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

Physician: Doctor, Example

Patient: Patient, Example

DOB	2/20/1978
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Pulmonary Arterial Hypertension (PAH) Panel, Sequencing and Deletion/Duplication

ARUP test code 2009345

PAH Pan. Seq/DelDup, Specimen	Whole Blood

PAH Pan. Seq/DelDup, Interp

Positive

RESULT
One likely pathogenic variant was detected in the BMPR2 gene.

LIKELY PATHOGENIC VARIANT
Gene: BMPR2 (NM_001204.7)
Nucleic Acid Change: c.1129-3C>G; Heterozygous
Inheritance: Autosomal dominant

INTERPRETATION
One likely pathogenic variant, c.1129-3C>G, was detected in the BMPR2 gene by massively parallel sequencing. Pathogenic variants in BMPR2 are inherited in an autosomal dominant manner with reduced penetrance and are associated with familial primary pulmonary hypertension, fenfluramine or dexfenfluramine-associated primary pulmonary hypertension (MIM: 178600), and pulmonary venooclusive disease 1 (MIM: 265450). This individual's offspring have a 50 percent chance of inheriting the causative variant; due to reduced penetrance, they have a 20 percent risk for developing pulmonary arterial hypertension (Cogan 2012).

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 BMPR2 c.1129-3C>G variant (rs748230358) is reported in the literature in several individuals and families affected with pulmonary arterial hypertension (Cogan 2006, Elliott 2006, Liu 2012, Machado 2001, Machado 2006). This variant is also reported in ClinVar (Variation ID: 425878) and is only observed on one allele in the Genome Aggregation Database, indicating it is not a common polymorphism. This is an intronic variant in a weakly conserved nucleotide, but computational analyses (Alamut Visual Plus v.1.5.1) predict that this variant may impact splicing by weakening the nearby canonical acceptor splice site. Functional assays show that the c.1129-3C>G variant results in an out-of-frame transcript that is targeted by nonsense mediated decay (Cogan 2006). Based on available information, this variant is considered to be likely pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified likely pathogenic BMPR2

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

variant (Familial Targeted Sequencing, ARUP test code 3005867).

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
Cogan et al. Role of BMPR2 alternative splicing in HPAH penetrance. Circulation 2012; 126(15): 1907-16. PMID: 22923426.
Cogan JD et al. High frequency of BMPR2 exonic deletions/duplications in familial pulmonary arterial hypertension. Am J Respir Crit Care Med. 2006 Sep 1;174(5):590-8. PMID: 16728714.
Elliott CG et al. Relationship of BMPR2 mutations to vasoreactivity in pulmonary arterial hypertension. Circulation. 2006 May 30;113(21):2509-15. PMID: 16717148.
Liu D et al. Molecular genetics and clinical features of Chinese idiopathic and heritable pulmonary arterial hypertension patients. Eur Respir J. 2012 Mar;39(3):597-603. PMID: 21737554.
Machado RD et al. BMPR2 haploinsufficiency as the inherited molecular mechanism for primary pulmonary hypertension. Am J Hum Genet. 2001 Jan;68(1):92-102. PMID: 11115378.
Machado RD et al. Mutations of the TGF-beta type II receptor BMPR2 in pulmonary arterial hypertension. Hum Mutat. 2006 Feb;27(2):121-32. PMID: 16429395.

This result has been reviewed and approved by [redacted]
BACKGROUND INFORMATION: Pulmonary Arterial Hypertension (PAH)Panel, Sequencing and Deletion/Duplication
CHARACTERISTICS: Pulmonary arterial hypertension (PAH) is caused by widespread occlusion or destruction of the smallest pulmonary arteries, leading to increased blood flow resistance, right ventricular hypertrophy, and heart failure. Approximately 80 percent of PAH is idiopathic and 20 percent is heritable.

EPIDEMIOLOGY: The incidence is 1-2 in 1,000,000.

INHERITANCE: Autosomal dominant (ACVRL1, BMPR2, CAV1, ENG, KCNA5, KCNK3, GDF2, and SMAD9); autosomal recessive (EIF2AK4, TBX4)

CLINICAL SENSITIVITY: 75-80 percent for familial cases, approximately 25 percent for simplex cases.

GENES TESTED: ACVRL1, BMPR2, CAV1, EIF2AK4, ENG,* KCNA5, KCNK3, GDF2, SMAD9, and TBX4

*One or more exons are not covered by deletion/duplication analysis; see limitations section below.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes (including the 5' UTR of ENG, and a region of ACVRL1 intron 9 encompassing the CT-rich variant hotspot region), 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/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. 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 PAH. 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) variants, 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.

Single exon deletions/duplications may not be called in the following exons: ENG (NM_001114753) 1

This test was developed and its performance characteristics determined by ARUP Laboratories. The U.S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use. The results are not intended to be used as the sole means for clinical diagnosis or patient management decisions.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
PAH Pan. Seq/DelDup, Specimen	23-124-402918	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
PAH Pan. Seq/DelDup, Interp	23-124-402918	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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