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

Physician: Doctor, Example

Patient: Patient, Example

DOB	6/18/1991
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Periodic Fever Syndromes Panel, Sequencing and Deletion/Duplication

ARUP test code 2007370

Periodic Fever Panel Specimen	Whole Blood
Periodic Fever Panel Interp	Positive

RESULT
One likely pathogenic variant was detected in the NOD2 gene. One variant of uncertain significance was detected in the MEFV gene.

LIKELY PATHOGENIC VARIANT
Gene: NOD2 (NM_022162.3)
Nucleic Acid Change: c.1001G>T; Heterozygous
Amino Acid Alteration: p.Arg334Leu
Inheritance: Autosomal Dominant

VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: MEFV (NM_000243.3)
Nucleic Acid Change: c.590G>A; Heterozygous
Amino Acid Alteration: p.Gly197Asp
Inheritance: Autosomal Recessive

INTERPRETATION
One likely pathogenic variant, c.1001G>T; p.Arg334Leu, was detected in the NOD2 gene by massively parallel sequencing. Pathogenic germline NOD2 variants are inherited in an autosomal dominant manner, and are associated with Blau syndrome (MIM: 186580). This result is consistent with a diagnosis of Blau syndrome. This individual's offspring have a 50 percent chance of inheriting the likely pathogenic variant.

Additionally, one variant of uncertain clinical significance, c.590G>A; p.Gly197Asp, was detected in the MEFV gene by massively parallel sequencing. Pathogenic variants in MEFV are primarily associated with autosomal recessive familial Mediterranean fever (FMF, MIM: 249100). Although most FMF carriers are asymptomatic, symptoms have been reported in some apparent carriers of a single pathogenic MEFV variant (autosomal dominant FMF, MIM: 134610). However, it is uncertain whether this variant is disease-associated or benign.

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 classifications:
The NOD2 c.1001G>T; p.Arg334Leu variant is reported in the literature in an individual with Blau syndrome (Li 2017). This variant is absent from the Genome Aggregation Database (v2.1.1), indicating it is not a common polymorphism. Computational analyses predict that this variant is deleterious (REVEL:

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

0.772). Additionally, other variants at this codon (c.1001G>A, p.Arg334Gln; c.1000C>T, p.Arg334Trp) have been reported in individuals with Blau syndrome and are considered pathogenic (Li 2017, Miceli-Richard 2001, Zhong 2022). Based on available information, the p.Arg334Leu variant is considered to be likely pathogenic.

The MEFV c.590G>A; p.Gly197Asp variant (rs906108610), to our knowledge, is not reported in the medical literature or gene specific databases. This variant is only observed on one allele in the Genome Aggregation Database (v2.1.1), indicating it is not a common polymorphism. Computational analyses are uncertain whether this variant is neutral or deleterious (REVEL: 0.213). Due to limited information, the clinical significance of this variant is uncertain at this time.

RECOMMENDATIONS
Medical screening and management should rely on clinical findings and family history. Genetic consultation is recommended. At-risk family members should be offered testing for the identified likely pathogenic NOD2 variant (Familial Targeted Sequencing, ARUP test code 3005867). Surveillance of the literature for new information concerning the uncertain variant is recommended.

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
Li C et al. Gene mutations and clinical phenotypes in Chinese children with Blau syndrome. Sci China Life Sci. 2017 Jul;60(7):758-762. PMID: 28639104.
Miceli-Richard C et al. CARD15 mutations in Blau syndrome. Nat Genet. 2001 Sep;29(1):19-20. PMID: 11528384.
Zhong Z et al. Genetic and Clinical Features of Blau Syndrome among Chinese Patients with Uveitis. Ophthalmology. 2022 Jul;129(7):821-828. PMID: 35314268.

This result has been reviewed and approved by [redacted]
BACKGROUND INFORMATION: Periodic Fever Syndromes Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Periodic fever syndromes, also called autoinflammatory disorders, are a group of disorders which often present with recurrent inflammatory symptoms such as fever. The etiology of periodic fever syndromes is broad and includes infectious diseases, neoplastic conditions, inflammatory disorders, autoimmune conditions, and hereditary conditions. Conditions tested with this panel include familial Mediterranean fever (FMF) (MEFV gene), cyclic neutropenia and severe congenital neutropenia (ELANE gene), Majeed syndrome (LPIN2 gene), hyperimmunoglobulinemia D syndrome (HIDS) (MVK gene), mevalonate kinase-associated periodic fever syndrome (MVK gene), familial cold autoinflammatory syndrome (FCAS) (NLRP3 gene, NLRP12 gene), Muckle-Wells syndrome (NLRP3 gene), neonatal onset multisystem inflammatory disease (NOMID)/chronic infantile neurological cutaneous and articular syndrome (CINCA) (NLRP3 gene), Blau syndrome/pediatric granulomatous arthritis (NOD2 gene), pyogenic sterile arthritis pyoderma gangrenosum acne (PAPA) (PSTPIP1 gene), Behcet-like familial autoinflammatory syndrome (TNFAIP3 gene), and tumor necrosis factor receptor-associated periodic syndrome (TRAPS) (TNFRSF1A gene).

GENES TESTED: ELANE, LPIN2, MEFV, MVK, NLRP12, NLRP3, NOD2, PSTPIP1, TNFAIP3, TNFRSF1A

INHERITANCE: Autosomal recessive for MVK and LPIN2; autosomal

dominant for TNFAIP3, TNFRSF1A, NOD2, NLRP12, NLRP3, ELANE, and PSTPIP1. MEFV variants are typically autosomal recessive, but some heterozygous individuals may be symptomatic.

METHODOLOGY: Probe hybridization-based 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. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications were confirmed using an orthogonal exon-level microarray. 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. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a heritable form of a periodic fever syndrome. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. 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. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. This test is not intended to detect duplications of two or fewer exons in size, though these may be identified. Single exon deletions are detected with a lower sensitivity. 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 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.

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Periodic Fever Panel Specimen	23-318-401262	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Periodic Fever Panel Interp	23-318-401262	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