### Condition Description

Von Hippel-Lindau syndrome (VHL syndrome) is characterized by hemangioblastomas of the brain, spinal cord, and retina; renal cysts and clear cell renal cell carcinoma; pheochromocytoma; and endolymphatic sac tumors. Cerebellar hemangioblastomas may be associated with headache, vomiting, and gait disturbances or ataxia. Retinal hemangioblastomas may be the initial manifestation of VHL syndrome and can cause vision loss. Renal cell carcinoma occurs in about 40% of individuals with VHL and is the leading cause of mortality. Pheochromocytomas can be asymptomatic but may cause sustained or episodic hypertension. Endolymphatic sac tumors can cause hearing loss of varying severity, which can be a presenting symptom.

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. Approximately 72% of VHL mutations are point mutations detected by sequence analysis. Approximately 28% of VHL mutations are partial or complete gene deletions detectable by gene-targeted CGH array. VHL syndrome is inherited in an autosomal dominant manner. Approximately 80% of individuals with VHL syndrome have an affected parent and about 20% have VHL syndrome as the result of a de novo gene mutation.

For patients with suspected VHL, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

### Genes

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<th>VHL</th>
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### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of VHL
- Individuals at-risk for VHL due to family history

### Methodology

PCR amplification of 3 exons contained in the VHL gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

### Detection

Clinical Sensitivity: Molecular genetic testing of the VHL gene detects mutations in nearly 100% of affected individuals. Approximately 72% of VHL mutations are point mutations detected by sequence analysis. Approximately 28% of VHL mutations are partial or complete gene deletions detectable by gene-targeted CGH array. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.
Analytical Sensitivity: ~99%

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

- In EDTA (purple top) or ACD (yellow top) tube:
  - Infants (2 years): 3-5 ml
  - Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

- Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Deletion/duplication analysis of the VHL gene by CGH array is available for those individuals in whom sequence analysis is negative (UW).
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.