

VHL gene

Associated Syndrome Name: von Hippel-Lindau syndrome (VHL)

VHL Summary Cancer Risk Table

CANCER	GENETIC CANCER RISK
Endocrine	High Risk
Other	High Risk
Renal	High Risk

VHL gene Overview

von Hippel-Lindau syndrome (VHL) ^{1, 2, 3, 4, 5}

- Individuals with *VHL* gene mutations have von Hippel-Lindau syndrome (VHL).
- Patients with VHL have a high risk for renal cancer, which is often diagnosed at young ages. VHL-related kidney cancers are usually clear cell carcinomas. They are usually multi-focal and bilateral (affecting both kidneys).
- Patients with VHL also have a high risk for pancreatic neuroendocrine tumors (pancreatic NET) and paragangliomas (tumors that form from nerve tissue in the head, neck, or abdomen). These often occur at young ages. The majority of paragangliomas seen in VHL patients occur in the adrenal glands and are called pheochromocytomas. These tumors can secrete hormones that cause symptoms such as high blood pressure, rapid and/or abnormal heartbeat, headaches, sweating, nausea, fatigue and psychological upset.
- VHL can be classified into one of five types (Type 1, Type 1B, Type 2A, Type 2B, and Type 2C). These classifications are based on the most common kinds of tumors seen in patients and the type of *VHL* gene mutation. Although there may be differences in the risk for various tumors and other features of VHL based on these classifications, at the current time there are no differences in the medical management recommendations based on the type of *VHL* gene mutation.
- Patients with VHL often have a wide variety of other non-malignant, but potentially serious, features of the condition. These include hemangioblastomas of the central nervous system and the eye, endolymphatic sac tumors in the ears (which can lead to hearing loss), visceral cysts (especially in the kidneys, pancreas, and liver), and papillary cystadenomas of the broad ligament and epididymis (which can cause infertility in both men and women). These non-malignant features are often the first noticeable symptoms of VHL and can be life-threatening.
- While individuals with VHL have a high risk of cancers and other serious health concerns, these can be greatly reduced with appropriate medical management. Guidelines from the Scientific Advisory Board of the VHL Alliance and National Comprehensive Cancer Network (NCCN) are listed below. Since VHL is a complicated disease affecting a wide variety of organs, it is recommended that individuals with VHL be managed by a multidisciplinary team with expertise in medical genetics and the care of patients with this condition, such as at a designated VHL Clinical Care Center.

VHL gene Cancer Risk Table

CANCER TYPE	AGE RANGE	CANCER RISK	RISK FOR GENERAL POPULATION
Renal	To age 60 ^{6, 7}	17%-70%	0.5%
Paraganglioma/Pheochromocytoma	To age 75 ^{6, 7}	10%-25%	<0.1%
Pancreatic Neuroendocrine Tumors (PNET)	To age 75 ^{4, 6}	5%-17% for tumors, only some of which will be malignant	<0.1%
Other - Non-malignant features of VHL	All ages ^{1, 3, 7, 8}	VHL is associated with a high risk for a wide range of non-malignant clinical features, some of which require medical intervention in early childhood.	NA

VHL Cancer Risk Management Table

The overview of medical management options provided is a summary of professional society guidelines. The most recent version of

each guideline should be consulted for more detailed and up-to-date information before developing a treatment plan for a particular patient.

This overview is provided for informational purposes only and does not constitute a recommendation. While the medical society guidelines summarized herein provide important and useful information, medical management decisions for any particular patient should be made in consultation between that patient and his or her healthcare provider and may differ from society guidelines based on a complete understanding of the patient's personal medical history, surgeries and other treatments.

CANCER TYPE	PROCEDURE	AGE TO BEGIN	FREQUENCY (UNLESS OTHERWISE INDICATED BY FINDINGS)
Renal	Abdominal MRI (preferred) or CT, with and without contrast ^{1, 5, 7}	15 years, or individualized to a younger age based on the earliest renal cancer diagnosis in the family	Every 2 years
Paraganglioma/Pheochromocytoma	Blood pressure and pulse monitoring ^{2, 5, 7}	2 years	Annually or at any medical visit
	Biochemical screening of blood and urine ^{1, 2, 5, 7}	5 years	Annually or prior to any surgical procedure
	Abdominal MRI (preferred) or CT, with and without contrast ^{1, 2, 5, 7}	15 years	Every 2 to 3 years
Pancreatic Neuroendocrine Tumors (PNET)	Abdominal MRI (preferred) or CT, with and without contrast ^{1, 5, 7}	15 years	Every 2 years
Other - Non-malignant features of VHL	Multiple screenings are recommended, including MRI and/or ultrasounds of the brain, spine and abdomen, vision and hearing exams, neurological and psychosocial assessments, blood and urine tests. ^{1, 2, 5, 7}	Some screenings are recommended from birth	Varies, but most are annually
For Patients With A Cancer Diagnosis	For patients with a gene mutation and a diagnosis of a VHL cancer/tumor, targeted therapies may be available as a treatment option for certain tumor types (e.g., inhibitors of HIF-2/03b1 or tyrosine kinase). ^{1, 2}	NA	NA

Information for Family Members

The following information for Family Members will appear as part of the MMT for a patient found to have a mutation in the VHL gene.

This patient's relatives are at risk for carrying the same mutation(s) and associated cancer risks as this patient. Cancer risks for females and males who have this/these mutation(s) are provided below.

Family members should talk to a healthcare provider about genetic testing. Close relatives such as parents, children, brothers and sisters have the highest chance of having the same mutation(s) as this patient. Other more distant relatives such as cousins, aunts, uncles, and grandparents also have a chance of carrying the same mutation(s). Testing of at-risk relatives can identify those family members with the same mutation(s) who may benefit from surveillance and early intervention.

Approximately 20% of individuals with VHL have not inherited the VHL mutation from a parent. In these cases, the mutation has developed spontaneously in that individual (a *de novo* mutation). Once this occurs, the children of that individual are each at 50% risk of inheriting that mutation.⁴

It is appropriate to offer genetic counseling to individuals with VHL who are of reproductive age to discuss reproductive risks and options. There are additional considerations during pregnancy for women with VHL.^{4, 8}

Since VHL mutations carry a risk for complications in children and some screenings are recommended to begin in infancy, mutation

testing should occur as soon as a diagnosis of VHL is suspected.⁷

In rare instances, an individual may inherit certain types of mutations in both copies of the *VHL* gene, leading to the condition familial erythrocytosis type 2, also known as VHL-related congenital erythrocytosis. Individuals with this condition have an abnormally high level of red blood cells, leading to a high risk for blood clots, strokes and other life-threatening medical problems. The children of this patient are at risk of inheriting this condition only if the other parent is also a carrier of a *VHL* mutation. Screening the other biological parent of any children for *VHL* mutations may be appropriate, even if they do not have a diagnosis of VHL.⁴

References

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