



## Disease Information

Von Hippel-Lindau (VHL) disease is an autosomal dominant familial cancer syndrome caused by mutations in the *VHL* tumor-suppressor gene.<sup>1</sup> VHL disease has a prevalence of approximately 1 in 50,000 and an incidence of 1 in 36,000 per year.<sup>2</sup> Affected patients have a predisposition for developing benign or malignant tumors or cysts in several organs of the body including hemangioblastomas in the central nervous system, renal cysts and renal cell carcinoma, pheochromocytomas, and endolymphatic sac tumors. The *VHL* gene encodes the VHL protein which is involved in multiple cellular processes including tumor suppression, oxygen-related gene expression, and protein assembly.<sup>3</sup> Onset of disease occurs upon the loss of function of both *VHL* alleles.

VHL disease can be classified into two types depending on the risk of developing pheochromocytomas. Type 1 individuals do not present with pheochromocytomas while Type 2 individuals do. Type 2 is further subdivided into Type 2A (patients with a low risk of developing renal cell carcinoma), Type 2B (patients with a high risk of developing renal cell carcinoma), and Type 2C (isolated pheochromocytoma without hemangioblastoma or renal cell carcinoma).<sup>4</sup> Genotypically, Type 2 patients have missense mutations, while deletions or nonsense mutations are usually found in Type 1 individuals.<sup>4</sup> Currently, there is no cure for von Hippel-Lindau disease, but there are treatment options available which have proven helpful for disease management once the VHL disease type has been determined.<sup>5</sup>

## Testing Benefits & Indications

- Diagnostic testing for individuals known or suspected to have von Hippel-Lindau disease can assist in appropriate and effective treatment.
- Carrier screening for relatives of VHL disease patients can also be effective in determining if mutations are present in asymptomatic or pre-symptomatic individuals.
- Carrier testing for known familial mutations can further aide in determining at-risk individuals.
- Prenatal diagnosis may be considered in families with a previous history of VHL disease.

## Test Description

This Ambry Test is a gene sequence analysis performed by PCR-based double-stranded automated sequencing in the sense and antisense directions for exons 1-3 of the *VHL* gene, plus at least 20 bases into the 5' and 3' ends of all the introns. Specific mutation analysis for individual *VHL* mutations known to be in the family is also available.

## Mutation Detection Rate

The Ambry Test: von Hippel-Lindau Disease (VHL) is designed and validated to be capable of detecting ~90% of described mutations in *VHL*. The clinical detection rate using the The Ambry Test: von Hippel-Lindau Disease (VHL) is expected to be ~70%.<sup>6</sup>

## Turn-Around-Time

Gene sequence analysis .....	10 – 21 days
Specific mutation analysis .....	10 – 14 days

## Specimen Requirements

**Blood:** Collect 3-5 cc from adult or 2 cc minimum from child into EDTA purple-top tube (first choice) or ACD yellow-top tube (second choice). Store at room temperature or refrigerate. Ship at room temperature.

**Blood Spot:** Call for availability.

**Saliva:** Collect 2 ml into Oragene™ DNA Self-Collection container. Store and ship at room temperature.

**DNA:** Send 20 µg in TE at 50-100 ng/µl. Store frozen and ship on ice or dry ice.

**Prenatal:** Prenatal testing is available. Please call an Ambry Genetic Counselor to discuss your case.

### CPT Codes

Gene sequence or specific mutation analysis .....83891, 83894x4, 83898x3, 83904x6, 83909x6, 83912

### References

- <sup>1</sup> Latif F et al. *Science*. 1993; 260(5112): 1317-20.
- <sup>2</sup> Maher ER et al. *J Med Genet*. 1991; 28(7): 443-7.
- <sup>3</sup> Gnarr JR et al. *Nat Genet*. 1994; 7(1): 85-90.
- <sup>4</sup> Maher ER et al. *J Med Genet*. 1996; 33(4): 328-32.
- <sup>5</sup> Lonser RR et al. *Lancet*. 2003; 361(9374): 2059-67.
- <sup>6</sup> Stolle C et al. *Hum Mut*. 1998; 12: 417-423.