The human PCSK9 gene is located at chromosome 1p32.3 and encompasses 12 exons spanning around 25.4 kb genomic distance. The encoded 692-amino-acid PCSK9 protein appears to control the number of low-density lipoprotein receptors, which are proteins on the surface of cells. These receptors play a critical role in regulating blood cholesterol levels. The receptors bind to particles called low-density lipoproteins (LDLs), which are the primary carriers of cholesterol in the blood. Low-density lipoprotein receptors are particularly abundant in the liver, the organ responsible for removing most excess cholesterol from the body. Several PCSK9 mutations are identified to cause an inherited form of high cholesterol (familial hypercholesterolemia 3). PCSK9 mutations demonstrate autosomal dominant 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 PCSK9 mutations. Individuals are tested by DNA sequencing of the coding exons of the PCSK9 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 familial hypercholesterolemia 3.

**METHODOLOGY**
Genomic DNA is analyzed for PCSK9 mutations by DNA sequencing of the coding exons of the PCSK9 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><strong>Direct and Institutional Billing</strong></th>
<th><strong>CPT Codes</strong></th>
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</thead>
<tbody>
<tr>
<td>Index Case (Male or Female)</td>
<td>$900 per sample</td>
<td>81406</td>
</tr>
<tr>
<td>Additional Family Members</td>
<td>$300 per sample; Known familial mutation only</td>
<td>81403</td>
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</tbody>
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**SENSITIVITY**
DNA Sequencing Analysis: Approximately 99 percent detection of mutations in the coding exons 1-12 of PCSK9.

**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 and Formalin-fixed, Paraffin-embedded Tissue:** Call to inquire