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

Physician: Doctor, Example

Patient: Patient, Example

DOB	5/23/2021
Sex:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Malignant Hyperthermia Panel, Sequencing

ARUP test code 3002688

Malignant Hyperthermia Specimen	Whole Blood
Malignant Hyperthermia Interp	Negative

RESULT
No pathogenic variants were detected in the CACNA1S and RYR1 genes.

INTERPRETATION
No pathogenic variants were identified by massively parallel sequencing of the coding regions and exon-intron boundaries of the CACNA1S and RYR1 genes. This result decreases the likelihood of, but does not exclude, a diagnosis of malignant hyperthermia susceptibility (MHS). Please refer to the background information included in this report for the limitations of this test.

RECOMMENDATIONS
Medical screening and management should rely on clinical findings and family history. If clinical findings and/or family history of MHS are present, caffeine/halothane contracture testing on muscle tissue is recommended. Genetic consultation is recommended.

COMMENTS
Likely benign and benign variants are not included in this report.

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	21-145-111181	5/25/2021 12:29:00 PM	5/25/2021 12 29:20 PM	5/25/2021 12:35:00 PM
Malignant Hyperthermia Interp	21-145-111181	5/25/2021 12:29:00 PM	5/25/2021 12 29:20 PM	5/25/2021 12:35:00 PM

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

END OF CHART

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