

## 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<sup>1,2</sup>

#### 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.<sup>3</sup>
  - 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.

### Tests to Consider

#### [Rapid Mendelian Genes Sequencing Panel, Trio 2012849](#)

**Method:** Massively Parallel Sequencing

Order for rapid diagnosis of a critically ill individual suspected to be affected with a Mendelian genetic condition

See [Related Tests](#)



## 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:

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

<sup>a</sup>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 Recommends Reporting Secondary Findings for These Genes<sup>3</sup>

Conditions	Associated Genes
Tumors/cancer syndromes	Familial adenomatous polyposis <i>APC</i>
	Familial medullary thyroid cancer Multiple endocrine neoplasia type 2 <i>RET</i>
	Hereditary breast and ovarian cancer <i>BRCA1, BRCA2</i>
	Hereditary paraganglioma/pheochromocytoma <i>SDHD, SDHAF2, SDHC, SDHB</i>
	Juvenile polyposis <i>BMPR1A, SMAD4</i>
	Li-Fraumeni syndrome <i>TP53</i>
	Lynch syndrome <i>MLH1, MSH2, MSH6, PMS2</i>



Conditions	Associated Genes
Multiple endocrine neoplasia type 1	<i>MEN1</i>
<i>MUTYH</i> -associated polyposis	<i>MUTYH</i>
Neurofibromatosis type 2	<i>NF2</i>
Peutz-Jeghers syndrome	<i>STK11</i>
<i>PTEN</i> hamartoma tumor syndrome	<i>PTEN</i>
Retinoblastoma	<i>RB1</i>
Tuberous sclerosis complex	<i>TSC1, TSC2</i>
Von Hippel-Lindau syndrome	<i>VHL</i>
<i>WT1</i> -related Wilms tumor	<i>WT1</i>
<b>Cardiovascular conditions/syndromes</b>	
Arrhythmogenic right-ventricular cardiomyopathy	<i>PKP2, DSP, DSC2, TMEM43, DSG2</i>
Brugada syndrome	<i>KCNQ1, KCNH2, SCN5A</i>
Romano-Ward long QT syndrome types 1, 2, and 3	
Catecholaminergic polymorphic ventricular tachycardia	<i>RYR2</i>
Ehlers-Danlos syndrome, vascular type	<i>COL3A1</i>
Familial hypercholesterolemia	<i>LDLR, APOB, PCSK9</i>
Familial thoracic aortic aneurysms and dissections	<i>SMAD3, ACTA2, MYLK, MYH11</i>
Hypertrophic cardiomyopathy, dilated cardiomyopathy	<i>MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA</i>
Loeys-Dietz	<i>TGFBR1, TGFBR2</i>
Marfan syndrome	<i>FBN1</i>
<b>Other conditions</b>	
Malignant hyperthermia susceptibility	<i>RYR1, CACNA1S</i>
Ornithine transcarbamylase deficiency	<i>OTC</i>
Wilson disease	<i>ATP7B</i>

## References

- Willig LK, Petrikin JE, Smith LD, et al. [Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings](#). *Lancet Respir Med*. 2015;3(5):377-387. PubMed



2. Daoud H, Luco SM, Li R, et al. [Next-generation sequencing for diagnosis of rare diseases in the neonatal intensive care unit](#). CMAJ. 2016;188(11):E254-E260. PubMed
3. Kalia SS, Adelman K, Bale SJ, et al. [Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update \(ACMG SF v2.0\): a policy statement of the American College of Medical Genetics and Genomics](#) [published correction appears in Genet Med. 2017 Apr;19(4):484]. Genet Med. 2017;19(2):249-255. PubMed

## Related Tests

### [Exome Sequencing, Proband 2006336](#)

**Method:** Massively Parallel Sequencing

### [Exome Sequencing, Trio 2006332](#)

**Method:** Massively Parallel Sequencing

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