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

Physician: Doctor, Example

Patient: Patient, Example

DOB	1/1/1989
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Polycystic Kidney Disease, Autosomal Dominant (PKD1 and PKD2) Sequencing and Deletion/Duplication (Temporary Referral as of 06/09/20)

ARUP test code 2012250

ADPKD Seq and Del/Dup Specimen	Whole Blood

ADPKD Seq, Del/Dup Interp

Positive *

TEST PERFORMED - 2012250
TEST DESCRIPTION - Polycystic Kidney Disease, Autosomal Dominant (PKD1 and PKD2) Sequencing and Deletion/Duplication
INDICATION FOR TEST - Confirm Diagnosis

RESULT
One pathogenic variant and one variant of uncertain significance were detected in the PKD1 gene. No pathogenic variants were detected in the PKD2 gene.

DNA VARIANTS
Classification: Pathogenic
Gene: PKD1
Nucleic Acid Change: c.4070delT; Heterozygous
Amino Acid Alteration: p.Leu1357fs

Classification: Uncertain
Gene: PKD1
Nucleic Acid Change: c.3486C>G; Heterozygous
Amino Acid Alteration: p.Asp1162Glu

INTERPRETATION
One copy each of a pathogenic variant, c.4070delT; p.Leu1357fs, and a variant of uncertain clinical significance, c.3486C>G; p.Asp1162Glu, were detected in the PKD1 gene by sequencing. The presence of the pathogenic variant is consistent with a diagnosis of autosomal dominant polycystic kidney disease (ADPKD); clinical manifestations are variable and age-dependent. This individual's offspring have a 50 percent chance of inheriting the causative pathogenic variant.

No pathogenic variants were detected by sequencing the PKD2 gene and deletion/duplication analysis of the PKD1 and PKD2 genes.

Evidence for variant classification: The PKD1 c.4070delT; p.Leu1357fs variant is reported in several individuals and families with autosomal dominant polycystic kidney disease (ADPKD; Audrezet 2012 Kim 2019, Rossetti 2007) and is listed in the ClinVar database (Variation ID: 636886). This variant is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. This variant causes a frameshift by deleting a single nucleotide, so it is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay.

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

Additionally, several downstream truncating variants have been described in individuals affected with ADPKD (Audrezet 2012, Rossetti 2007). Based on available information, this variant is considered to be pathogenic.

The PKD1 c.3486C>G; p.Asp1162Glu variant (rs144211349), to our knowledge, is not reported in the medical literature or gene specific databases. This variant is found in the general population with an overall allele frequency of 0.015% (32/220,520 alleles) in the Genome Aggregation Database. The aspartic acid at codon 1162 is highly conserved, but computational analyses (SIFT: Tolerated, PolyPhen-2: Possibly Damaging) predict conflicting effects of this variant on protein structure/function. Due to limited information, the clinical significance of the p.Asp1162Glu variant is uncertain at this time.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. Renal imaging is recommended for at-risk adult family members. If imaging results are equivocal, targeted testing for the pathogenic PKD1 variant should be considered (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). To clarify the clinical significance of the identified variant with unknown significance and to determine if it exists on the same or different copy of the PKD1 gene as the c.4070delT variant, contact ARUP's licensed genetic counselor (800-242-2787 x2141) to determine the possibility for performing a family correlation study.

COMMENTS
Reference Sequences: GenBank # NM_001009944.2 (PKD1), NM_000297.3 (PKD2)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not included in this report.

REFERENCES
Audrezet MP et al. Autosomal dominant polycystic kidney disease: comprehensive mutation analysis of PKD1 and PKD2 in 700 unrelated patients. Hum Mutat. 2012 Aug;33(8):1239-50.
Kim H et al. Genetic Characteristics of Korean Patients with Autosomal Dominant Polycystic Kidney Disease by Targeted Exome Sequencing. Sci Rep. 2019 Nov 18;9(1):16952.
Rossetti S et al. Comprehensive molecular diagnostics in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 2007 Jul;18(7):2143-60.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Polycystic Kidney Disease, Autosomal Dominant (PKD1 and PKD2) Sequencing and Deletion/Duplication

CHARACTERISTICS: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is typically an adult-onset, multisystem disorder. Renal findings include: bilateral renal cysts, renal insufficiency, renal pain, hypertension, dilated renal tubules, enlarged kidneys, and end-stage renal disease (ESRD). Extra-renal findings include cysts in other organs, including liver, pancreas, seminal vesicles, and arachnoid membrane. Connective tissue findings include intracranial aneurysms, dolichoectasia, dilation of the aortic root, aortic dissections, mitral valve prolapse, and abdominal wall hernias. Fifty percent of individuals with ADPKD will develop ESRD by age 60.

PREVALENCE: 1:500-1:1,000 in the U.S.

INHERITANCE: Autosomal dominant; 5-10 percent of cases are de novo.

PENETRANCE: Age-dependent; nearly all older adults develop multiple renal cysts. The average age of onset for ESRD in individuals with PKD1 and PKD2 mutations is 54 and 74 years, respectively.

CAUSE: Pathogenic PKD1 or PKD2 gene mutations. In cases with an identifiable molecular cause, 85 percent are attributed to PKD1 and 15 percent are attributed to PKD2.

CLINICAL SENSITIVITY: 90 percent for ADPKD. Approximately 87 percent of cases are due to sequence variants and up to 3 percent of cases result from large deletions/duplications in PKD1 or PKD2.

METHODOLOGY: Bidirectional sequencing of the entire coding region and intron/exon boundaries of the PKD1 and PKD2 genes. A large region of PKD1, including exons 1-33, is duplicated six times on the same chromosome; therefore, to distinguish the PKD1 gene from the PKD1-like pseudogenes, long range PCR followed by site-specific PCR is used to sequence PKD1 exons 1-33. Multiplex ligation-dependent probe amplification (MLPA) is used to detect large exonic deletions/duplications of PKD1 or PKD2.

ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.

LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Regulatory region mutations and deep intronic mutations in PKD1 or PKD2 will not be detected. Large deletions/duplications of PKD1 exons 1, 2, 4, 8, 17, 24, 28, 32, 34, and 45 will not be detected. Mosaic mutations in PKD1 or PKD2 may not be detected. Breakpoints for large deletions/duplications will not be determined. Mutations in genes other than PKD1 and PKD2 are not assessed by this assay.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
ADPKD Seq and Del/Dup Specimen	20-092-400225	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
ADPKD Seq, Del/Dup Interp	20-092-400225	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