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

Physician: Doctor, Example

Patient: Patient, Example

DOB	11/7/1979
Sex:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Hereditary Erythrocytosis Panel, Sequencing

ARUP test code 3005721

ECYT Specimen	Whole Blood
ECYT Interp	Positive

RESULT
One likely pathogenic variant was detected in the HBB gene. Please note, this test cannot differentiate between germline (inherited) and somatic (acquired) variants when performed on whole blood from individuals with active hematological disease or abnormal complete blood count. Further testing may be warranted.

LIKELY PATHOGENIC VARIANT
Gene: HBB (NM_000518.5)
Nucleic Acid Change: c.293A>T; Heterozygous
Amino Acid Alteration: His97Leu
Commonly Known As: Hb Wood
Inheritance: Autosomal Dominant

INTERPRETATION
One likely pathogenic variant, c.293A>T; His97Leu, was detected in the HBB gene by massively parallel sequencing in this whole blood sample. Pathogenic germline HBB variants are associated with autosomal dominant familial erythrocytosis 6 (MIM: 617980), delta-beta thalassemia (MIM: 141749), Heinz body anemia (MIM: 140700), hereditary persistence of fetal hemoglobin (MIM: 141749) and methemoglobinemia (MIM: 617971) and autosomal recessive sickle cell disease (MIM: 603903; OMIM(R)). This particular HBB variant is associated with autosomal dominant erythrocytosis. Therefore, this result is consistent with a diagnosis of erythrocytosis if this variant is determined to be germline in origin. If determined to be germline, this individual s offspring have a 50 percent chance of inheriting the likely pathogenic variant.

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 classification:
The Hb Wood variant (HBB: c.293A>T; p.His98Leu, also known as His97Leu when numbered from the mature protein, rs33951978, HbVar ID: 445, ClinVar Variation ID: 15390) is reported in the literature in individuals with erythrocytosis (McClure 2006, HbVar and references therein). This variant is absent from the Genome Aggregation Database (v2.1.1), indicating it is not a common polymorphism. Additionally, other variants at this codon (c.294C>A and c.294C>G, p.His98Gln, Hb Malmo, HbVar ID: 444) have been reported in individuals with erythrocytosis and are considered pathogenic (HbVar and references therein).

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

Computational analyses predict that the p.His98Leu variant is deleterious (REVEL: 0.9), and functional studies showed Hb Wood is a high-oxygen affinity hemoglobin (HbVar and references therein). Based on available information, this variant is considered to be likely pathogenic.

RECOMMENDATIONS
Genetic and hematologic consultations are indicated, including a discussion of medical screening and management. Close correlation with clinical findings, family history, and laboratory data including hematologic parameters is recommended. If this variant was detected in a whole blood sample from an individual with active hematological disease or abnormal complete blood count, confirmation of this variant in an unaffected sample type (i.e. cultured skin fibroblasts) is necessary to establish germline variant status. Additionally, interpretation of this test result may be impacted if the patient had an allogeneic stem cell transplant. If determined to be germline, at-risk family members, especially potential stem cell donors, may consider testing for the identified likely pathogenic HBB variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

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 limitations: None

REFERENCES
Link to HbVar database: https://globin.bx.psu.edu/hbvar/menu.html
McClure RF et al. The JAK2 V617F mutation is absent in patients with erythrocytosis due to high oxygen affinity hemoglobin variants. Hemoglobin. 2006;30(4):487-9. PMID: 16987804

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Hereditary Erythrocytosis Panel, Sequencing

CHARACTERISTICS: Hereditary erythrocytosis, also known as familial erythrocytosis or congenital polycythemia, is a group of disorders in which inherited/germline pathogenic variants cause increased red blood cell (RBC) production, leading to elevated hemoglobin and hematocrit levels. Symptoms may include headaches, dizziness, dyspnea, and epistaxis. Overabundance of RBC may lead to hemorrhagic or thrombotic events, including myocardial infarction and deep vein thrombosis, although many individuals with erythrocytosis experience mild symptoms and may even be asymptomatic. Hereditary erythrocytosis can be categorized as primary, caused by pathogenic variants leading to intrinsic defects in hematopoietic stem cells that increase RBC production, or secondary caused by pathogenic variants that drive RBC production by increasing erythropoietin (EPO). Hereditary erythrocytosis is suspected in individuals for whom acquired erythrocytosis (either primary or secondary) has been excluded, and in those with early age of onset or a family history of erythrocytosis.

EPIDEMIOLOGY: Hereditary erythrocytosis is rare but the exact prevalence is unknown. Up to 70 percent of cases have no identified cause and are classified as idiopathic erythrocytosis.

CAUSE: Pathogenic germline variants in genes associated with erythrocytosis

INHERITANCE: Mostly autosomal dominant with some autosomal recessive disorders

GENES TESTED: BPGM, EGLN1 (PHD2), EPAS1 (HIF2), EPOR, HBB, HIF1A, JAK2, SH2B3, VHL*
*One or more exons are not covered by sequencing 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. 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. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a diagnosis of erythrocytosis. 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, deep intronic variants, and large deletions/duplications will not be identified. 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 variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) mutations, or repeat expansions. This assay is also not intended to detect somatic variants associated with hematologic malignancy, though such variants may be detected incidentally. Though this test is designed to identify germline variants associated with erythrocytosis, it cannot definitively determine the germline or somatic origin of detected variants when the patient has acquired erythrocytosis or hematologic malignancy and the assay is performed on blood or other tissue that may be contaminated by clonal or malignant cells. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

SNVs and indels will not be called in the following regions due to technical limitations of the assay: VHL (NM_001354723) exon 2

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. 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
ECYT Specimen	25-129-131126	5/9/2025 11:09:00 AM	5/9/2025 11:48:15 PM	5/22/2025 2:52:00 PM

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

ECYT Interp	25-129-131126	5/9/2025 11:09:00 AM	5/9/2025 11:48:15 PM	5/22/2025 2:52:00 PM

END OF CHART

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