VHL (Von Hippel-Lindau Tumor Suppressor, E3 Ubiquitin Protein Ligase) gene, located on chromosome 3p25.3, is a dominantly inherited familial cancer factor, predisposing to a variety of malignant and benign tumors. A germline mutation of this gene is the basis of familial inheritance of von Hippel-Lindau syndrome. The protein encoded is involved in the ubiquitination and degradation of hypoxia-inducible-factor (HIF), which is a transcription factor that plays a central role in the regulation of gene expression by oxygen. Mutations in the VHL gene have been found to cause familial erythrocytosis or Chuvash polycythaemia, a rare autosomal recessive disorder characterized by the overproduction of red blood cells caused by a specific defect in VHL that reduces its ability to destroy HIF and may lead to cardiopulmonary hypertension, cardiac muscle degeneration and the development of severe heart failure. VHL mutations demonstrate autosomal recessive inheritance with a broad range of clinical severity both within and between families. Definitive genotype/phenotype correlations have not been described.

The John Welsh Cardiovascular Diagnostic Laboratory offers molecular genetic testing for VHL mutations. Individuals are tested by DNA sequencing of the coding exons of the VHL gene. We strongly recommend initial testing of a clearly affected individual, if available, in order to provide the greatest test sensitivity and clearest interpretation of results for subsequent family members. Genetic counseling is recommended for all individuals.

REASONS FOR REFERRAL
Molecular confirmation of the diagnosis of CHD, von Hippel-Lindau syndrome and Chuvash polycythaemia.

METHODOLOGY
Genomic DNA is analyzed for VHL mutations by DNA sequencing of the coding exons of the VHL gene, as well as the exon/intron junctions and a portion of the 5’ and 3’ untranslated region. Patient DNA is sequenced in both the forward and reverse orientations. If a mutation is identified, additional family members are analyzed only for the familial mutation by automatic fluorescent DNA sequencing.

SERVICE FEES

<table>
<thead>
<tr>
<th></th>
<th>Direct and Institutional Billing</th>
<th>CPT Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index Case (Male or Female)</td>
<td>$500 per sample</td>
<td>81404</td>
</tr>
<tr>
<td>Additional Family Members</td>
<td>$300 per sample; known familial mutation only</td>
<td>81403</td>
</tr>
</tbody>
</table>

SENSITIVITY
DNA Sequencing Analysis: Approximately 99 percent detection of mutations in the coding exons 1-3 of VHL.

SPECIMEN REQUIREMENTS

Blood (preferred): EDTA (purple-top) tubes: Adult: 5 cc    Child: 5 cc    Infant: 2-3 cc
Tissue: Frozen (preferred), RNAlater
Other Body Fluids or Formalin-fixed, Paraffin-embedded Tissue: Call to inquire