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

Physician: Doctor, Example

Patient: Patient, Example

DOB	2/15/1955
Gender:	Female
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	Positive

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 the genes analyzed and limitations of this test.

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

SUSCEPTIBILITY VARIANT
MTHFR (NM_005957.5): c.665C>T, p.Ala222Val; Heterozygous
The MTHFR c.665C>T; p.Ala222Val variant (rs1801133), also known as C677T or the thermolabile variant, is listed in the ClinVar database (Variation ID: 3520) and is observed in the general population with an overall allele frequency of 30.8% (87,234/282,784 alleles including 15,819 homozygotes) in the Genome Aggregation Database. The thermolabile c.665C>T variant in the homozygous state has been correlated with reduced enzyme activity and increased homocysteine (Frosst 1995). The practice guidelines from The American College of Medical Genetics state that this variant in the heterozygous state is unlikely to be of clinical significance (Hickey 2013); however, a possible effect of this variant when paired with a pathogenic MTHFR variant on the opposite chromosome cannot be excluded. Additionally, the practice guidelines state that an individual who is homozygous for the c.665C>T; p.Ala222Val variant and has elevated homocysteine may be at mildly increased risk for venous thromboembolism and recurrent pregnancy loss (Hickey 2013). The variant is considered a ''susceptibility'' or an ''association'' variant.

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

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

limitations; reportable variants are confirmed by Sanger sequencing:
NONE

REFERENCES
Frosst P et al. A candidate genetic risk factor for vascular disease: A common mutation in methylenetetrahydrofolate reductase. Nat. Genet. 10, 111-113. PMID: 7647779
Hickey SE et al. ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. Genet Med 2013; 15(2):153-156. PMID: 23288205

This result has been reviewed and approved by [redacted]
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 in the vitamin B metabolic pathway. Abnormal biochemical findings may include elevated propionylcarnitine level and/or propionyl/acetylcarnitine ratio in plasma and increased methylmalonic acid in blood; vitamin B12 levels may be normal or elevated. The clinical features of these disorders are highly variable, with multiple systems affected, and onset ranges from the neonatal period to adulthood.

EPIDEMIOLOGY: The true prevalence of the disorders of cobalamin metabolism is unknown. The frequency of isolated methylmalonic acidemia is 1 in 50,000-100,000; overall frequency of methylmalonic aciduria and homocystinuria, cblC type is estimated at 1 in 200,000; worldwide frequency of homocystinuria due to cystathionine beta-synthase deficiency is reported as 1 in 200,000 to 1 in 344,000; propionic acidemia incidence is 1 in 105,000-130,000 in the United States. Prevalence is rare for the other disorders included in the panel.

CAUSE: Pathogenic germline variants in genes associated with the cobalamin metabolic pathway

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

PENETRANCE: Reduced for MAT1A, MCEE, and LMBRD1 genes.

GENES TESTED: ABCD4,* ACSF3, ADK, AHCY, AMN,* CBLIF, CBS,* CD320, CTH, CUBN, HCFC1, IVD,* LMBRD1, MAT1A, MCEE, MLYCD, MMAA, MMAB, MMACHC, MMADHC, MMUT, MTHFR, MTR, MTRR, PCCA,* PCCB, SUCLA2,* SUCLG1, TCN2
*One or more exons are not covered by sequencing and/or deletion/duplication analysis for the indicated gene; see limitations section below.

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 to confirm reported variants that do not meet acceptable quality metrics. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: 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 cobalamin metabolism disorders. 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 2 or fewer exons in size, though these may be identified. Single exon deletions are reported but called at 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.

The following regions are not sequenced due to technical limitations of the assay:
ABCD4 (NM_001353592, NM_001353599, NM_001353600, NM_001353609) partial exon(s) 17 (Chr14:74753377-74753383)
ABCD4 (NM_001353594, NM_001353601, NM_001353606, NM_001353608) partial exon(s) 16 (Chr14:74753377-74753383)
ABCD4 (NM_001353607) partial exon(s) 15(Chr14:74753377-74753383)
ABCD4 (NM_001353610) partial exon(s) 14(Chr14:74755363-74755398)
ABCD4 (NM_020325) partial exon(s) 18(Chr14:74753377-74753383)
CBS (NM_001321072) exon(s) 1
IVD (NM_001354597) exon(s) 1
IVD (NM_001354598, NM_001354600) exon(s) 12,13
IVD (NM_001354601) exon(s) 12
IVD (NM_001354599, NM_001354600) partial exon(s) 2(Chr15:40699947-40700010)
PCCA (NM_001352609) exon(s) 22
SUCLA2 (NM_003850) partial exon(s) 8(Chr13:48528275-48528320)

Single exon deletions/duplications will not be called for the following exons:
AMN (NM_030943) 10; CBS (NM_001321072) 1; IVD (NM_001354597) 1; IVD (NM_001354598, NM_001354600) 12-13; IVD (NM_001354601) 12; PCCA (NM_001352609) 22

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
Cobalamin/Propionate/Homocysteine Spec	22-228-401439	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Cobalamin/Propionate/Homocysteine Int	22-228-401439	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