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

Physician: Doctor, Example

Patient: Patient, Example

DOB	1/10/1975
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Alpha Thalassemia (HBA1 and HBA2) Deletion/Duplication with reflex to Hb Constant Spring

ARUP test code 3003651

HBA DDCS Interpretation	See Note

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

Indication for testing: Carrier screening or diagnostic testing for alpha thalassemia.

RESULT
Two copies of a pathogenic deletion, resulting in the deletion of two alpha globin gene copies, were detected in the alpha globin gene cluster.

DNA VARIANT
Pathogenic Deletion: -alpha3.7; Homozygous
Predicted Genotype: -a/-a

INTERPRETATION
Two copies of the pathogenic 3.7kb deletion were detected by deletion/duplication analysis of the alpha globin gene cluster. The hemoglobin Constant Spring variant was not detected. This individual is predicted to have a single functional alpha globin gene on both chromosomes. This result is consistent with alpha thalassemia trait often associated with mild anemia and microcytosis. The clinical presentation may vary due to other genetic modifiers or coexisting conditions.

Evidence for variant classification: The pathogenic -alpha3.7 deletion is a common large deletion observed in numerous populations, including African, Indian, Far East and Mediterranean (HbVar database and references therein). This deletion removes approximately 3.7kb of the alpha globin cluster, resulting in a single functional alpha globin gene on the affected chromosome. Heterozygosity for this deletion does not result in clinical symptoms, but may be mistaken for iron deficiency. Homozygosity for this deletion is often associated with mild anemia and microcytosis.

RECOMMENDATIONS
Medical management should rely on clinical findings and family history. If clinical findings are suggestive of alpha thalassemia disease, consider alpha globin gene sequencing. Screening for alpha globin gene variants should be offered to the reproductive partner and the relatives of this individual. Genetic consultation is recommended.

COMMENTS
Reference Sequences: GenBank # NM_000517.4 (HBA2), NG_000006.1 (alpha globin gene cluster) Nucleotide numbering begins at the "A" of the ATG initiation codon.

REFERENCES
HbVar 3.7kb deletion link: http://globin.bx.psu.edu/cgibin/hbvar/query_vars3?mode=output&display_format=page&i=1076

This result has been reviewed and approved by [redacted]

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INTERPRETIVE INFORMATION: Alpha Thal (HBA1/2) DelDup w/rflx HbCS

Characteristics of Alpha Thalassemia: Decreased or absent synthesis of the hemoglobin (Hb) alpha-chain resulting in clinical presentations ranging from asymptomatic silent carriers to severe anemia and fetal lethality. Alpha thalassemia silent carrier commonly results from deletion of a single alpha globin gene (-a/aa) and is clinically asymptomatic. Alpha thalassemia trait may be caused by deletion of a single alpha globin gene from both chromosomes (-a/-a), or deletion of the HBA1 and HBA2 globin genes from the same chromosome (--/aa). Heterozygosity for Hb Constant Spring (HbCS) is usually asymptomatic but may be associated with mild microcytic anemia. Homozygous HbCS is characterized by overt hemolytic anemia, jaundice and splenomegaly. Hemoglobin H disease occurs due to inactivation of three alpha globin genes and results in hemolysis with Heinz bodies, moderate anemia, and splenomegaly. Hb Bart hydrops fetalis syndrome results from deletion of all four alpha globin genes (--/--) and is lethal in the fetal or early neonatal period. Alpha globin gene duplication results in three or more active alpha globin genes on a single chromosome.
Epidemiology: Carrier frequency of alpha thalassemia in African, African-American (1:3), Mediterranean (1:30-50), Middle Eastern, Southeast Asian (1:20).
Inheritance: Autosomal recessive.
Cause: Pathogenic variants in the alpha globin gene cluster (HBZ, HBM, HBA2, HBA1, HBQ1) or regulatory region.
Clinical Sensitivity: Varies by ethnicity, at least 90 percent.
Methodology: Multiplex ligation-dependent probe amplification (MLPA) for the HBZ, HBM, HBA2, HBA1, and HBQ1 genes, the HS-40 regulatory region, and Hb Constant Spring (HbCS) HBA2 c.427T>C; p.Ter143Gln. To determine copy number of HbCS in absence of a concurrent deletion of HBA2, PCR and bidirectional sequencing for HbCS is performed.
Analytical Sensitivity and Specificity: 99 percent.
Limitations: Diagnostic errors can occur due to rare sequence variations. Specific breakpoints of large deletions/duplications will not be determined; therefore, it may not be possible to distinguish variants of similar size. Non-deletional variants within the coding or regulatory regions of the alpha globin cluster genes, other than HbCS, will not be targeted. Individuals carrying both a deletion and duplication within the alpha globin gene cluster may appear to have a normal number of alpha globin gene copies. Rare syndromic or acquired forms of alpha thalassemia associated with ATRX gene variants will not be detected.

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
HBA DDCS Interpretation	24-142-402777	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART