# von Hippel-Lindau Syndrome

## Indications for Ordering

- Confirm diagnosis of von Hippel-Lindau (VHL) syndrome
  - Indicated for all individuals known to have or suspected of having VHL syndrome
  - Evaluate individuals with single *VHL*-associated tumor and negative family history for VHL syndrome
- Confirm diagnosis of *VHL*-associated polycythemia (Chuvash polycythemia)
- Determine whether at-risk family members have a *VHL* gene variant

## Test Description

- Polymerase chain reaction followed by bidirectional sequencing of *VHL* coding regions and intron/exon boundaries
- Multiplex ligation-dependent probe amplification to detect large deletions/duplications

## Tests to Consider

### Primary tests

von Hippel-Lindau (*VHL*) Sequencing and Deletion/Duplication 2002965
- Preferred test to confirm a suspected diagnosis of VHL syndrome

von Hippel-Lindau (*VHL*) Sequencing 2002970
- Acceptable initial test to confirm a suspected diagnosis of VHL syndrome
- Preferred test to confirm a suspected diagnosis of *VHL*-associated polycythemia

### Related tests

Familial Mutation, Targeted Sequencing 2001961
- Useful when a familial pathogenic variant identifiable by sequencing is known

Cancer Panel, Hereditary, Sequencing and Deletion/Duplication 2012032
- Confirm diagnosis of a hereditary cancer syndrome with personal or family history consistent with features of more than one cancer syndrome

Hereditary Renal Cancer Panel, Sequencing and Deletion/Duplication 2010214
- Preferred test to confirm a diagnosis of hereditary renal cancer syndrome in individuals with personal or family history of renal cancer

## Disease Overview

### VHL syndrome

**Incidence –** 1/36,000 Caucasian births (Maher, 1991)

**Age of onset**
- Mean age – 26 years
- Life expectancy – <50 years

**Symptoms**
- Penetrance of symptoms in individuals with VHL syndrome (Frantzen, 2015)
  - CNS hemangioblastoma – 80% brain, 20% spinal cord
  - Retinal hemangioblastoma – 70%
  - Renal cell carcinoma – 70%
  - Pheochromocytoma – 10-20%
  - Endolymphatic sac tumor – 10%
  - Pancreatic endocrine tumor – 5-10%
- Other symptoms
  - Hemangiomas in adrenals, lungs, and liver
  - Cysts in kidneys, pancreas, and epididymis

### *VHL*-associated polycythemia

**Prevalence** – rare worldwide, endemic in the Chuvash region of Russia

**Age of onset**
- Birth to early childhood
- Life expectancy – <40 years

**Symptoms**
- Increased serum erythropoietin levels and hemoglobin concentrations during normoxia
  - Leads to increased circulating red blood cell mass
- Increased risk for mortality caused by thrombosis and/or hemorrhage
- No increased risk for tumors that are associated with VHL syndrome

## Genetics

**Gene –** *VHL*

**Inheritance**
- VHL syndrome – autosomal dominant
- *VHL*-associated polycythemia – autosomal recessive

**Penetrance –** nearly complete by age 65 for VHL syndrome

**De novo variants –** ~20% of VHL syndrome cases

**Pathogenic variants –** >300 identified

- Specific *VHL* sequence variants have been associated with *VHL*-associated polycythemia (eg, c.598C>T, p.R200W)

## Test Interpretation

**Sensitivity/specificity**

- Clinical sensitivity
  - VHL syndrome – >99% (Stolle, 1998)
    - ~72% for sequence analysis
    - ~28% for deletion/duplication analysis
  - *VHL*-associated polycythemia (familial erythrocytosis, Chuvash polycythemia) – ~20% (Cario, 2005)
- Analytical sensitivity/specificity of sequencing – 99%
- Analytical sensitivity of deletion/duplication analysis – 90%
- Analytical specificity of deletion/duplication analysis – 98%

**Results**

- Positive
  - *VHL* pathogenic variant detected
    - Diagnosis of VHL syndrome
  - Two pathogenic variants associated with polycythemia are identified
    - *VHL*-associated polycythemia is confirmed
- Negative
  - No *VHL* gene variant detected
    - *VHL*-related syndrome is unlikely, but not excluded
- Inconclusive
  - *VHL* gene variant detected, but whether variant is benign or pathogenic is unknown

**Limitations**

- Not detected
  - Deep intronic or regulatory region variants
- Large deletion/duplication breakpoints will not be determined
- Diagnostic errors can occur due to rare sequence variations

## References


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- Stolle C, et al. Improved detection of germline mutation in the von Hippel-Lindau disease tumor suppressor gene. Human Mutation. 1998:12(6):417-23