NOTCH1 MUTATION ANALYSIS
JOHN WELSH CARDIOVASCULAR
DIAGNOSTIC LABORATORY

*NOTCH1* gene encodes a member of the Notch family. Notch family members play a role in a variety of developmental processes by controlling cell fate decisions. The Notch signaling network is an evolutionarily conserved intercellular signaling pathway which regulates interactions between physically adjacent cells. This protein functions as a receptor for membrane bound ligands and may play multiple roles during development. *NOTCH1* gene contains 34 exons spanning 51 kb of genomic distance that was mapped to chromosome 9q34.3. Multiple mutations in *NOTCH1* have been identified in patients with ventricular septal defects (VSD), tetralogy of Fallot (TOF), bicuspid aortic valve (BAV), a common defect in the aortic valve in which two rather than three leaflets are present. It is often associated with aortic valve calcification and insufficiency. In extreme cases, the blood flow may be so restricted that the left ventricle fails to grow, resulting in hypoplastic left heart syndrome. *NOTCH1* 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 *NOTCH1* mutations. Individuals are tested by DNA sequencing of the coding exons of the *NOTCH1* 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 bicuspid aortic valve (BAV), hypoplastic left heart syndrome, ventricular septal defects (VSD), tetralogy of Fallot (TOF).

## METHODOLOGY

Genomic DNA is analyzed for *NOTCH1* mutations by DNA sequencing of the coding exons of the *NOTCH1* 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

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<tr>
<th></th>
<th>Direct and Institutional Billing</th>
<th>CPT Codes</th>
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<tbody>
<tr>
<td>Index Case (Male or Female)</td>
<td>$1500 per sample</td>
<td>81407</td>
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<tr>
<td>Additional Family Members</td>
<td>$300 per sample; known familial mutation only</td>
<td>81403</td>
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## SENSITIVITY

DNA Sequencing Analysis: Approximately 99 percent detection of mutations in the coding exons 1-34 of *NOTCH1*

## 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