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

Cobalamin/Propionate/Homocysteine Metabolism Related Disorders Panel, Sequencing and Deletion/Duplication

ARUP test code 2011157

Cobalamin/Propionate/Homocysteine Spec	Whole Blood
Cobalamin/Propionate/Homocysteine Int	Negative

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

Section 79-1 of New York State Civil Rights Law requires informed consent be obtained from patients (or their legal guardians) prior to pursuing genetic testing. These forms must be kept on file by the ordering physician. Consent forms for genetic testing are available at www.aruplab.com. Incidental findings are not reported unless clinically significant but are available upon request.

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 a cobalamin/propionate/homocysteine metabolism related disorder. Please refer to the background information included in this report for a list of genes analyzed and limitations of this test.

RECOMMENDATIONS
Medical screening and management should rely on biochemical and clinical findings and family history. Genetic consultation is recommended.

LIKELY BENIGN VARIANT
Gene: MTR (NM_000254.2) Variant: c.3712-7T>G - Heterozygous
The MTR c.3712-7T>G variant (rs151081130) to our knowledge, is not reported in the medical literature but is reported in ClinVar (Variation ID: 296585). This variant is found in the East Asian population with an allele frequency of 1.3% (240/18,870 alleles) in the Genome Aggregation Database. This is an intronic variant in a weakly conserved nucleotide, and computational analyses (Alamut v.2.11) predict that this variant does not alter splicing. Based on available information, the c.3712-7T>G variant is considered to be likely benign.

COMMENTS
Benign variants are not included in this report, but are available upon request.

This result has been reviewed and approved by Yuan Ji, PhD, FACMG.

BACKGROUND INFORMATION: Cobalamin/Propionate/Homocysteine Metabolism Related Disorders Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Inherited disorders of cobalamin metabolism include defects of absorption, transport, and intracellular metabolism. Defects of cobalamin metabolism lead to the accumulation of methylmalonic acid, methionine, and/or homocysteine in blood and urine. Usually, an elevated propionylcarnitine level and/or propionyl/acetylcarnitine ratio is detected in plasma, and increased methylmalonic acid is detected in blood, despite normal or elevated vitamin B12 levels. The clinical features of these disorders are highly variable, with onset ranging from the neonatal period to adulthood.

EPIDEMIOLOGY: The frequency of methylmalonic aciduria from all causes in North America is 1 in 48,000-61,000; isolated methylmalonic acidemia is 1 in 50,000-100,000; combined malonic/methylmalonic aciduria is estimated to be 1 in 30,000; methylmalonic aciduria and homocystinuria, cblC type is 1 in 67,000; homocystinuria due to cystathionine beta-synthase

deficiency is reported as 1 in 1,800 in Qatar, 1 in 6,400 in Norway, and 1 in 17,800 in Germany; homocystinuria, B6-responsive and nonresponsive types combined are 1 in 58,000-1,000,000; propionic acidemia is 1 in 50,000-100,000 but higher in the Inuit in Greenland with 1 in 1,000-2,000, and in Saudi Arabia with 1 in 5,000. Prevalence is rare for the other disorders included in the panel.

CAUSE: Pathogenic germline variants in genes associated with cobalamin metabolism.

INHERITANCE: X-linked for HCFC1; autosomal dominant or autosomal recessive for MAT1A; and autosomal recessive for all the other genes tested.

PENETRANCE: Reduced for MAT1, MCEE, LMBRD1, and TCN1 genes.

GENES TESTED: ABCD4, ACSF3, ADK**, AHCY**, AMN, CBS, CD320, CUBN, GIF, GNMT**, HCFC1, LMBRD1, MAT1A, MCEE, MMAA, MMAB, MMACHC, MMADHC, MTHFR, MTR, MTRR, MUT, PCCA, PCCB, SUCLA2, SUCLG1, TCN1, TCN2

** - 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 cobalamin metabolism disorders. 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:
ABCD4(NM_005050) 1;HCFC1(NM_005334) 26;MTHFR(NM_001330358) 1;PCCB(NM_001178014) 4;SUCLA2(NM_003850) 11

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
Cobalamin/Propionate/Homocysteine Spec	19-091-114752	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Cobalamin/Propionate/Homocysteine Int	19-091-114752	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