The **BRAF** gene is located at 7q34 and encodes a protein belonging to the raf/mil family of serine/threonine protein kinases that are part of the ras-MAPK signaling cascade. Upon growth factor stimulation, Raf-1 (or c-Raf) is activated by GTP-bound Ras and recruited to the cell membrane. This activation process is tightly regulated by a number of factors including phosphatases (e.g. PP1, PP2A, PP5), kinases (e.g. Src, ERK, Akt, PKC) and proteins that bind directly to Raf-1 (e.g. RKIP, 14-3-3zeta, KSR, Hsp90). Raf-1 also dimerizes with wild type B-Raf in a Ras-dependent process. Mutations in this gene are associated with cardiofaciocutaneous syndrome, a disease characterized by heart defects, mental retardation and a distinctive facial appearance. These mutations are passed on in an autosomal dominant fashion. Definitive genotype/phenotype correlations have not been described.

The John Welsh Cardiovascular Diagnostic Laboratory offers molecular genetic testing for **BRAF** mutations. Individuals are tested by DNA sequencing of the coding exons of the **BRAF** 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 braf-related cardiofaciocutaneous syndrome and cardiomyopathy.

### METHODOLOGY

Genomic DNA is analyzed for **BRAF** mutations by DNA sequencing of the coding exons of the **BRAF** 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>Service Description</th>
<th>Direct and Institutional Billing</th>
<th>CPT Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index Case (Male or Female)</td>
<td>$1,300 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>
</tr>
</tbody>
</table>

### SENSITIVITY

DNA Sequencing Analysis: Approximately 99 percent detection of mutations in the coding exons 1-18 of **BRAF**.

### SPECIMEN REQUIREMENTS

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