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

Physician: Doctor, Example

Patient: Patient, Example

DOB	7/21/1967
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Familial Mediterranean Fever (MEFV) Sequencing

ARUP test code 3004434

FMF Specimen	Whole Blood
FMF Interp	Positive

RESULT
Two pathogenic variants were detected in the MEFV gene.

PATHOGENIC VARIANT
Gene: MEFV (NM_000243.3)
Nucleic Acid Change: c.2080A>G; Heterozygous
Amino Acid Alteration: p.Met694Val
Inheritance: Autosomal recessive

PATHOGENIC VARIANT
Gene: MEFV (NM_000243.3)
Nucleic Acid Change: c.2177T>C; Heterozygous
Amino Acid Alteration: p.Val726Ala
Inheritance: Autosomal recessive

INTERPRETATION
Two pathogenic variants, c.2080A>G; p.Met694Val, and c.2177T>C; p.Val726Ala, were detected in the MEFV gene by massively parallel sequencing. Based on the sequencing reads, we were able to determine that these two pathogenic variants are on opposite chromosomes. This individual is predicted to be affected with familial Mediterranean fever (FMF, MIM: 249100).

Please refer to the background information included in this report for the methodology and limitations of this test.

Evidence for variant classification:
The MEFV c.2080A>G;p.Met694Val variant (rs61752717) has been published as a common familial Mediterranean fever (FMF) pathogenic variant (The International FMF Consortium 1997, Touitou 2001). Functional analysis of the variant protein shows diminished capacity to suppress IL-8 secretion in synovial cell cultures (Sugiyama 2014). This variant is reported as pathogenic by multiple laboratories in ClinVar (Variation ID: 2538), and is seen in the general population at an overall frequency of 0.03% (77/282876 including 1 homozygote) in the Genome Aggregation Database. Additionally, another variant at this codon (Met694Ile) has been reported in individuals with FMF and is considered pathogenic (Sugiyama 2014). Based on the above information, this variant is considered pathogenic.

The MEFV c.2177T>C; p.Val726Ala variant (rs28940579) has been published in the literature in individuals with familial Mediterranean fever, juvenile idiopathic arthritis, ankylosing spondylitis, systemic lupus erythematosus and multiple sclerosis

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

with or without another pathogenic variant (Camus 2012, Comack 2013, Cosan 2010, Shinar 2012, Unal 2010). The variant is listed in the ClinVar database (Variation ID: 2540), and is observed in the general population at an overall frequency of 0.19% (561/282870 alleles) in the Genome Aggregation Database. Based on available information, this variant is considered to be pathogenic. Pathogenic MEFV variants are causative for familial Mediterranean fever (MIM: 608107).

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. Parental testing should be considered to confirm the chromosomal origin of the identified variants. At risk family members should be offered testing for the variant in their family lineage (Familial Targeted Sequencing, ARUP test code 3005867). This individual's reproductive partner should be offered carrier screening for FMF.

COMMENTS
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
The International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. 1997 Cell. 90:797-807. PMID: 9288758.
Camus D et al. 'Silent' carriage of two familial Mediterranean fever gene mutations in large families with only a single identified patient. Clin Genet. 2012 82(3):288-91. PMID: 21995303.
Comak E et al. MEFV gene mutations in Turkish children with juvenile idiopathic arthritis. Eur J Pediatr. 2013 172(8):1061-7. PMID: 23588594.
Cosan F et al. Association of familial Mediterranean fever-related MEFV variations with ankylosing spondylitis. Arthritis Rheum. 2010 62(11):3232-6. PMID: 20669279.
Shinar Y et al. Familial Mediterranean FeVer gene (MEFV) mutations as a modifier of systemic lupus erythematosus. Lupus. 2012 21(9):993-8. PMID: 22532615.
Sugiyama R et al. Defect of suppression of inflammasome-independent interleukin-8 secretion from SW982 synovial sarcoma cells by familial Mediterranean fever-derived pyrin mutations. Mol Biol Rep. 2014 Jan;41(1):545-53. PMID: 24318677.
Touitou I. The spectrum of Familial Mediterranean Fever (FMF) mutations. Eur J Hum Genet. 2001 9(7):478-483. PMID: 11464238.
Unal A et al. Evaluation of common mutations in the Mediterranean fever gene in Multiple Sclerosis patients: is it a susceptibility gene? J Neurol Sci. 2010 294(1-2):38-42. PMID: 20483145.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Familial Mediterranean Fever (MEFV) Sequencing

CHARACTERISTICS: Familial Mediterranean fever (FMF) is a genetic condition characterized by recurrent but short-lived attacks of fever, abdominal pain, joint pain, and/or skin rashes. Symptoms and frequency of these attacks are highly variable. Renal amyloidosis is another common complication in untreated individuals and may be the only manifestation in some patients.

CAUSE: Pathogenic germline variants in the MEFV gene

INHERITANCE: Autosomal recessive, although some heterozygous individuals may have symptoms

CLINICAL SENSITIVITY: 75-90%

GENE TESTED: MEFV (NM_000243)

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted MEFV gene, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics. Human genome build 19 (Hg 19) was used for data analysis.

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

LIMITATIONS: A negative result does not exclude a diagnosis of familial Mediterranean fever. This test only detects variants within the coding regions and intron-exon boundaries of the MEFV gene. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) mutations, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. 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
FMF Specimen	23-318-136849	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
FMF Interp	23-318-136849	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