Rapid Mendelian Genes Sequencing Panel, Trio

Mendelian diseases are inherited conditions linked to individual genes. This test entails rapid sequencing of ~4,900 genes of known function from a critically ill individual and both parents to quickly diagnose a Mendelian disease to improve medical management.

**TEST OVERVIEW**

- Although humans have ~19,000 genes, the function of only ~4,900 genes is known.
  - This test only sequences genes with known function
- See Rapid Mendelian Sequencing Gene List for genes included in this panel.
- Parental specimens are required to identify de novo variants and to determine phase and clinical significance of variants detected in proband.

**Required for Testing**

- Blood specimens from the proband and both parents
- Completed Informed Consent for Rapid Mendelian Genes Sequencing Panel, Trio form for proband
- Completed Patient History for Rapid Mendelian Genes Sequencing Panel, Trio form
- Clinical summary from genetic consultation (if available)
- Three-generation medical pedigree
- Copy of abnormal results, which may include:
  - Genomic microarray
  - Skeletal survey
  - Magnetic resonance imaging (MRI)

**TEST INTERPRETATION**

**Clinical Sensitivity**

50% for infants (Willig, 2015; Daoud, 2016)

**Reporting and Interpretation**

- Accurate representation of biological relationships between family members is imperative for correct test interpretation.
- Only variants predicted to be related to the patient’s medical issues are reported.
- Interpretation is based on information available at the time of testing and may change in the future.
- Results are typically reported in 14-28 days.

**Secondary Findings**

- American College of Medical Genetics and Genomics (ACMG) recommends that disease-causing variants in specific genes (see ACMG list in table below) be reported whether or not they are related to the patient’s medical issues (Kalia, 2016).
  - This information may enable disease monitoring or early treatment.
  - Single pathogenic variants in autosomal recessive genes from this list are not reported.
- Additional medically actionable secondary findings may be reported at ARUP’s discretion.
- Pathogenic variants in genes recommended by ACMG, or other medically actionable secondary findings in non-ACMG genes, are reported if elected on the consent form.
- Parental inheritance is not reported for secondary variants detected in the proband.
• Parents are not issued reports of secondary findings.
• Familial Mutation, Targeted Sequencing (2001961) can be ordered on the parents to test for a medically actionable secondary finding reported in the proband.

Limitations
• A negative result does not exclude the possibility of a genetic condition.
• Diagnostic errors can occur due to rare sequence variations.
• Interpretation of this test result may be impacted if the individual or his/her parents have had an allogeneic stem cell transplantation.
• The following will not be evaluated:
  - Genes with unknown function
  - Variants outside coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Large deletions/duplications
  - Noncoding transcripts
• The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Pathogenic ACMG variants that cannot be detected by massively parallel sequencing
  - Low-level mosaic variants

Analytic Sensitivity
For massively parallel sequencing:

<table>
<thead>
<tr>
<th>Variant Class</th>
<th>Analytical Sensitivity (PPA) Estimate</th>
<th>Analytical Sensitivity (PPA) 95% Credibility Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNVs</td>
<td>99.2</td>
<td>96.9-99.4</td>
</tr>
<tr>
<td>Deletions 1-10 bp</td>
<td>93.8</td>
<td>84.3-98.2</td>
</tr>
<tr>
<td>Deletions 11-44 bp</td>
<td>100</td>
<td>87.8-100</td>
</tr>
<tr>
<td>Insertions 1-10 bp</td>
<td>94.8</td>
<td>86.8-98.5</td>
</tr>
<tr>
<td>Insertions 11-23 bp</td>
<td>100</td>
<td>62.1-100</td>
</tr>
</tbody>
</table>

a Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.
bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

ACMG (Kalia, 2016) Recommends Reporting Secondary Findings for These Genes

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Associated Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumors/cancer syndromes</td>
<td></td>
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<tr>
<td>Familial adenomatous polyposis</td>
<td>APC</td>
</tr>
<tr>
<td>Familial medullary thyroid cancer</td>
<td>RET</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 2</td>
<td>RET</td>
</tr>
<tr>
<td>Hereditary breast and ovarian cancer</td>
<td>BRCA1, BRCA2</td>
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<tr>
<td>Hereditary paraganglioma/pheochromocytoma</td>
<td>SDHD, SDHAF2, SDHC, SDHB</td>
</tr>
<tr>
<td>Juvenile polyposis</td>
<td>BMPR1A, SMAD4</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>TP53</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 1</td>
<td>MEN1</td>
</tr>
<tr>
<td>MUTYH-associated polyposis</td>
<td>MUTYH</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>NF2</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK11</td>
</tr>
<tr>
<td>PTEN hamartoma tumor syndrome</td>
<td>PTEN</td>
</tr>
<tr>
<td>Conditions</td>
<td>Associated Genes</td>
</tr>
<tr>
<td>------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>RB1</td>
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<tr>
<td>Tuberous sclerosis complex</td>
<td>TSC1, TSC2</td>
</tr>
<tr>
<td>Von Hippel-Lindau syndrome</td>
<td>VHL</td>
</tr>
<tr>
<td>WT1-related Wilms tumor</td>
<td>WT1</td>
</tr>
</tbody>
</table>

**Cardiovascular conditions/syndromes**
- Arrhythmogenic right-ventricular cardiomyopathy: PKP2, DSP, DSC2, TMEM43, DSG2
- Brugada syndrome: KCNQ1, KCNH2, SCN5A
- Romano-Ward long QT syndrome types 1, 2, and 3: KCNQ1, KCNH2, SCN5A
- Catecholaminergic polymorphic ventricular tachycardia: RYR2
- Ehlers-Danlos syndrome, vascular type: COL3A1
- Familial hypercholesterolemia: LDLR, APOB, PCSK9
- Familial thoracic aortic aneurysms and dissections: SMAD3, ACTA2, MYLK, MYH11
- Hypertrophic cardiomyopathy, dilated cardiomyopathy: MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA
- Loeys-Dietz: TGFB1, TGFB2
- Marfan syndrome: FBN1

**Other conditions**
- Malignant hyperthermia susceptibility: RYR1, CACNA1S
- Ornithine transcarbamylase deficiency: OTC
- Wilson disease: ATP7B

**REFERENCES**


**RELATED TESTS**

**Exome Sequencing, Trio 2006332**
Method: Massively Parallel Sequencing

**Exome Sequencing, Proband 2006336**
Method: Massively Parallel Sequencing