

RENAL CELL CARCINOMA AND GENETIC TESTING

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The recommendations contained in this guideline are a consensus of the Alberta Provincial Genitourinary Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

Renal cell carcinomas (RCCs) are the major malignant neoplasm in von Hippel Lindau (VHL) syndrome and a primary cause of inherited renal cancer. Renal cell carcinoma is reported to develop in 24%–45% of VHL patients; if renal cysts are included, the finding of renal lesions increases to 60%.¹ The incidence of VHL has been estimated at 1 in 36,000 births with a mean age at presentation of 39 years,² which is 20 years earlier than the mean age of discovery for sporadic RCC.³⁻⁵ Renal tumors have been reported in individuals with VHL as young as 15 years of age and has over 90% penetrance by age 65.³

Unlike sporadic RCC, the male to female ratio is approximately equal in RCC associated with VHL. Metastatic RCC historically has caused about one third of deaths among VHL patients and in some studies it is the leading cause of death.⁶⁻¹⁰ Renal cell carcinoma the first manifestation of VHL in <20% of cases;^{3,4} eye and central nervous system (CNS) findings usually precede the discovery of renal involvement.⁵ Rarely, VHL may present as atypical autosomal dominant polycystic kidney disease.⁶ RCC in VHL disease is invariably clear cell type, and is both macroscopically and microscopically indistinguishable from sporadic clear cell RCC. However the presence of multiple primary tumours and renal cysts are highly suggestive of VHL disease.⁷

Clinical diagnosis of VHL is based on the presence of at least two characteristic tumors. Therefore, diagnosis of VHL often lags several years behind onset of the first characteristic symptoms.⁸ However, early diagnosis of VHL has been shown to increase survival of patients with VHL-associated RCC, one of the leading causes of mortality in VHL.⁹

Multiple enhancing lesions, or a family history of renal-cell carcinoma, particularly in persons younger than 50 years of age, suggests a hereditary predisposition to the disease. Since VHL has been associated with autosomal dominant mutations in the gene VHL,¹⁰ genetic testing can confirm a diagnosis of VHL and identify family members at risk for developing the disease before they become symptomatic. American Society of Clinical Oncology (ASCO)¹¹ includes VHL as a category 1 hereditary cancer risk and includes patients with a well defined inherited cancer syndrome where the genetic result will affect medical care. Families with VHL disease have been divided into types I and II, based upon the likelihood of developing pheochromocytoma.¹² The subtypes of VHL are illustrated in Table 1.

Table 1. Subtypes of VHL (ASCO)

Subtype of VHL	RCC and/or pancreatic tumors	Typical VHL mutation
Type 1	high risk	large deletion or truncation
Type 2A	low risk	amino acid substitution
Type 2B	high risk	large deletion or truncation
Type 2C	low risk	amino acid substitution

Use of molecular genetic testing for early identification of at-risk family members improves diagnostic certainty and reduces the need for costly screening procedures in those at-risk family members who have not inherited the disease-causing mutation.¹³ ASCO¹¹ identifies VHL syndrome as a Group 1 disorder, i.e., a hereditary syndrome for which genetic testing is considered part of the standard management for at-risk family members.

Early recognition of manifestations of VHL syndrome may allow for timely intervention and improved outcome; thus, clinical surveillance of asymptomatic at-risk individuals, including children, for early manifestations of VHL syndrome is appropriate.

Screening is needed for people who test positive for a VHL mutation, and people who are found not to have the family mutation can be spared from lifelong screening procedures. Genetic testing can also be used to determine if a pregnant woman is carrying a fetus affected with VHL. Families work with a physician, geneticist, or genetic counselor familiar with the most up-to-date information on VHL when having genetic testing, in order to understand the risks, benefits, and current technological limitations prior to testing. One goal of such testing is to free unaffected family members from continued cancer screening.

GUIDELINE QUESTIONS

- What are the best strategies for facilitating earlier detection of von Hippel Lindau (VHL) syndrome in patients presenting with renal cell carcinoma?
- How can treatment outcomes be improved for patients with renal cell carcinoma caused by VHL syndrome?
- What strategies can be used to identify the presence or absence of the VHL gene in symptomatic and asymptomatic individuals (e.g. at-risk family members)?

DEVELOPMENT PANEL

This guideline was reviewed and endorsed by the Alberta Provincial Genitourinary Tumour Team. Members of the Alberta Provincial Genitourinary Tumour Team include medical oncologists, radiation oncologists, urologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Genitourinary Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Utilization Resource Unit Handbook](#).

SEARCH STRATEGY

Entries to MEDLINE (April 2005 to December 2007) and clinical practice guideline databases were searched for evidence relevant to this topic. A total of 20 citations were included in this review.

RECOMMENDATIONS

VHL is the only gene known to be associated with VHL syndrome. Molecular genetic testing of the *VHL* gene detects mutations in nearly 100% of affected individuals and is indicated in all individuals known to have or suspected of having VHL syndrome.¹⁴ The tests outlined in Table 2 are used to establish the diagnosis and determine the extent of clinical manifestations.¹⁵

Table 2. Molecular Genetic Testing Used in VHL Syndrome (Schimke, et al. 2007)¹⁵

Test Method	Mutations Detected	Mutation Detection Frequency *
Sequence analysis ¹⁶	<i>VHL</i> sequence variants	~72%
Deletion analysis ^{16,17}	<i>VHL</i> partial or complete deletion	~28%

* proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

Evaluation criteria for von Hippel-Lindau (VHL)

- Individuals with a VHL associated lesion* AND a family history of VHL associated lesion(s)
- Any individual with TWO VHL-associated lesions including any from the list below, and including one or more hemangiomas of the retina, especially if diagnosed <50 years old
- An individual with any of the following:
 - Hemangioblastoma (HB) diagnosed <30 years old
 - > 2 CNS hemangioblastomas (any age of diagnosis)
 - 1 HB plus (RCC or pheochromocytoma or pancreatic neuroendocrine tumor)
 - Clear cell Renal Carcinoma (RCC) diagnosed <40 years old
 - Bilateral and/or multiple RCC
 - RCC with a positive family history
 - Pheochromocytoma (PHEO) diagnosed <40 years old
 - Bilateral and/or multiple PHEO
 - PHEO with a positive family history
 - >1 pancreatic serous cystadenoma
 - >1 pancreatic neuroendocrine tumor
 - Multiple pancreatic cysts plus any VHL associated lesion
 - Endolymphatic sac tumor (ELST)
 - Epididymal papillary cystadenoma
 - Any blood relative (see Table 3) of an individual diagnosed with VHL disease.

*VHL-associated lesions: hemangioblastoma (HB), clear cell renal carcinoma (RCC), pheochromocytoma (PHEO), endolymphatic sac tumor (ELST), epididymal papillary cystadenoma, pancreatic serous cystadenomas, pancreatic neuroendocrine tumors.

Table 3. Risk for VHL based on relationship to proband (Schimke, et al. 2007)¹⁵

Parents	<ul style="list-style-type: none"> • About 80% of individuals diagnosed with VHL syndrome have an affected parent. • <i>De novo</i> mutations of the <i>VHL</i> gene are estimated to occur in about 20% of probands.¹⁸ <ul style="list-style-type: none"> ○ Recommendations for the evaluation of parents of a proband with an apparent <i>de novo</i> mutation include molecular genetic testing if the <i>VHL</i> disease-causing mutation in the proband is known. ○ If the disease-causing <i>VHL</i> mutation in the proband is not known, ophthalmologic screening and abdominal ultrasound evaluation, at a minimum, should be offered to both parents.
Siblings of a proband	<ul style="list-style-type: none"> • The risk of VHL syndrome to siblings depends upon the genetic status of the parents. • If a parent of a proband is clinically affected or has a disease-causing <i>VHL</i> mutation, the siblings of the proband are at 50% risk of inheriting the altered gene. • If neither parent has the disease-causing <i>VHL</i> mutation identified in the proband, the siblings have a small risk of VHL syndrome because of the possibility of germline mosaicism in one parent. <p><i>Note: Mosaicism has been described; the incidence is not known</i>¹⁸</p>
Offspring of a proband	<ul style="list-style-type: none"> • Each offspring of an affected individual has a 50% risk of inheriting the mutant <i>VHL</i> gene; the degree of clinical severity is not predictable.
Other family members	<ul style="list-style-type: none"> • The risk to other family members depends upon their biological relationship to the affected family member and can be determined by pedigree analysis and/or molecular genetic testing

Since the detection rate for *VHL* gene mutations is nearly 100%, molecular testing may also be used to evaluate individuals with a single *VHL*-associated tumor and a negative family history of the disease. For individuals with manifestations of *VHL* syndrome who do not meet strict diagnostic criteria and who do not have a detectable *VHL* germline mutation, somatic mosaicism for a *de novo VHL* disease-causing mutation should be considered.¹⁸ In some instances, molecular genetic testing of the offspring of such individuals reveals a *VHL* mutation.

Because not all people with *VHL* will meet these diagnostic criteria, *VHL* may be an under-diagnosed disease. Genetic testing can confirm a diagnosis of *VHL* in a person with clinical symptoms, who may or may not meet the above diagnostic criteria.

Surveillance

Individuals with known *VHL* syndrome, individuals without clinical manifestations but known to have a *VHL* disease-causing mutation, and at-risk relatives who have not undergone DNA-based testing need regular clinical monitoring by a physician or medical team familiar with the spectrum of *VHL* syndrome.

Monitoring includes the following:

- Annual ophthalmologic screening, preferably beginning before age five years.¹⁹
- Annual blood pressure monitoring supplemented by measurement of urinary catecholamine metabolites beginning at age five years in those families with a high incidence of pheochromocytoma.
- Annual abdominal ultrasound examination beginning at age 16 years. Suspicious lesions in the kidney, adrenal gland, or pancreas should be evaluated by more sophisticated techniques, such as CT or MRI.
- Audiologic evaluation of individuals with any recognized hearing deficit, followed by T1-weighted MRI of the temporal bone if abnormalities are found.²⁰

Even with the *VHL* gene, once an individual has reached the age of sixty and still has no evidence of *VHL* on these screening tests of *VHL* and has no known children with *VHL*, imaging tests may be recommended every two years for CT and every three years for MRI.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
ASCO	American Society of Clinical Oncology
CNS	central nervous system
CT	computed tomography
ELST	endolymphatic sac tumor
HB	hemangioblastoma
MRI	magnetic resonance imaging
PHEO	pheochromocytoma
RCC	renal cell carcinoma
VHL	von Hippel Lindau

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.

- Send an electronic notification of the new guideline to all members of Alberta Health Services, Cancer Care.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2012. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Genitourinary Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Health Services, Cancer Care recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Genitourinary Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES

- ¹ Zbar B, Brauch H, Talmadge C, Linehan M. Loss of alleles of loci on the short arm of chromosome 3 in renal cell carcinoma. *Nature* 1987;327:721-724.
- ² Maher E, Iselius L, Yates J, Littler M, Benjamin C, Harris R, Sampson J, Williams A, et al. Von Hippel-Lindau disease: a genetic study. *J Med Genet.* 2000 Jan;37(1):62-3.
- ³ Maher E, Yates J, Harries R, Benjamin C, Harris R, Moore A, Ferguson-Smith M. Temporal Sequence. *Q J Med* 1990;77:51-63.
- ⁴ Choyke P, Glenn G, Walther M, Patronas N, Linehan W, Zbar B. von Hippel-Lindau disease: genetic, clinical, and imaging features. *Radiology* 1995; 194(3): 629-642
- ⁵ Malek R, Omess P, Benson R, Zincke H. Renal carcinoma in von Hippel Lindau syndrome. *Am J Med* 1987;82:236-238.
- ⁶ Chatha R, Johnson A, Rothberg P, Townsend R, Neumann H, Gabow P. Von Hippel-Lindau disease masquerading as autosomal dominant polycystic kidney disease. *Am J Kidney Dis.* 2001 Apr;37(4):852-8
- ⁷ Chauveau D, Duvic C, Chretien Y, Paraf F, Droz D, Meli P, Helenon O, Richard S, Grunfield J. Renal involvement in von Hippel-Lindau disease. *Kidney Int,* 1996; 50: 944-951.
- ⁸ Maddock I, Moran A, Maher E, Teare M, Norman A, Payne S, Whitehouse R, Dodd C, Lavin M, et al. A genetic register for von Hippel-Lindau disease. *J Med Genet.* 1996 Feb;33(2):120-7
- ⁹ Richards F, Webster A, McMahon R, Woodward E, Rose S, Maher E. Molecular genetic analysis of von Hippel-Lindau disease: *J Intern Med.* 1998 Jun;243(6):527-33
- ¹⁰ Latif F, Tory K, Gnarr J, Yao M, Duh F, Orcutt M, Stackhouse T, Kuzmin I, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science.* 1993 May 28;260(5112):1317-20
- ¹¹ American Society of Clinical Oncology (2003) Statement on genetic testing for cancer susceptibility.

- ¹² Zbar B, Kishida T, Chen F, Schmidt L, Maher E, Richards F, Crossey P, Webster A, et al. Germline mutations in the Von Hippel-Lindau disease (VHL) gene in families from North America, Europe, and Japan. *Hum Mutat* 1996;8(4):348-57.
- ¹³ Priesemann M, Davies K, Perry L, Drake W, Chew S, Monson J, Savage M, Johnston L. Benefits of screening in von Hippel-Lindau disease--comparison of morbidity associated with initial tumours in affected parents and children. *Horm Res*, 2006; 66:1-5
- ¹⁴ Rasmussen A, Nava-Salazar S, Yescas P, Alonso E, Revuelta R, Ortiz I, Canizales-Quinteros S, Tusie-Luna M, Lopez-Lopez M. Von Hippel-Lindau disease germline mutations in Mexican patients with cerebellar hemangioblastoma. *J Neurosurg*. 2006; 104:389-94
- ¹⁵ Schimke R, Collins D, Stolle C. Von Hippel-Lindau Syndrome. *Gene Reviews*, 2007.
<http://www.geneclinics.org/servlet/access?id=8888892&key=7Vj8uhuK7ugz1&gry=INSERTGRY&fcn=y&fw=bhQi&filename=/glossary/profiles/vhl/details.html#gclD14586#gclD14586>
- ¹⁶ Stolle C, Glenn G, Zbar B, Humphrey JS, Choyke P, Walther M, Pack S, Hurley K, Andrey C, Klausner R, Linehan W. Improved detection of germline mutations in the von Hippel-Lindau disease tumor suppressor gene. *Hum Mutat*, 1998; 12:417-23.
- ¹⁷ Hoebeek J, van der Luijt R, Poppe B, De Smet E, Yigit N, Claes K, Zewald R, de Jong GJ, De Paepe A, Speleman F, Vandesompele J. Rapid detection of VHL exon deletions using real-time quantitative PCR. *Lab Inves*, 2005; 85:24-33.
- ¹⁸ Sgambati M, Stolle C, Choyke P, Walther M, Zbar B, Linehan W, Glenn G. Mosaicism in von Hippel-Lindau disease: lessons from kindreds with germline mutations identified in offspring with mosaic parents. *Am J Hum Genet*. 2000; 66:84-91.
- ¹⁹ Kreusel K, Bechrakis N, Krause L, Neumann H, Foerster M. Retinal angiomas in von Hippel-Lindau disease: a longitudinal ophthalmologic study. *Ophthalmology*. 2006; 113:1418-24
- ²⁰ Kim H, Butman J, Brewer C, Zalewski C, Vortmeyer A, Glenn G, Oldfield E, Lonser R. Tumors of the endolymphatic sac in patients with von Hippel-Lindau disease: implications for their natural history, diagnosis, and treatment. *J Neurosurg*. 2005; 102:503-12.

Additional References:

- Glenn G, Choyke P, Zbar B et al. von Hippel Lindau disease: Clinical aspects and molecular genetics. In: Anderson EE (ed): *Problems in Urologic Surgery: Benign and malignant tumors of the kidney*. Philadelphia, JB Lippincott, 1990;p 312-337
- Horton W, Wong V, Eldridge R. Clinical and pathological manifestations in nine families with 50 affected members. *Arch Intern Med* 1976;136:769-77.
- Joerger M, Koeberle D, Neumann H, Gillissen S. Von Hippel-Lindau Disease – a Rare Disease Important to Recognize. *Onkologie* 2005;28:159-163
- Lamiell J, Salazar F, Hsia Y. von Hippel Lindau disease affecting 43 members of a single kindred. *Medicine* 1989;1-29.
- Neumann H. Basic criteria for clinical diagnosis and genetic counselling in von Hippel Lindau syndrome. *VASA* 1987;16:220-226.
- Richard S, Chavveau D, Chretien Y, et al. Renal lesions and pheochromocytoma in von Hippel Lindau disease. *Adv Nephrol* 1994;23:1-27.