (AICR), 15 Aug. 2011. aicr.org/reduce-your-cancer-risk/physical-activity/reduce_physical_add.html.

Moderate Physical Activities		
Activity	**In 60 Mins.**	**In 30 Mins.**
Hiking	370	185
Light gardening/yard work	330	165
Dancing	330	165
Golf (walking and carrying clubs)	330	165
Bicycling (less than 10 miles per hour)	290	145
Walking (3½ miles per hour)	280	140
Weight training (general light workout)	220	110
Stretching	180	90

Vigorous Activity

Vigorous activity means raising your heart rate so that you warm up, start to sweat and feel out of breath. A 154-pound man (5′ 10″; 70 kg, 1.8 m) will use up about the number of calories listed doing each activity below. Those who weigh more will use more calories, and those who weigh less will use fewer.

Table 8. "Reduce your cancer risk: physical activity" American Institute for Cancer Research (AICR), 15 Aug. 2011. aicr.org/reduce-your-cancer-risk/physical-activity/reduce_physical_add.html.

Vigorous Physical Activities		
Activity	**In 60 Mins.**	**In 30 Mins.**
Running/jogging (5 miles per hour)	590	295
Bicycling (more than 10 miles per hour)	590	295
Swimming (slow freestyle laps)	510	255
Aerobics	480	240
Walking (4½ miles per hour)	460	230
Heavy yard work (chopping wood)	440	220
Weight lifting (vigorous effort)	440	220
Basketball (vigorous)	440	220

The VHL Athlete

"In preparing myself for a delicate spinal surgery, I was naturally not looking forward to the experience, but knew that I had to get through it if I wanted to alleviate the growing numbness and have use of my arms and hands. I looked for a good role model. I noticed that marathon runners, or competitors in triathlons, also push themselves up to and beyond their physical limits. They endure pain, thirst, and suffering, all to win the prize, to compete sometimes more with themselves than with the others in the race.

In addition to the careful preparation my doctors and I went through, consulting with specialists throughout the world to choose the best approaches for the surgery, I trained myself for this even as if I were training for a sports event. I made sure my body was healthy and strong, tuned with vitamins and healthy natural foods, and that my mind was strong as well. Through meditation and guided imagery, I pictured the surgery going well, the surgeons confident and successful, and my body helping to minimize bleeding and recover quickly. I worked with a sports trainer and used sports psychology.

The day of the surgery arrived, and our team—my doctors and I—worked through the day. By evening, I was awake, squeezing my husband Bruce's hand and wiggling my toes. Everyone cheered. We had won the first event in the triathlon—now on to physical therapy and back to normal life."

—Jennifer K., Australia

References

American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention, cancer.org, last medical review 1/11/2012, last revised 4/9/2015

American Heart Association Recommendations for Physical Activity in Adults, last reviewed 02/2014, http://www.heart.org/HEARTORG/GettingHealthy/PhysicalActivity/FitnessBasics/American-Heart-Association-Recommendations-for-Physical-Activity-in-Adults

Bickel CS, et al., Exercise dosing to retain resistance training adaptations in young and older adults, *Medicine & Science in Sports & Exercise*, 2011; 43(7):1177-87.

Cohen J. 10 Chores That Burn 100 Calories, *Fox News Magazine*, Fox News, 24 Apr. 2013. http://magazine.foxnews.com/food-wellness/10-chores-burn-100-calories.

Corliss, J. Too much sitting linked to heart disease, diabetes, premature death. *Harvard Health Blog*, Jan 22, 2015

How much physical activity do children need?, *Centers for Disease Control and Prevention*, last reviewed June 4, 2015, www.cdc.gov/physicalactivity/basics/children/

Klein S. Spring Cleaning: How Many Calories Do You Burn Doing Chores? *The Huffington Post*. TheHuffingtonPost.com, 24 Mar. 2013. http://www.huffingtonpost.com/2013/03/24/spring-cleaning-calories-burned_n_2934204.html.

Physical Activity and Cancer, *National Cancer Institute at the National Institute of Health*, 22 July 2009. www.cancer.gov/cancertopics/factsheet/prevention/physicalactivity.

Recommendations for Cancer Prevention, *AICR Reduce Your Risk*, American Institute for Cancer Research (AICR), 30 July 2011. http://www.aicr.org/reduce-your-cancer-risk/recommendations-for-cancer-prevention/recommendations_02_activity.html.

Reduce Your Cancer Risk: Physical Activity, *AICR Reduce Your Risk*. American Institute for Cancer Research (AICR), 30 July 2011. http://www.aicr.org/reduce-your-cancer-risk/recommendations-for-cancer-prevention/recommendations_02_activity.html.

Rock CL, et al., Nutrition and physical activity guidelines for cancer survivors. *CA: A Cancer Journal for Clinicians*, 2012; 62(4): 242–274. doi: 10.3322/caac.21142

Weight and Obesity, Physical Activity, Diet, *Energy Balance*. National Cancer Institute at the National Institute of Health, 2012. http://www.cancer.gov/cancertopics/prevention/energybalance.

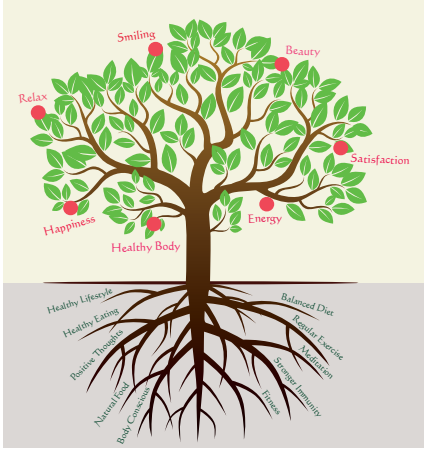
Emotional Health

Stress constantly creeps into our lives. 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 with anyone, particularly someone, directly or indirectly, impacted by a long-term medical condition such as VHL. Anxiety may be triggered by events such as the diagnosis, preparing for annual scans, decisions on when to operate, and thoughts about future health. 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 using a technique such as Conscious Living.

The Art of Conscious Living



"When we are able to mobilize our inner resources to face our problems artfully, we find we are usually able to orient ourselves in such a way that we can use the pressure of the problem itself to propel us through it, just as a sailor can position a sail to make the best use of the pressure of the wind to propel the boat. You cannot sail straight into the wind, and if you only know how to sail with the wind at your back, you will only go where the wind blows you. But if you know how to use the wind energy and are patient you can sometimes get where you want to go. You can still be in control… We all accept that no one controls the weather. Good sailors learn to read it carefully and respect its power. They will avoid storms if possible, but when caught in one, they know when to take down the sails, batten down the hatches, drop anchor, and ride things out, controlling what is controllable and letting go of the rest… Developing skill in facing and effectively handling the various "weather conditions" in your life is what we mean by the art of conscious living."

—Jon Kabat-Zinn, Ph.D., Founding Executive Director of the Stress Reduction Clinic at the University of Massachusetts Medical Center, Worcester, Massachusetts. As quoted from his book, Full Catastrophe Living: Using the Wisdom of your Body and Mind to Face Stress, Pain and Illness, p. 3. (Delta Books, New York, 1990).

Figure 16. The Art of Conscious Living

What is stress?

Stress describes what people feel when they are under mental, physical, or emotional pressure. 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.

Who experiences stress?

Everyone! 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 your life on a day-to-day basis, every once in a while they will come up and demand your 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. Dealing with the stress of living with VHL and/or caring for someone affected with VHL is an important part of self-care.

Find support. Join a support group 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 and the VHL discussion group on Inspire. The VHL Alliance also offers numerous support programs. To learn more about support offerings, visit the website at vhl.org/support or contact VHLA (800-767-4845 x4)

How does stress affect health?

Research has shown that people who experience intense and long-term (i.e., chronic) 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 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. He or she can evaluate you and may 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 on a direct link between stress and risk factors for cancer is controversial, stress is known to affect biological processes that are critical to help control cancer growth. There is more definitive research demonstrating that stress, often measured as high levels of anxiety and depression, is associated with tumor progression and overall mortality.

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 renal cell carcinoma 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 compared to the least depressed.

VHL and Family Distress

It is important to talk with your family about how you are feeling. You are not burdening them; you are helping them understand how to help you and allowing them to participate in this experience with you. In general, it is less stressful for everyone if you turn to your family for help and let them be your partner in dealing with VHL. A chronic disease like VHL can put strain on even the best of marriages. Do not be shy to ask for help or counseling. You are not alone. VHL is not a punishment; it is a medical condition. It is not your fault. It is not something you 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 significantly related to 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.

The study found that a substantial percentage of family members experience clinically relevant levels of distress. While only about one-third of those who reported heightened levels of distress had received professional psychosocial support, 62% of the total sample felt that professional support should be offered routinely. Based on the study findings, the authors of the paper emphasized the importance of screening and dealing with distress for VHL patients and their families.

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 were spared. Affected or not, children often harbor unspoken fears for themselves or for their parents, 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* can be used to help explain VHL to all of the children in your family.

Caregiver Needs and Stress

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 high-risk spouses and partners.

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. If you are a caregiver, you may often wrestle with stress as well as exhaustion, anger, guilt, grief, and other difficult emotions. It is common to feel stressed and overwhelmed. Try to share your feelings with others who can help you. It can help to talk about how you feel. You could even talk to a counselor or social worker.

While you attend to the needs of others, your own sense of well-being may decline. 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, you need stress relief, support, and time for yourself and your family.

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 you can do. Think about tasks you can give to others and let go of tasks that aren't important at this time.

Protect your own health. Boost your resistance by eating well, getting enough rest and exercise, and pursuing activities that bring you pleasure.

Practice self-care. Make time for yourself and your needs. Consider the airplane analogy—you must put on your own oxygen mask before helping others. You need to take care of yourself before you can effectively care for others. It is not selfish to take care of yourself, it is vital.

Combat caregiver stress. Relaxation response techniques and self-nurturing techniques will enable you 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. You can still be close as a couple 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, you are 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 support group offerings including the VHL Partners program and the Telephone Discussion Group. (800-767-4845 x4 or info@vhl.org)

Stress Prevention and Management

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

Once the threat is gone, your body is meant to return to a normal relaxed state. Unfortunately, the nonstop stress of modern life means that your 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 your 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 you typically handle stress can help you 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

Schedule or Store Your Worries

For some, it can be helpful to structure their worry—either by setting aside a time to worry or by creating a place to "hold" your worries—to help keep negative thoughts and fears from persisting throughout the day.

At times when your mind is racing, you feel overwhelmed and anxious, and you cannot seem to focus, call a time-out for yourself. Set a timer for 15 minutes and write down everything that you're worried about. But when the buzzer sounds, put your worries away and allow yourself to be fully present. Try to accept your concerns and fears without judgment. If you are going through a particularly tumultuous or difficult time and feel that worry is persistent, you may find it helpful to set aside a specific time each day to record (and release) your worries.

It may also be helpful to make a worry box. Having a place to contain your worries (quite literally) allows you to focus on the more pleasurable and meaningful parts of your life. Begin by finding or making a worry box, any type of box will work. This is a great exercise for children that are having difficulty coping with life stressors or anxiety. Children might enjoy the activity even more if they can decorate the box and keep it in a special place. At the end of the day, take a few minutes to write down two or three of your concerns on slips of paper and place them inside the box. The worry box allows you to mentally let go of your worries. Once the worries are placed in the box, try to turn your attention to other matters.

Meditation and Relaxation

Research has shown that meditation can be an effective coping mechanism for stress. The simple act of changing ones thought patterns through meditation can decrease metabolism, heart rate, and blood pressure, and, ultimately, can decrease the severity

and extent of illness and build long-term resiliency and the ability to cope. There are many online and printed resources that teach meditation skills as well as listings of meditation instructors such as the International Association of Meditation Instructors (meditationinstructors.com).

Depression and Anxiety

Most people feel anxious or depressed 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. But each disorder has its own causes and its own emotional and behavioral symptoms.

Many people who develop depression have a history of an anxiety disorder earlier in life. There is no evidence one disorder causes the other, but there is clear evidence that many people suffer from both disorders.

It is not uncommon for someone with an anxiety disorder to also suffer from depression or vice versa. Nearly ½ 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.

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 US 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; the risk of depression increases with the possible complications of a chronic illness. A person may be successfully managing a chronic illness, but the illness may have so many possible complications (frequent hospitalizations, depletion of financial resources, decreased ability to maintain gainful employment) that even one who is in control of the disease may have a high rate of depression.

Up to one-third of people with a serious medical condition are estimated to have symptoms of depression as compared to one-tenth of the general public. Depression is particularly common in those with recent heart attacks (45%), recent stroke survivors (40%), and diabetes (33%). Depression is also a problem for 15–25% of cancer patients. One study found that one-third of patients with advanced cancer and one-fifth with terminal cancer experience a depressive disorder, with less than half of these individuals receiving treatment for 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

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, startle easily, and 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 average age of onset is 31 years old and women are twice as likely to be affected as men. 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:

Fatigue

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

DECIDING WHETHER OR NOT TO SEEK PROFESSIONAL HELP

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?

What types of professionals treat depression and anxiety? Clinical social workers, psychologists, psychiatric nurses, and psychiatrists are the primary treatment providers for depression. In addition, there is a wide range of professionals who can also help people, including your primary care provider or internal medicine doctor, members of the clergy, and school guidance counselors who are trained to detect the disorder, and can provide referrals.

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.

Antidepressants: There are a variety of antidepressant medications available, but they can be separated into three main categories: *Tricyclics* (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. Certain people may respond better to particular antidepressants. It is important that the physician and patient work closely together in order to determine an appropriate regimen.

Counseling: There are two main categories of counseling—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.

How do I find a counselor in my community?

A good place to start may be with the physician who knows you best. You are probably not the first person to ask this question; he or she may have a few names to recommend. In the US, your health insurance is another resource for finding a counselor. Mental health services are required by the Affordable Care Act, and your plan will give you details about your personal coverage.

There are many agencies across the country that provide excellent services to people coping with depression and anxiety as it relates to chronic illness. These include hospitals, Catholic Charities, and Jewish Social Services. Individuals in private practice may be willing to consider a fee lower than their established rate, but you will not know unless you ask.

One can also contact the following professional organizations than can assist in finding a mental health professional in the US:

National Association of Social Workers	800-638-8799
American Psychological Association	800-964-2000
American Psychiatric Nurses Association	202-857-1133
American Psychiatric Association	202-682-6000

Similar psychosocial resources exist internationally. Please contact the closest VHL Clinical Care Center (vhl.org/ccc), or the VHL Alliance (info@vhl.org).

VHL 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. The VHL Alliance published a book of vignettes, VHL Patient Vignettes, written by patients and caregivers, who have offered their insights on how they deal with the challenges of a VHL diagnosis. Call or write the VHL Alliance for more information (info@vhl.org) or purchase directly at vhl.org/store.

VHLA Group and Personal Support

VHLA Annual Meeting: Held every fall, this is the best way to meet others with VHL face-to-face. The location of the meeting moves each year to provide access to as many people as possible. In addition to meeting with others, there is an entire day of presentations from medical experts in VHL plus participation sessions. You are encouraged to attend with your family.

VHLA Telephone Discussion Group: This group meets monthly for a supportive hour of discussion moderated by a professional counselor. Please register in advance to join.

VHL Partners: This is an individual mentoring program where you will be matched with a trained VHL mentor, either a patient or a caregiver. You and your mentor choose how you prefer to communicate with each other. Mentors are available for both adults and children (parental permission required).

Contact the VHLA office at info@vhl.org or 800-767-4848 x4 to find out more about these programs.

VHLA Online Support Networks

VHL Facebook Discussion Page:	facebook.com/groups/VHLawareness
Inspire:	Inspire.com/groups/vhl-alliance
VHLA Fan Page:	facebook.com/VHLFA

References

AARP National Poll Highlights Personal Challenges of Caregivers in the United States, *AARP: Real Possibilities*. AARP, 7 Nov. 2013. http://www.multivu.com/mnr/63968-ad-council-aarp-caregiver-assistance.

Anxiety, *Anxiety and Depression Association of America*, ADAA. http://www.adaa.org/understanding-anxiety/generalized-anxiety-disorder-gad.

Benson H, et al., Stress Management: Approaches for Preventing and Reducing Stress, Rep. Harvard Health Publications, 2013. http://www.health.harvard.edu/special_health_reports/stress-management-approaches-for-preventing-and-reducing-stress.

Bourdeau T, et al., Coping with a Diagnosis of Chronic Illness, *American Psychological Association*. APA, Aug. 2013. http://www.apa.org/helpcenter/chronic-illness.aspx.

Caldwell, E. The Stress and Cancer Link: 'Master-Switch' Stress Gene Enables Cancer's Spread. *Research and Innovation Communications*. Ohio State University, 22 Aug. 2013. http://researchnews.osu.edu/archive/ATF3.htm.

Caring for the Caregiver, *National Cancer Institute*. National Cancer Institute at the National Institute of Health, 29 June 2007. 28 Apr. 2014. http://www.cancer.gov/cancertopics/coping/caring-for-the-caregiver.

Coping With Chronic Illnesses and Depression, *WebMD Medical Reference*. Ed. Joseph Goldberg. WebMD, LLC., 8 Feb. 2014. http://www.webmd.com/depression/guide/chronic-illnesses-depression?page=2.

Depression, *Anxiety and Depression Association of America*, ADAA. http://www.adaa.org/understanding-anxiety/depression.

Duckworth K. *Depression and Chronic Illness: Fact Sheet.* N.p.: Ken Duckworth, n.d. *The National Alliance on Mental Illness*. www.nami.org, Oct. 2009.

An Estimated 1 in 10 U.S. Adults Report Depression, *Centers for Disease Control and Prevention*. CDC.org, 31 Mar. 2011. http://www.cdc.gov/features/dsdepression/.

Enayati A. Fighting Loneliness and Disease with Meditation, *CNN Health*. Cable News Network, 25 Aug. 2012. 28 Apr. 2014. http://www.cnn.com/2012/08/25/health/meditation-loneliness-inflammation-enayati/index.html.

Enayati A. Stress, Depression May Affect Cancer Survival, *CNN Health*. Cable News Network, 14 Jan. 2012. http://www.cnn.com/2012/09/14/health/stress-cancer-survival-enayati.

Lammens CM, et al., Distress in partners of individuals diagnosed with or at high risk of developing tumors due to rare hereditary cancer syndromes, *Psycho-Oncology* 20, no. 6 (2011): 631-638.

Lammens CM, et al., Psychosocial impact of von Hippel–Lindau disease: levels and sources of distress, *Clinical Genetics* 77, no. 5 (2010): 483-491.

Paddock C. Stress Fuels Cancer Spread by Triggering Master Gene, *Medical News Today*. MediLexicon International, 27 Aug. 2013. http://www.medicalnewstoday.com/articles/265254.php.

Peterson S. Communicating with Your Children regarding Risk for Adult Onset Disorders, *32nd Annual Education Conference California, Anaheim*, 11 Oct. 2013. Lecture.

Psychological Stress and Cancer, *Fact Sheets: Risk Factors and Possible Causes*, National Cancer Institute, 10 Dec. 2012.

Rowland E, et al., Communicating inherited genetic risk between parent and child: a meta-thematic synthesis. *International Journal of Nursing Studies*, 2013; 50(6): 870-880.

Support for Caregivers, *For Caregivers, Family, and Friends*. National Cancer Institute, 1 Aug. 2013. http://www.cancer.gov/cancertopics/pdq/supportivecare/caregivers/patient/.

Thornton S. von Hippel Lindau Syndrome, *The Children's Hospital of Philadelphia*, 2012 http://www.chop.edu/conditions-diseases/von-hippel-lindau-syndrome#.VEZ9B8tATcs.

Stress Management, *Mayo Clinic*. Mayo Foundation for Medical Education and Research, 8 Apr. 2014. http://www.mayoclinic.org/healthy-living/stress-management/basics/stress-basics/hlv-20049495.

Understanding Genetics: A New England Guide for Patients and Health Professionals, *New England Public Health Genetics Education Collaborative*, 2010.

SECTION 4

Discussing VHL with Your Family

Family Members and VHL

Genetic disorders can affect families in significant ways. Since our genes are inherited and passed down through families, a genetic disorder has implications for the health of 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 health problems. In addition to the medical implications, genetic disorders present emotional challenges and special reproductive implications. Families may be concerned about the risk that additional children will inherit the condition and worry about the decision to test a child or a pregnancy.

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.

When communicating information about VHL to family members, you may want to give them the name and contact information for your genetic counselor. This will give them a knowledgeable third party to contact with questions that they may not want to ask you. This may 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 has been shown to 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. The VHL Alliance website has some tips for parents to talk with their children about VHL (vhl.org) and you can also ask your health care provider or a social care professional for information and help in starting a discussion with your family members.

Adult Issues and Family Planning

As you might remember from the How Do People Get VHL? section, an individual affected with VHL has a 50% chance of having a child who is also affected with VHL. This is because our genes are passed on by parents to children—someone with VHL will either pass on the healthy VHL gene, or the copy of the gene with a mutation that causes VHL. It's a 50–50 chance, the same odds as flipping a coin.

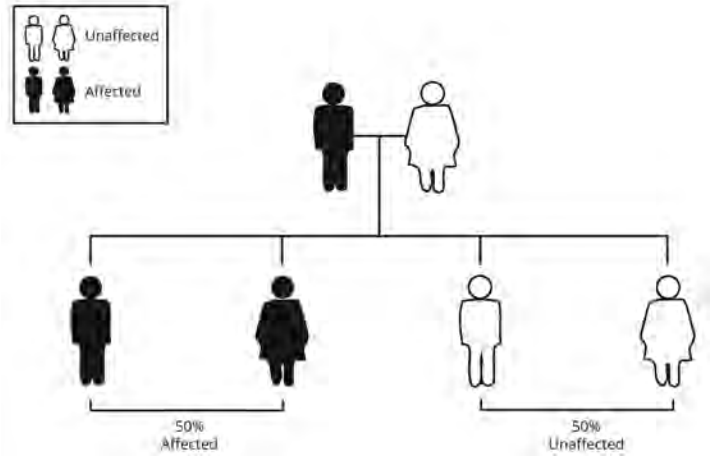


Figure 17. VHL inheritance (from Greenwood Genetics)

Some people feel OK with the idea of having children affected with VHL; other people feel worried and anxious about the risk of passing the mutation on. 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 health care 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 as well as 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.

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 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 feel 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 you **can** control. Work on being present within relationships, using good coping skills, and taking care of yourself. Teach your children valuable skills and lessons about coping with VHL by setting a good example; your children will model your behaviors. You may feel guilty about taking any time for yourself, but you cannot take care of others effectively if you are not also taking care of you. Focusing on your needs and your health will not only help you be a better parent, it will also help your children learn 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.

REMEMBER… The worst way to hear something is to OVERHEAR IT

Children are often aware of more than we might think. They might have learned about VHL by overhearing a phone call, a private conversation, etc. Only knowing part of the story can be even more distressing than being told everything. Additionally, frustration with being kept from the truth and not given answers might drive children and teens to seek out information on their own using the Internet. This is a dangerous way to learn, since conclusions might be falsely made based on unreliable sources and misinformation.

Are you ready to talk to your child?

There is no right or wrong answer for how and when to have this conversation. You know your child best; it is up to you to say when is the right age and how old is old enough for a child to be ready to learn about VHL.

If you or a loved one has been diagnosed with VHL very recently, you might not be ready to talk. Wait until you are over the initial shock period. You need to process this news first before you can really talk to them in a helpful or meaningful way.

Can you say in a sentence or two why or how telling your child will help you and the family? If you are able to acknowledge and verbalize the benefits of telling your child, you are ready to have this conversation.

Are you going to be able to give your child emotional space? You need to be able to listen to them, not just try to talk at them and fix the problem with words and reassurances. This needs to be a two-sided conversation.

How can you help yourself and your child?

Maintain normalcy, spend time together. Try to spend time with your kids in any way you can. Take them to the store with you or eat meals with them. Ask them about their day. Leave them notes or call them when you can. Try to keep a normal routine and schedule—meals, sleep schedule, school, etc. Keep children in contact with peers and friends and make sure your child has time to play and participate in appropriate activities.

REMEMBER… VHL is more like a marathon than a sprint

Assign age appropriate responsibilities. Everyone benefits from having a way to control a chaotic situation. Empower your child by giving them a daily task or responsibility that allows them to actively care for their health or the health of a relative, depending on whom in the family is affected with VHL. For example, the child can use stickers and mark the days of upcoming doctor visits and scheduled screening appointments. Being able to contribute to family wellbeing can ease the stress of dealing with a medical condition like VHL and help your child feel in control and less overwhelmed.

Do not keep secrets. Your child might already be aware that they or someone else in the family is having health problems. Not acknowledging these health problems can make them seem even scarier and more overwhelming than they actually are. Nothing is scarier than the fear of the unknown; telling your child what is going on can protect them from believing something that is worse than the reality.

Anticipate needs. You know your child best. Consider how your child might cope and respond to learning about VHL. You might want to plan ahead and prepare resources you can provide for your child to help them handle learning about VHL. This might be a physical activity you and your child do to release stress, a ritual you can do to reduce fear and anxiety (such as making a worry box), or finding a counselor or trained professional for your child to meet with and with whom to talk.

Tips for talking with kids:

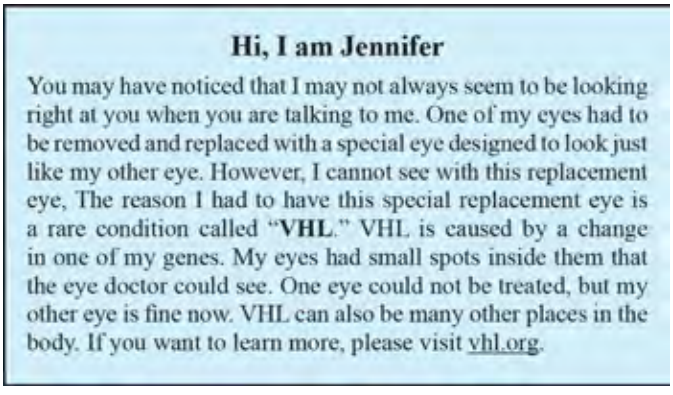
Listen and build on what the child already knows. Have your child tell you what they know or think they know, then correct any misinterpretations they might have.

Let them know their feelings are okay. Tell them you understand if they are upset, angry, sad, or scared. Remind them that no matter what happens, you will always love them. 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 you 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 you are not able to keep.

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. You might have one initial conversation about VHL that is followed by many other little 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. An example of when to do this might be for a child with a prosthetic eye.



Hi, I am Jennifer

You may have noticed that I may not always seem to be looking right at you when you are talking to me. One of my eyes had to be removed and replaced with a special eye designed to look just like my other eye. However, I cannot see with this replacement eye, The reason I had to have this special replacement eye is a rare condition called "**VHL**." VHL is caused by a change in one of my genes. My eyes had small spots inside them that the eye doctor could see. One eye could not be treated, but my other eye is fine now. VHL can also be many other places in the body. If you want to learn more, please visit vhl.org.

Teens and VHL

Transition is when we move from one thing to another, such as moving from childhood to adulthood. While 18 or 21 years old are often the ages when people are thought to officially become an "adult," growing up does not happen on a single birthday. It is a process that happens over time. People start to learn skills in childhood that will help them be a successful adult. People continue to learn and grow and change in lots of different ways throughout their life. Learning how to transition and become independent will help you prepare for life as an adult. The transition to adulthood involves many aspects of life, including life at school, at home, at work, and with friends. Health care is an important piece of the transition process, especially with a medical condition like VHL. It is important to learn to advocate for yourself at an early age so you will feel comfortable taking control of your medical needs as you move from the health care you received as a child to the health care you will need as an adult.

Independence and Transition

Adults and teens do not always agree or get along. There will be clashes between parents and children, whether it is over punishment for a rule that is broken, disagreements about style, fights over curfew, etc. The struggle for independence can be especially complicated for teens with VHL. It can be frustrating for teens to feel treated like a small child and told what to do, especially when they feel ready to take care of themselves and make their own choices. However, teens can sometimes feel overwhelmed with the responsibility of managing their health care and might just want someone else to take care of everything. It can be exhausting to keep track of appointments, when to do screenings, anticipate future needs and problems, all while planning for the future and trying to make healthy choices every day.

Parents and teens should work for a balance of responsibility that shifts as the child gets older and becomes more responsible for managing their health care needs. Sometimes it helps to sit down together and make a plan for transition outlining when and what specific tasks the child or teen will take responsibility for. It is important for parents to prepare for transition by educating children about VHL and involving them in health decisions and discussions. Practicing independence helps teens understand their medical needs and learn important skills for self-advocacy and healthy living.

Stress

Taking on new responsibilities while also dealing with having a chronic condition like VHL can lead to increased stress. It is important to manage your stress levels and talk to your parents if you feel you cannot handle any additional responsibilities. Teenage years are a time of great changes and having a disease like VHL can heighten your level of stress. There are a number of resources to help you learn to cope with stress and develop strategies to lessen its effect on you. The American Academy of Pediatrics has a stress management guide that helps you create a personalized plan.

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 yourself and knowing what you want and what you need. Things might not always work out in the way you want, but having the skills and confidence to communicate your needs is an important first step in reaching your goals.

How to be a health care advocate:
Communicate as best you can about what you need and feel.
Ask questions and keep asking them until you are sure you understand.
Do what you can for yourself but know when you need help.
Become an expert learning about VHL is the best way to be your own advocate.
Try to make healthy lifestyle choices.

Remember that taking care of your health and health care will help you reach your goals and allow you to live the life that is right for YOU!

Transition Overview

Transition is not one-size-fits-all. Because an individual's transition needs are different depending on their experience with VHL, the information provided may not be applicable or relevant for everyone. VHL can affect people in very different ways; some teens may have symptoms and VHL manifestations at a young age, while others may not. There is no one right way to make a plan and no one plan is right for everyone. It is up to you to make a transition plan that fits you and your needs.

Transition planning starts with you. A transition planning process includes the steps you take to move into the adult world. There is new information that you will need to learn about—independent living skills to develop, decisions to be made, and actions to take. You are the most important person in planning your own transition. But you do not have to do it alone. Others can help provide information and review your hopes and plans for the future to assist you in developing a transition plan.

Transition planning is a team effort. You are the most important person in planning your own transition. But while you are the leader in your transition, many young adults benefit from having others to help with this process. All of the people who help you with transition are part of your transition team.

The purpose of this team is to support you to make the transition to adult living and be as independent as possible.

The team includes everyone who helps with transition planning and services.

The Transition Team

Health care team. The purpose of the health care team is to plan and support your transition from pediatric to adult care. The health care team includes you, your family, primary care provider, specialty care, medical care staff, and other health care providers.

In preparation for adult life, young adults with medical conditions such as VHL must consider how to manage their own health care needs. It is important to understand VHL so you can manage your unique VHL medical needs. Everyone must know how to get in touch with their doctor, keep track of their follow-up and screening appointments, monitor their symptoms, and know when to seek urgent medical care. It is also important for you to understand health risks, how to make healthy life choices, and how to exercise independence in health-related issues. Learning about your health needs in a supportive team environment will help you take charge and advocate for yourself as an adult.

School team. While not everyone with VHL will have symptoms at a young age or symptoms that affect them in school, those that do might need some assistance or modifications in the school setting. It might be helpful to meet with a school team, which can consist of you, your family, teachers, and resource specialists, to go over your needs in school. Some people have a plan outlining the resources and accommodations they need in school; this is called an Individualized Education Program (IEP).

Even if you do not have an IEP, it might be helpful to inform people like teachers, school administrators, guidance counselors, and school nurses about VHL so they can be more sensitive to your individual needs. Providing this type of information may help explain why you are sometimes late or absent from school. The decision is up to you. You do not have to tell your school about VHL if you do not want to do so.

Community living team. The purpose of the community living team is to help you plan and support your transition to adult living. The community living team includes everyone involved in helping you plan and live within your community.

You may choose to live with your family into adulthood or you may want to experience independent living. Perhaps you will go back and forth between living with your family and living independently. Regardless of where you live as an adult, you will need to develop skills to be as independent as possible in your daily life. Important skills for adult living include knowing how to make decisions, taking time for friends and family, advocating for yourself, managing activities of daily living, being safe, maintaining a healthy lifestyle, accessing transportation, engaging in recreational activities, and making sure you have health insurance coverage.

Your Health Care

AGE OF MAJORITY

In most countries, including the US, you are legally considered to be an adult (age of majority) at 18 years of age (except Alabama (19), Nebraska (19 or upon marriage), Puerto Rico (21), and Mississippi (21)). Although you may still not have "legal license" to do some things (purchase tobacco or alcohol or be elected to certain offices, for example), you are now treated as any other adult, and not the child of your parents.

This has important implications for your medical care. Medical privacy rules in the US (HIPAA) will not allow your medical records to be shared with another person outside of your medical care team without your consent unless the medical provider, in their professional judgement, decides that it is in your best interest. If unsure, many providers will choose to protect patient privacy and not share your information. This decision is independent of who is paying for your health plan or family relationships (parent, spouse, etc.). Thus, it is smart to plan ahead and have a signed HIPAA authorization in advance of when you may need it; you can scan it and keep it on file in your smartphone, tablet, or computer. This form can also be combined with a Medical Power of Attorney (which varies by state) and will allow the person you designate to make your health care decisions in an emergency.

TIPS FOR TALKING WITH DOCTORS

Take control. Talk to your parents about practicing independence during medical visits. Let them know that you would like to be more involved in your medical appointments, answer the doctor's questions, and help make health decisions. Ask them for help if you need it. One of the ways you can practice being independent is by spending time alone with your doctor.

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

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

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

It is all about YOU. Remember, your needs are the priority. Tell your doctors what you are worried about or what you want to address. Sometimes health care professionals focus on something that they feel is important, even if you do not agree. Let them know. You can help redirect your doctors to see the big picture of your life and what you 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.
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, at age 18, you are the one who must agree to the plan of care.
Do	Do your part in following the plan!

LIVING INDEPENDENTLY WITH VHL

Health care transition is all about providing you with a healthy foundation on which to build your life goals. Going away to college, vocational training, or leaving home and living independently may be part of your plans for the future. If so, there are some things you can do to help make this transition to a new school and new health care providers easier.

The transition of leaving home takes some planning. If you are going away, your parents will not be there to help you with the car, make decisions, or solve problems. It will be important to plan ahead and make sure you are as prepared as possible to be in charge of your health care.

Medical care. Regardless of where you are moving, you will need to make arrangements ahead of time to make sure you can get the health care you need. Even if you have still been receiving services from pediatric providers at home, you should not expect to get care from pediatric providers in your new location. Talk to your doctor at home to see what they recommend and if they can help set you up with any medical providers in your new location. It is important to do this before you move; the quality of medical care in the area should be a consideration when finding a place to live. Figure out what medical needs could be met by local providers and what could not; you might have to travel to a different medical center for some of the more specialized appointments or screenings. The VHL Clinical Care Centers (vhl.org/ccc) is a resource to help you find centers that can handle all of your needs as a VHL patient.

College. It is important to plan ahead to receive the best care. Try to anticipate any bumps in the road or special needs that might come up while you are at college. Then check to see if these services are available at the college you will be attending. All colleges have an Office for Students with Disabilities. This office is a great resource for students with various types of medical conditions. They can help with problems like getting your prescriptions on campus, working the meal plan around certain dietary restrictions and setting up transportation to medical appointments. It is a good idea to contact this office to learn more about what they can and cannot help you with. Some colleges have worked hard to make their campus and educational programs very accessible. These colleges tend to have more comprehensive programs to help you stay healthy as you adjust and succeed in college life.

REMEMBER… The student health center is not sufficient for VHL care

Student health centers might be helpful if you get a cold or sprain your ankle, but they do not have the staff or expertise to meet the needs of students with rare and serious conditions such as VHL. It is important to find local health care providers close to where your college is located, ideally one of the VHL Clinical Care Centers (vhl.org/ccc). Finding new providers takes some effort on your part, so you should start the process as early as possible. Once you find a new provider, arrange an introductory meeting so you can discuss your care and management, answer any questions they might have about you or VHL, and ask questions of your own. Have your medical records sent to the new provider.

It is a good idea to let your academic advisor at college know about VHL and how it might affect your ability to manage a full course load. Some people might not have any problems balancing their VHL and college life while others might struggle a little more. Doctor's appointments, recovery time after a surgery, or other health complications from VHL could make it difficult to stay involved and on top of everything going on in your life. You might need to reschedule exams or take an incomplete for a class.

Anticipate how VHL could complicate your life at college, then take steps to prepare for this situation by ensuring you have access to accommodations and services you may need. In some situations, for example, students with health conditions are allowed to take a reduced course load while still maintaining status as a full-time student.

Housing. If you think that you will need special housing arrangements because of your health care needs, be sure to look for housing that will meet these needs. Talk to the landlord, the housing tenants, roommates, etc., to get a sense of what the living situation would be like and how your needs will or will not be met. If you are going to college, make sure you discuss housing with the Office for Students with Disabilities. Many colleges only have a few dorm rooms that are specially equipped for students with special needs and these spaces fill up quickly. Let your school know about your needs as soon as possible, so they can make your living arrangements as comfortable, accessible, and safe as possible.

Advocate, advocate, advocate. When you were younger, you relied on other people to help you and care for you. Now that you are an adult, you are responsible for your needs. Remember, you are your own best advocate. Speak up and ask for what you need.

Teen Experiences

SOCIAL AND PERSONAL LIFE

Having a strong network of friends and support can have a positive effect on your emotional sense of self. If you have not already done so, it might be helpful to open up to friends and peers at school and talk about your condition. By sharing information about VHL and answering their questions, you can help friends understand what you are dealing with and why you may have certain limitations. It can also explain why you may have so many doctors' appointments. The more your peers understand about VHL, the more likely they will be sensitive towards your condition, which may help you feel more socially accepted.

You may also find support through advocacy groups like the VHL Alliance (see VHL Support Resources section). Meeting other teens with the same diagnosis can provide valuable insight as to how others manage the challenges of having or dealing with VHL. Whether you choose to share your story and experience or just listen to what others have to say, everyone is welcome.

HOW TO TALK ABOUT VHL

The decision to share your diagnosis with different people in your life is personal. It is up to you to decide whether or not you want to talk about VHL at all; it is OK to not talk about it. Some teens are uncertain about what to say to their peers and they are nervous about how their friendships with peers may be impacted. If you are worried about this, you are not alone. Teens who do talk to friends feel that it has been helpful to have people understand and can support them. Remember that you are in control over how you share information with others. Some people prefer to be honest and straightforward, while others prefer to joke and be funny. Regardless of your approach, here are some tips to help you explain VHL and start the conversation with friends:

Keep it simple. Use your own words and keep it basic, at least in the beginning. You do not have to explain everything at once; people can ask if they want more specific details.

Your parents or relatives can help. It might be helpful to talk to your parents or another family member if you are feeling anxious about telling people about VHL. You can practice the conversation with them to get comfortable with what you plan to say. You can also ask them for advice, since one of them has probably had conversations about VHL with their own friends.

Don't worry. You might be stressed out about telling people and imagine that the news will change everything, but it won't. It probably will not even be that surprising. Your friends and classmates may have already guessed that something is going on in your life, either with you or a family member.

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

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

References

Age of majority, *Wikipedia*, accessed 7/30/2015, https://en.wikipedia.org/wiki/Age_of_majority

Being a Teen with a Genetic Condition Fact Sheet. *Shire*. BraveCommunity.org, 2013. http://www.bravecommunity.com/.

Create a Personal Stress Management Guide, Building Resilience- A Teen's Plan, *American Academy of Pediatrics*, n.d. 21 Oct. 2014. http://www2.aap.org/stress/teen1-a.cfm.

Feinstein S. Will you be able to help your college-age child in a medical emergency? *Consumer Reports*, July 22, 2015

Gibson R, et al., Envisioning My Future: A Young Person's Guide to Health Care Transition, Children's Medical Services. *Health Care Transition Initiative of the Institute for Child Health Policy, University of Florida*, 2005

Reiss J. Now that you're in High School, *Children's Medical Services. Health Care Transition Initiative of the Institute for Child Health Policy, University of Florida*, 2008

Reiss J. When You're 18, You Are In Charge of Your Health, *Children's Medical Services. Health Care Transition Initiative of the Institute for Child Health Policy, University of Florida*, 2009.

Roberson K. Being a healthy adult: How to advocate for your health and health care. New Brunswick, NJ: The Elizabeth M Boggs Center on Developmental Disabilities, 2010.

Rowland, e, et al, Communicating inherited genetic risk between parent and child: a meta-thematic synthesis, Int J Nurs Stud 2013 Jun; 50(6):870-80

Students Living with a Genetic Condition: A Guide for Parents, *Genetic Alliance*. 2013. http://www.geneticalliance.org/sites/default/files/publicationsarchive/attending_with_genetic.pdf.

Transition for Children, *Genes in Life*. Genesinlife.org, 2014. http://genesinlife.org/after-diagnosis/plan-future/transition-children.

Transition Health Care Checklist: Preparing for Life as an Adult, *Wisconsin Community of Practice on Transition*, Madison, WI: Waisman Center, University of Wisconsin-Madison, 2009

SECTION 5

VHL Research

The VHL Alliance is constantly striving to increase the level of VHL research. Once considered only an obscure medical curiosity, in reality, VHL is becoming one of the most important diseases in the study of cancer. It is the leading hereditary cause of kidney cancer. Even in cases of sporadic kidney cancer in the general population, damage that may occur to the VHL gene is implicated in the advance of kidney and other cancers. While it is estimated that only 1 person in 36,000 in the US has VHL, it is estimated that 60,000 people will develop kidney cancer each year, of which 75% are clear cell renal cell carcinoma, 90% of whom will have changes in the VHL gene in their tumors (without having VHL disease). Curing VHL will thus play a vital role in curing cancer.

VHL is also one of four major genetic causes of *pheochromocytoma (pheos)*, accounting for approximately 20–35% of all pheos. Again, studying VHL and the other genetic causes of pheos is giving 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 cure them.

Two types of research are needed to ultimately 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. You can be an important part of both types of research effort. Financial donations are needed to support both types of research, and your participation is needed in clinical research. The Cancer in our Genes International Patient Databank is an online clinical research study open to everyone diagnosed with VHL, or with symptoms of VHL. See the section, You can be Part of Finding a Cure, for detailed information. Please contact the VHL Alliance at info@vhl.org, or at 800-767-4845 x4 to learn how you can be a part of finding a cure for VHL.

Genetic Research and VHL

DNA (deoxyribonucleic acid) is the biochemical basis of life and of heredity. All of an individual's characteristics are written in DNA in a kind of code. 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.) and one pair of the *sex chromosomes*, XX for females and XY for males. On each chromosome are the genes that contain the specific information necessary for the manufacture of proteins. Each gene has two copies—one inherited from the father and one from the mother.

The condition called VHL is caused by an *autosomal dominant mutation*, since only one altered copy of the VHL gene will cause the condition. Although a VHL mutation

is present and the person is considered to have VHL, the expression of the mutation as a VHL tumor or cyst, and the age of onset are highly variable. VHL occurs in both men and women because the VHL mutation is on an autosomal chromosome. Each child of a person with VHL is at 50% risk of inheriting the altered copy of the gene.

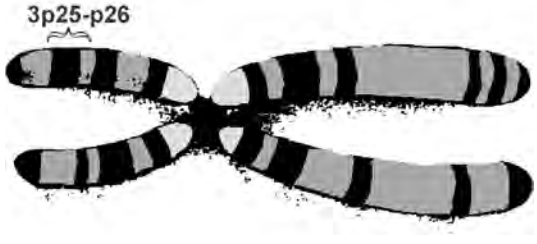


Figure 18. VHL gene location: The VHL gene is in the region 3p25-p26, near the tip of the short arm of chromosome 3. Illustration by Karen Barnes, Stansbury Ronsaville Wood, Inc., for Howard Hughes Medical Institute, as published in Blazing a Genetic Trail, 1991

The VHL gene is located on the short arm of chromosome 3 at a site called 3p25-p26. (See Figure 18.) An international team of scientists identified the precise sequence of this gene in 1993. Alterations in the normal structure of this gene are known to result in the condition called VHL. The VHL gene encodes the formula for a protein with the extremely important function of *transcription*. Transcription is the process from which DNA is transformed into a molecule, *RNA*. It is then the RNA that is involved in creating the protein.

The normal VHL gene acts as a *tumor-suppressor gene*, with the function of suppressing 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 VHL gene to undergo some change that inactivates the VHL protein in the same cell and allows a tumor to form. This may take some time because multiple damaging "hits" to the genes in this cell are required in order to enable a tumor to form. This explains why, when these tumors occur in the general population, they are usually single occurrences in a single organ at an older age. For example, the average age of onset of symptomatic kidney cancer in the general population is age 62. Mutation or inactivation of the VHL gene has been found in 90% of the random clear cell kidney cancers in the general population, studied by the US National Cancer Institute. This demonstrates the importance of this gene and the protein it manufactures in every human being.

In the case of people who have inherited one copy of the gene that does not work correctly in the beginning, it is only necessary to deactivate the one remaining copy before a tumor is likely to form. This is a much more probable occurrence meaning that tumors develop more often, at younger ages, and in more organs than in people in the general population. (See Figure 19.) Without preventive action, the most common age at diagnosis for people with VHL ranges from 25–50 years.

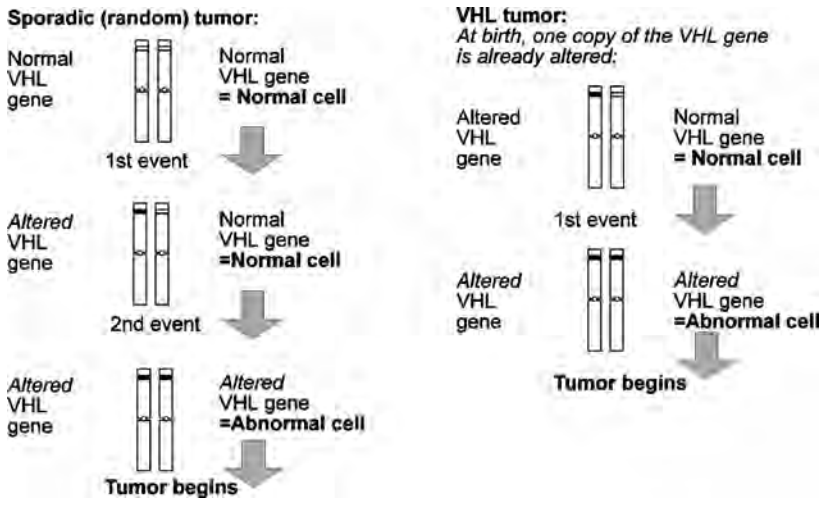


Figure 19. Path to development of a tumor. In people with VHL, one VHL gene is already inactive, and only one additional step is required for a tumor to start. Illustration from S. Richard and the French VHL Alliance.

These 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. More than 1,548 individual mutations have already been described in the medical literature. There is a significant relationship between certain kinds of mutations and the likelihood of pheochromocytomas or the aggressiveness of *Pancreatic NETs*. Researchers are studying other specific mutations which may be responsible for different aspects of VHL.

Progress Toward a Cure

With the VHL gene identified, there is also increased hope of a cure, or at least of better management for VHL. 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. As drugs are made available for clinical trials, announcements are posted on the website, vhl.org/trials.

"The identification of tumor suppressor genes whose loss of function results in predisposition to cancer has taken center stage in our attempts to understand human carcinogenesis."

—Dr. Richard Klausner, Chief, US National Cancer Institute, 1995

If VHL tumors can be kept small or made smaller, the frequency of surgical intervention required to manage VHL can be minimized. Meanwhile the best defenses are "early detection and appropriate treatment." Currently, knowledge and partnership with an experienced healthcare team are the best defense.

Remember that the vast improvements in the survivability of prostate and breast cancer have been made without a cure—the most important advances have been in early detection and better treatment. The same is true for VHL.

Research also shows that the VHL gene plays a role in a signaling system that tells the cell how much oxygen is available to it. When the VHL protein is missing, the cell believes, even if it is not true, that it is starving for oxygen. Its oxygen-sensing mechanism is broken. The cell puts out distress signals to the surrounding tissues. Nearby blood vessels respond by building *capillaries* reaching toward the faulty cell to bring more blood to bring more oxygen. This response creates a mass of capillaries. Thus, VHL tumors seem to be a normal self-protective response gone wrong. As more is understood about the function of the normal VHL protein, there is a better chance of finding a therapy that will fix or replace its function and keep tumors from growing.

In 1993, when the VHL gene was first discovered, the best description looked like diagram depicted in Figure 20.

Figure 20. Black box: All was known in 1993 was that the VHL protein was essential to the healthy existence of the cell. When the protein was missing, its ability to regulate growth and replication was disrupted and cell growth went out of control.

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.

As part of its function, the VHL protein combines with other proteins in the cell. (See Figures 21 and 22.) Depending on where the genetic alteration occurs, its ability to form connections with these other proteins may be impaired. A great deal has been learned about these differences by studying the relationship between the *genotype* (the place where the alteration occurs in the gene) and the *phenotype* (the set of symptoms experienced by these individuals).

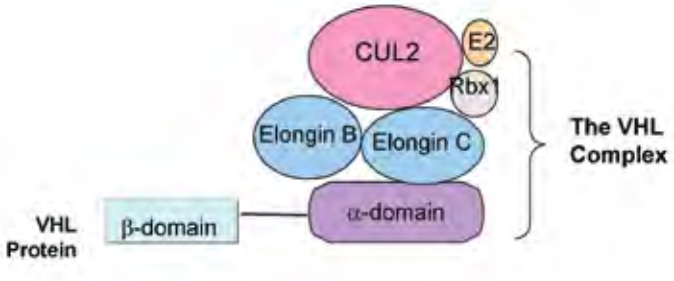


Figure 21. The VHL complex: The VHL protein combines with Elongins B and C and CUL2 to form a "complex", a kind of sub-assembly, which works as a machine to connect to other proteins in the cell and mark them for degradation and elimination—a kind of clean-up machine or "off" switch to stop processes from continuing. When this "off" function does not work properly, certain compounds are in over-supply and the process of cell growth and duplication goes out of control, resulting in a tumor or other malfunction. Source: US National Cancer Institute, *Science*, 269:1995, PNAS, 94:1997.

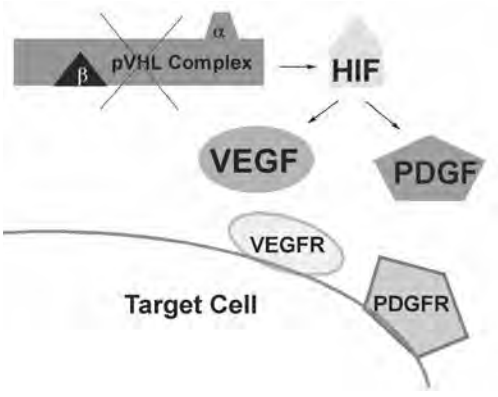


Figure 22. Pathways in the cell: If the pVHL complex is not functioning properly, then the levels of Hypoxia Inducible Factor (HIF) rise, which in turns allows the overproduction of Vascular Endothelial Growth Factor (VEGF) and Platelet-derived Growth Factor (PDGF) and others. These proteins send out signals to the target cell to stimulate the growth and reproduction of the cell. The signals are received by corresponding "receptors" (like VEGFR and PDGFR in this picture). In order to stop the signal from getting through, drugs may attempt to halt the signal, trap it in transit, or block the receptor. Source: W. G. Kaelin Jr., Dana-Farber Cancer Research Institute. *Clin Cancer Res*. 2004 Sep 15;10(18 Pt 2):6290S-5S.

Much has been learned about the VHL protein from the study of other diseases with similar effects, such as the many genetic flaws that can lead to a pheochromocytoma or kidney cancer. (See Figure 23.) In fact, the body is an elegant system of sensors and controls and backup systems. More than one path is provided to ensure that essential functions are carried out reliably. VHL may be on one path, but there is frequently a second or third path that serves as a backup.

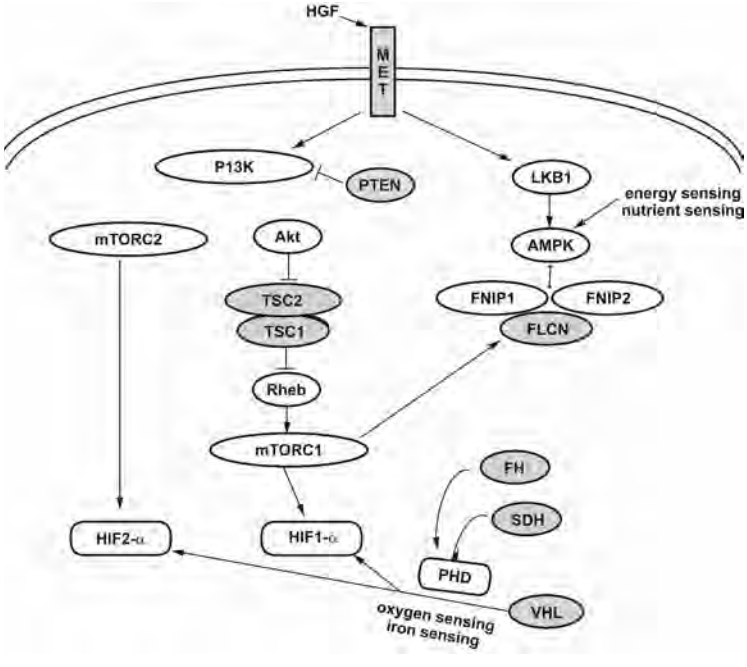


Figure 23. The genetics of kidney cancer: This diagram shows the kidney cancer pathways. Notice that on this one map we can see the genes responsible for the seven known genetic causes of kidney cancer: VHL, FH (for HLRCC), FLCN (for BHD), TSC1 & 2 (for TS), MET (for HPRCC) and SDH (for SDHB & D). Linehan et al., "The genetic basis of kidney cancer: a metabolic disease," *Nat Rev Urol* 2010 May:7(5):277-85.

Most are also multi-function controls—they not only turn on one feature, they may have the ability to control a large number of functions. For example, it is now known that the VHL protein not only influences angiogenesis, it also plays a role in oxygen sensing, iron sensing, and the metabolism of glucose (*glycolysis*). **VHL controls the major feeding pipeline of every tumor.** All of this is necessary information needed in order to select drugs for clinical trials.

At the time of 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. They include: Axitibnib (Inlyta), Bevacizumab (Avastin), Cabozantinib (Cometriq), Everolimus (Afinitor), Pazopanib (Votrient), Sunitinib (Sutent), Sorafenib (Nexavar), and Temsirolimus (Torisel).

There have been some small trials of these drugs for VHL. Some of the new drugs look promising but none have yet been approved for VHL specifically. In addition, each of these agents is known to have side effects which may impact a patient's willingness to follow a treatment regimen which is necessary for completion of clinical trials. More drugs will be coming on the market, targeting different points on the signaling shown on these pathways, inhibiting the production of a protein or inhibiting the ability of its "receptor" to receive its signal. As these drugs are developed further, it is expected that their next generations will be more "specific" (go directly to the right spot and do the job more effectively) and will have fewer side effects.

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

You Can Be Part of Finding a Cure

VHL Research Needs Your Support

There have been many advances in VHL research, and improvement in diagnosis and treatment has resulted in an increased life expectancy of more than 16 years. Yet, despite this progress, a cure for VHL is still in the future.

VHL Research Study for Participation by Everyone with VHL

In 2014, the VHL Alliance (VHLA, vhl.org), in partnership with the National Organization of Rare Disorders (NORD, rarediseases.org) launched a first of its kind patient databank. The **Cancer in Our Genes International Patient (CGIP) Databank** (vhl.org/databank) is an innovative and comprehensive clinical research study designed through the work of an International Task Force made up of some of the leading VHL researchers and clinicians in the world.

The information from the Databank is helping researchers to:

1. Better understand the natural history of VHL
2. Determine the relationship between lifestyle and VHL progression
3. Identify best practices for VHL treatment and diagnosis
4. Identify patients to participate in future clinical trials—as a means of accelerating a cure.

The Databank also includes conditions similar to VHL, including Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC), Birt-Hogg-Dubé (BHD), and Succinate Dehydrogenase Complex (SDH). This will allow researchers to learn from the similarities and the differences of these related genetic cancer conditions.

The more people who participate in the Databank, the more we will learn. For example, your information will provide answers to questions like:

Do commonly available over-the-counter medications impact tumor growth rate?

What about diet or nutrition?

Is there a relationship between anxiety, stress, or depression and cancer?

Can exercise help decrease the rate at which tumors develop and grow?

Does pregnancy or changes in hormone levels put women at greater risk for tumor progression?

Does oral health influence cancer severity? (Oral hygiene has been tied to cardiac disease; evidence is accumulating for a link to pancreatic disease.)

Log onto: vhl.org/databank

Email databank@vhl.org with any questions or help with the Databank, or telephone 617-277-5667 x4

The VHL Alliance wants everyone to participate in the Databank! It is simple and can be done from your own home computer, your smartphone or tablet, or even at a library computer. If you are not comfortable using a computer, you can have a friend enter your information or contact the VHL Alliance at 617-277-5667 x4 to be assigned a volunteer to ask you the survey questions over the telephone. The databank is designed so that you do not need to complete all of the questionnaires or even one survey in a single sitting.

You are also encouraged to enter data for as many affected relatives as possible, including those who have passed away. This will help establish the natural history of the disease.

The Databank is a *longitudinal study*, meaning it collects information from the same participants over multiple years. You will be asked to update your information at least annually, but you can do it more frequently if you would like. It is up to you to decide what works best for you. Your Databank account also gives you the option to set your account up to send reminders for screening and, of course, your information can be printed and used as a medical record to take to your medical appointments.

In any research study, data review is an important step needed before analyzing and determining results. In order to confirm accuracy of the data entered, you will be asked to upload or send your medical records and/or your image scans as an important step in ensuring accurate conclusions. Instructions for obtaining these documents from your medical team are provided through the Databank (you may also download the Databank Personal Health Information Consent and Release from the VHLA website: vhl.org/hipaa. The staff is always available to help you with the process or answer any questions that you may have. Please call them at 800-767-4845 x4 or databank@vhl.org.

Every possible effort is being made to protect the participants; the Databank's security system has met stringent *Institutional Review Board* approval. Your privacy is the VHL Alliance's highest priority. Only *de-identified* (information from which no one can determine your identity) data will 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 responsible for reviewing and approving all researchers and their requests.

Researchers are currently limited to data compiled by clinicians at a single hospital or research team. Many institutions, including NIH, have their own databases or registries, limiting researchers to patients seen at that institution. In addition, clinician-sourced data provides only a limited picture. The Databank is designed to allow researchers access to the annually updated compiled information of hundreds of patients.

Current VHL Clinical Trials

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

The VHL Alliance urges everyone who thinks that they may be qualified 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.

Tissue Sample Donation

You and your family can also help to move the progress of VHL research forward by contributing samples of saliva, blood and tumor tissue to the National Disease Research Interchange (NDRI). See vhl.org/bank for information about tissue banking.

There are a number of efforts to identify biomarkers. If such markers were found in blood or urine, they would indicate the level of tumor activity in the body without expensive scans. In order to find such biomarkers, researchers need samples of blood and urine from a large number of people with VHL.

Tissue from VHL tumors is needed to test potential therapies in the lab and determine which therapies might be good candidates for clinical trials. When surgery is planned, call NDRI at 800-222-6374 and register to donate the tissue your surgeon will be removing. NDRI will arrange for tissue collection with your surgeon.

Give a gift that only you can give and help promote research on VHL.

References

Frew IK, et al., Multitasking by pVHL in tumour suppression, *Curr Opin Cell Biol*, 2007 Dec:19(6):685-90, PMID: 18006292

Kaelin WG Jr. The von Hippel-Lindau tumor suppressor gene and kidney cancer, *Clin Cancer Res*, 2004 Sep 15;10(18 Pt 2):6290S-5S. PMID: 15448019

Kaelin WG Jr. Role of VHL gene mutation in human cancer, *J Clin Oncol*, 2004 Dec 15;22(24):4991-5004., PMID: 15611513

Kaelin WG Jr. von Hippel-Lindau disease. *Annu Rev Pathol*, 2007;2:145-73. PMID: 18039096

Kaelin WG Jr. Treatment of kidney cancer: insights provided by the VHL tumor-suppressor protein, *Cancer*, 2009 May 15;115(10 Suppl):2262-72, PMID: 19402056

Latif F, et al., Identification of the von Hippel-Lindau Disease Tumor Suppressor Gene. *Science*, 1993 260:1317-1320. PMID: 8493574

Li L, et al., New insights into the biology of renal cell carcinoma, *Hematol Oncol Clin North Am*, 2011 Aug; 25(4):667-86. PMID: 21763962

Linehan WM, et al., Molecular diagnosis and therapy of kidney cancer, *Annu Rev Med*, 2010; 61:329-43. PMID 20059341; *Nat Rev Urol*, 2010 May;7(5):277-85. PMID: 20059341

Linehan WM, et al., The genetic basis of kidney cancer: a metabolic disease. *Nat Rev Urol*, 2010 May;7(5):277-85., PMID: 20448661

Nordstrong-O'Brien M, et al., Genetic analysis of von Hippel-Lindau disease. *Hum Mutat 2010*, May;31(50):521-37. PMID: 20151405

Shen C, Kaelin WG, et al., Genetic and Functional Studies Implicate HIF 1a as a 14q Kidney Cancer Suppressor Gene, *Cancer Discov*, 2011 Aug;1(3):222-235., PMID: 22037472

Tsuchiva MI, Shuin T, et al., Renal cell carcinoma- and pheochromocytoma-specific altered gene expression profiles in VHL mutant clones, *Oncol Rep*, 2005 Jun;13(6):1033-41., PMID: 15870918.

SECTION 6

Glossary of Medical Terms

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 CORTEX: The outer layer of the *adrenal glands*; produces steroid and mineral cortecoid hormones.

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.

ANGIOGRAM: 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). In VHL, angiomas are made up of blood vessels and are benign, so are technically *hemangioblastomas*.

ANGIOMATOSIS: Formation of multiple blood vessel *angiomas*. Cerebroretinal angiomatosis is due to von Hippel-Lindau disease.

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

ASYMPTOMATIC: The patient is not experiencing discomfort or other symptoms.

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

AUDIOMETRIC: An audiometric examination 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.

BASIC SCIENCE RESEARCH: Research to prove scientific theories and improve basic understanding of a process. An example is learning more about the mechanisms by which VHL *mutations* cause VHL *tumors*.

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.

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.

CAPILLARIES: The smallest of the 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.

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

CERVICAL SPINE: The part of the spine forming 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.

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*.

CLINICAL RESEARCH: Research which involves interaction with human subjects.

CLONIDINE TEST: A test for growth hormone deficiency.

CODON: A triplet of three bases in a *DNA* molecule, a code for making a single amino acid of a protein.

COMPUTED TOMOGRAPHY (CT) SCAN: A diagnostic procedure using a combination 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*.

CORPUSCLE: A minute body or cell in an organism, especially a red or white cell in the blood.

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.

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

CRYOSURGERY (cryotherapy)**:** 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.

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.

DIFFERENTIAL DIAGNOSIS: Many of the *tumors* of VHL occur in the general population 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.

DIVERTICULITIS: Inflammation or infection of one or more of the pouches in the lining of the intestine.

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.

-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.

EMBRYOLOGICAL: Having to do with the process of development of the baby before birth. The baby starts out as a single cell, from which all organs and tissues develop. As the embryo forms, the cells evolve.

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.

EPIDEMIOLOGIST: A public health professional who studies patterns of disease, causes, and effects in human populations.

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 corticosteroid drug used to replace *aldosterone* in *Addison's Disease*.

FLUORESCEIN ANGIOGRAM: 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.

FUNDUS: The interior of the back of the eye including the *retina* and optic disc.

GADOLINIUM: A *contrast medium* 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*, gall bladder, 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.

GENOME: The entire array of *genes* of an organism or species.

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 testes in men and the ovaries in women, that produce the sperm and eggs that may become children.

GHRELIN: The "hunger hormone" produced in the gastrointestinal tract; inhibits *insulin* secretion stimulated by glucose.

GLOMERULAR FILTRATION RATE (GFR): Calculated from a creatinine test to determine the level of the *kidney* function. This test will be ordered periodically to monitor 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.

GLYCOLISIS: A series of ten reactions using enzymes to convert sugar (glucose) into energy that can be used by the body's cells.

-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 *hemangioma* found especially in VHL, in the eye, brain, or spinal cord.

HEREDITARY: Occurring because of something in the *genes* you got from your parents, something you inherited. Not due to infection or an event during your lifetime.

HYPERNEPHROMA: Now called *renal cell carcinoma (RCC)*.

ICD-10 Code: International Classification of Diseases, 10th revision. The current ICD-10 code for VHL is Q85.8. Codes can be found at cms.gov/medicare-coverage-database/staticpages/icd-10-code-lookup.

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.

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

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

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

KIDNEY: One of a pair of organs in back of the abdominal cavity that filter waste materials out of the blood and pass them out of the body as urine.

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 TREATMENT: 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*.

LEPTIN: The "satiety hormone" suppresses hunger; research is being conducted into other roles of this hormone.

LIPASE: Enzyme involved in the absorption of fats.

LIQUID CHROMATOGRAPY: 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 *phechromocytoma*, 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 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.

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. There is no radiation exposure. 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.

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*. Fractionated *metanephrines* 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.

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*.

MYELOGRAM: A diagnostic procedure which creates an image of the spinal cord. A dye is injected into the spinal canal and *x-ray* pictures are taken of the spinal cord.

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.

NEURAXIS: 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*.

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.

NUCLEAR MEDICINE: Medical procedures for diagnosis and treatment which involve some sort of radioactive isotope.

NYSTAGMUS: Rapid, involuntary eye movements.

OCTREOTIDE SCAN: A scan using octreotide, a radioactive drug similar to somatostatin. The drug is injected into the bloodstream and attaches to *tumor* cells that have somatostatin receptors. A specific device is used to detect where the radioactive drug has attached and creates images. Sometimes called somatostatin receptor scintography (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 .

OPTOMETRIST: An optometrist, or doctor of optometry (OD), is a health care 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 (or *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: 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.

PENETRANCE: The probability that a *gene* will make any effect of its *mutation* evident. The VHL gene has almost complete penetrance, but widely variable expression. In other words, if someone has the altered VHL gene, they will almost certainly have some manifestation of VHL disease within their lifetime, however, the severity of those manifestations will vary widely.

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 technique 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 brain stem and *cerebellum*.

PRE-IMPLANTATION GENETIC DIAGNOSIS (PIGD): 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.

PRE-NATAL DIAGNOSIS: Testing of the child before birth; includes genetic testing of an embryo prior to implantation (*PIGD*).

PROSPECTIVE STUDY: Proposes a scientific question, decides what information is needed to answer the question, and collects data moving forward to obtain the information necessary for the study.

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*.

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

RENAL CELL CARCINOMA (RCC): The most common type of *kidney cancer* in adults; it begins in the lining of the kidney tubules.

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*.

RETROSPECTIVE STUDY: Proposes a scientific question and then "looks back" at existing data.

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.

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

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.

SIGN: Physical evidence of the existence of something which can be demonstrated by a medical doctor.

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

STRABISMUS: A condition where both eyes do not point together at the object being looked at; also known as an eye turn or squint.

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, but small ganglia 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.

THORACIC SPINE: The vertebrae between the neck and the lower back which are connected to the ribs in the back.

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.

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 male genital organs, including the penis and scrotal structures.

VANILLYL MANDELIC ACID (VMA): A urinary metabolite of *epinephrine* and *norepinephrine*. Increased concentration may indicate tumors of the adrenal glands or nervous system, myasthenia gravis, or muscular dystrophy. They may also be due to exercise or stress, as well as certain drugs or foods.

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 normally functioning VHL *gene*.

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

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 7

VHL Support Resources

The world of medicine is changing rapidly. Working together since 1993, the VHL community—patients, physicians, and scientists—has made great strides in learning to control VHL and manage health.

Once you have learned how VHL affects you, you will need the latest information on how to manage your individual screenings 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 (wellness@vhl.org), the VHL Alliance affiliate in your country, or contact a VHL Clinical Care Center (vhl.org/ccc). You can also reach out to the online support resources which can be found at vhl.org/support.

The VHL Alliance can be reached via the telephone at 800-767-4845 x4 toll-free in the US, Canada, and Mexico, or at 617-277-5667 x4. Fax (858-712-8712 or toll-free at 858-712-8712), and mail (1208 VFW Pkwy, Suite 303, Boston, MA 02132) are other methods of communication with the VHL Alliance.

Health care professionals are welcome to call these same numbers or to contact any of our VHL Clinical Care Centers or members of our Clinical Advisory Council to request input on a case. The VHL Alliance has also created list serves to ease the process of acquiring input from multiple sources.

The VHL Handbook Kids' Edition (2009) is also available through the VHL Alliance to help in speaking with your children, whether or not they themselves have VHL. A committee of parents and professionals worked to create this book to help you have a constructive and hopeful conversation with your children about VHL. The future for children with VHL is not like the past. People with VHL today who take an active role in maintaining their health have a better opportunity than ever before to live a full and productive life.

Please share what you have learned and tap into the wonderful support community of which you are now a part. The best way to share your experience with VHL is through the VHL Alliance's **Cancer in Our Genes International Patient (CGIP) Databank** (vhl.org/databank). Your participation in this important clinical study will help us better understand the natural history of VHL and what environmental or lifestyle factors can influence VHL outcomes as well as identify the best procedures for treatment and diagnosis.

Contributions to the VHL Alliance are essential to achieve our common vision of finding a cure!

VHL Alliance's *VISION:*

The VHL Alliance envisions a cure for 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.

Please help to achieve that goal!

Publications of the VHL Alliance

VHL Handbook (2012, 2015)
VHL Handbook Kids' Edition (2009)
VHL Patient Vignettes (2014)
Your Family Health Tree (2013)

Resources on the Internet

Online support groups
Latest information on diagnosis and treatment
See vhl.org

Support VHL Alliance Efforts!

Help cure VHL and other forms of cancer!

Give to the VHL Alliance

Please mail to VHL Alliance, 1208 VFW Parkway, Suite 303, Boston, MA 02132
or send to info@vhl.org. Find us on the web at vhl.org.

Name _____

Billing Address _____

_____

Email _____ Phone _____

☐ **Enclosed is my tax-deductible contribution of:**

☐ $1,000 ☐ $500 ☐ $250 ☐ $100 ☐ $25 ☐ $ _____

☐ **My employer will match my donation. I am enclosing the required paperwork.**

The VHL Alliance is a 501(c)3 non-profit organization—Tax ID: 04-3180414

☐ **Please charge my donation to my credit card**

Card number _____ Expiration date mm/yy_____

Name on card _____

Charge this amount $_____ ☐ One time or ☐ **Sustainer (Monthly)**

Please dedicate my donation ☐ in honor ☐ in memory _____

Please send an acknowledgement card to _____

Address _____

I am a ☐ Person with VHL ☐ Family member ☐ Friend ☐ Sponsor ☐ Health professional _____ (specialty)

☐ Contact me about including the VHLA in my will

Thank you!

I would like to help!

☐ Business Development	☐ Nominating
☐ Clinical Care	☐ Outreach/Mentoring
☐ Marketing	☐ Strategic Planning
☐ Education/Support	☐ Online Communities
☐ Finance	☐ Clinical Advisory Council
☐ Fundraising	☐ Research Council
☐ Leadership Development	☐ Other

THE VHL HANDBOOK:
What You Need to Know About VHL

Edition 5, Revised 2015
Written by the VHL Alliance

International edition (English)
ISBN 978-151941-30-93

VHL ALLIANCE
1208 VFW Pkwy, Suite 303
Boston, MA 02135 USA
800.767.4845 x4
info@vhl.org • vhl.org

VHL Alliance