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

Physician: Doctor, Example

Patient: Patient, Example

DOB	[redacted]
Gender:	Male
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	Negative

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

INDICATION FOR TESTING
Not provided.

RESULT
No pathogenic variants were detected in any of the genes tested.

INTERPRETATION
No pathogenic variants were identified by massively parallel sequencing of the coding regions and exon-intron boundaries of the genes tested. No large exonic deletions and duplications were identified in the genes tested. This result decreases the likelihood of, but does not exclude, a diagnosis of periodic fever syndromes. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

RECOMMENDATIONS
Medical screening and management should rely on clinical findings and family history. Genetic consultation may be helpful.

LIKELY BENIGN VARIANT
Gene: NOD2 (NM_022162.2) Variant: c.866A>G; p.Asn289Ser - Heterozygous
The NOD2 c.866A>G; p.Asn289Ser variant (rs5743271) is reported in the medical literature in one individual with an autoinflammatory disease (Yao 2015), but is most often published in association with Crohn's disease (Giradelli 2018, Huang 2017, Lesage 2002). The variant is reported in the ClinVar database (Variation ID: 319440) and in the European (non-Finnish) population with a 0.7% (850/128880 alleles including 5 homozygotes) in the Genome Aggregation Database. The amino acid at this position is highly conserved but computational algorithms (PolyPhen-2, SIFT) predict this variant is tolerated. This variant is published at an increased frequency in individuals with Crohn's disease (Huang 2017) and may be a risk factor for Crohn's disease, possibly together with other genetic and/or environmental factors. However, due to a population frequency incompatible with a periodic fever disease such as Blau syndrome, this variant is considered to be likely benign.

COMMENTS
Additional likely benign and benign variants are not included in this report.

REFERENCES
Girardelli M et al. Genetic profile of patients with early onset inflammatory bowel disease. Gene. 2018 Mar 1;645:18-29.
Huang H et al. Fine-mapping inflammatory bowel disease loci to single-variant resolution. Nature. 2017 Jul 13;547(7662):173-178.
Lesage S et al. CARD15/NOD2 mutational analysis and genotype-phenotype correlation in 612 patients with inflammatory bowel disease. Am J Hum Genet. 2002 Apr;70(4):845-57.
Yao Q et al. NOD2-associated autoinflammatory disease: a large cohort study. Rheumatology (Oxford). 2015 Oct;54(10):1904-12.

This result has been reviewed and approved by Weimin Sun, Ph.D.

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) syndrome (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), autoinflammatory syndrome, familial, Behcet-like (TNFAIP3 gene), and tumor necrosis factor receptor-associated periodic syndrome (TRAPS) (TNFRSF1A gene).

EPIDEMIOLOGY: The prevalence varies by condition and ethnicity.

INHERITANCE: Autosomal recessive for MEFV, MVK, LPIN2; autosomal dominant for TNFAIP3, TNFRSF1A, NOD2, NLRP12, NLRP3, ELANE, and PSTPIP1.

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

** - Deletion/duplication detection is not available for this gene.

METHODOLOGY: Targeted 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 custom tiled comparative genomic hybridization array (aCGH) was used to detect large deletions or duplications in the indicated subset of genes. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: The analytical sensitivity of this test 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 a periodic fever syndrome. 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 and breakpoints of large deletions/duplications will not be determined. Single exon deletions/duplications or deletions/duplications less than 1kb may not be detected. Deletions/duplications/insertions of any size may not be detected by massive 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 somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

Single exon deletions/duplications will not be called for the following exons:
LPIN2(NM_014646) 13,16;MVK(NM_000431) 11;PSTPIP1(NM_001321136) 2;PSTPIP1(NM_003978) 10;TNFRSF1A(NM_001346092) 6

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Periodic Fever Panel Specimen	19-363-400079	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Periodic Fever Panel Interp	19-363-400079	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