Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	Unknown
Gender:	Unknown
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Malignant Hyperthermia Panel, Sequencing

ARUP test code 3002688

Malignant Hyperthermia Specimen	Whole Blood

Malignant Hyperthermia Interp

Positive

RESULT
One pathogenic variant was detected in the RYR1 gene.

PATHOGENIC VARIANT
Gene: RYR1 (NM_000540.3)
Nucleic Acid Change: c.742G>C; Heterozygous
Amino Acid Alteration: p.Gly248Arg
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.742G>C; p.Gly248Arg, was detected in the RYR1 gene by massively parallel sequencing. Pathogenic gain-of-function RYR1 variants are inherited in an autosomal dominant manner, and are associated with malignant hyperthermia susceptibility (MHS). Individuals who are susceptible to MH should avoid triggering volatile anesthetics and succinylcholine. Guidelines for genotype-based dosing are published by the Clinical Pharmacogenetic Implementation Consortium (CPIC; see link below).

Please refer to the background information included in this report for a list of the genes analyzed, methodology and limitations of this test.

Evidence for variant classification:
The RYR1 c.742G>C; p.Gly248Arg variant (rs1801086) is published in the literature in several individuals affected with malignant hyperthermia (MH), confirmed by caffeine/halothane contracture test (Brandom 2013, Gillies 2008, Sambuughin 2001, Sei 2004) and is considered diagnostic for MH by the European Malignant Hyperthermia group. The variant is described as pathogenic by several sources in the ClinVar database (Variation ID: 133203) and is only found on 4 alleles in the Genome Aggregation Database, indicating it is not a common polymorphism. The glycine at codon 248 is highly conserved and computational analyses predict that this variant is deleterious (REVEL: 0.883). In support of this prediction, functional studies show variants in this region cause hyperactive RYR1 channels (Tong 1997). Based on available information, this variant is classified as pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical management. At-risk family members should be offered testing for the identified pathogenic RYR1 variant (Familial

H=High, L=Low, *=Abnormal, C=Critical

Targeted Sequencing, ARUP test code 3005867).

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics. Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations:
NONE

REFERENCES
Brandom BW et al. Ryanodine receptor type 1 gene variants in the malignant hyperthermia-susceptible population of the United States. Anesth Analg. 2013 May;116(5):1078-86.
CPIC Guideline for Potent Volatile Anesthetic Agents and Succinylcholine and RYR1 and CACNA1S: https://cpicpgx.org/guidelines/cpic-guideline-for-ryr1-and-cacna1s
Gillies RL et al. Identification of genetic mutations in Australian malignant hyperthermia families using sequencing of RYR1 hotspots. Anaesth Intensive Care. 2008 May;36(3):391-403.
Sambuughin N et al. North American malignant hyperthermia population: screening of the ryanodine receptor gene and identification of novel mutations. Anesthesiology. 2001 Sep;95(3):594-9.
Sei Y et al. Malignant hyperthermia in North America: genetic screening of the three hot spots in the type I ryanodine receptor gene. Anesthesiology. 2004 Oct;101(4):824-30.
Tong J et al. Caffeine and halothane sensitivity of intracellular Ca2+ release is altered by 15 calcium release channel (ryanodine receptor) mutations associated with malignant hyperthermia and/or central core disease. J Biol Chem. 1997 Oct 17;272(42):26332-9.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Malignant Hyperthermia Panel, Sequencing

CHARACTERISTICS: Malignant hyperthermia (MH) is a pharmacogenetic disorder of skeletal muscle calcium regulation, which is commonly triggered by volatile anesthetics, either with or without the depolarizing muscle relaxant succinylcholine. Excessive calcium release from the sarcoplasmic reticulum leads to disturbance of the intracellular calcium ion homeostasis causing skeletal muscle contraction and hypermetabolism. The hypermetabolic state generates heat and excess lactate and can result in hypercarbia, tachycardia, hyperkalemia, hyperthermia, acidosis, muscle rigidity, compartment syndrome, rhabdomyolysis, myoglobinuria, and potentially death. Episodes of MH require prompt diagnosis and treatment to reduce mortality.

EPIDEMIOLOGY: Approximately 1 in 2,000 individuals has a pathogenic variant in an MH susceptibility gene. As not all MH-susceptible individuals are exposed to triggering agents, the estimated prevalence of anesthesia-related MH is 1-2 per 100,000.

CAUSE: Pathogenic germline gain-of-function variants in the RYR1 or CACNA1S genes.

INHERITANCE: Autosomal dominant.

PENETRANCE: Incomplete; overall penetrance of 40 percent for RYR1-associated MH susceptibility.

CLINICAL SENSITIVITY: Up to 60 percent for MH susceptibility.

GENES TESTED: RYR1*, CACNA1S
*One or more exons are not covered by sequencing for the indicated gene; see limitations section below.

METHODOLOGY: Capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity of sequencing is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a heritable form of malignant hyperthermia susceptibility. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants and deep intronic variants will not be identified.
Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level mosaic or somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
RYR1 (NM_000540) exon 91

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Malignant Hyperthermia Specimen	22-307-112046	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Malignant Hyperthermia Interp	22-307-112046	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical