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

Physician: Doctor, Example

Patient: Patient, Example

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

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

ARUP test code 2012255

ADPKD Sequencing Specimen: Whole Blood

ADPKD Sequencing Interpretation: **Positive** *

TEST PERFORMED - 2012255
TEST DESCRIPTION - Polycystic Kidney Disease, Autosomal Dominant (PKD1 and PKD2) Sequencing
INDICATION FOR TEST - Confirm Diagnosis

RESULT
One pathogenic variant was detected in the PKD1 gene. No pathogenic variants were detected in the PKD2 gene.

DNA VARIANT
Classification: Pathogenic
Gene: PKD1
Nucleic Acid Change: c.6736C>T; Heterozygous
Amino Acid Alteration: p.Gln2246Ter

INTERPRETATION
One pathogenic variant, c.6736C>T; p.Gln2246Ter, was detected in the PKD1 gene by sequencing. This result 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 variant.

No additional pathogenic variants were detected by sequencing the PKD2 gene.

Evidence for variant classification: The PKD1 c.6736C>T; p.Gln2246Ter variant has been described in individuals with autosomal dominant polycystic kidney disease (ADPKD; see link to Mayo ADPKD database, Trujillano 2014). It is absent from general population databases (1000 Genomes Project, Exome Variant Server, and Genome Aggregation Database), indicating it is not a common polymorphism. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Additionally, truncating nonsense and frameshift variants in PKD1 are a common mechanism of disease, and several truncating variants downstream from codon 2246 have been described in individuals with ADPKD (Rossetti 2007, Trujillano 2014). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. Renal imaging is recommended

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

for at-risk adult family members. If imaging results are equivocal, targeted testing for the identified pathogenic variant should be considered (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

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
Link to Mayo ADPKD database: http://pkdb.mayo.edu/cgi-bin/v2_display_mutations.cgi?GENE=PKD1&apkd_mode=PROD

Rossetti S et al. Comprehensive molecular diagnostics in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 2007 Jul;18(7):2143-60.

Trujillano D et al. Diagnosis of autosomal dominant polycystic kidney disease using efficient PKD1 and PKD2 targeted next-generation sequencing. Mol Genet Genomic Med. 2014 Sep;2(5):412-21.

This result has been reviewed and approved by [redacted]

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

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

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: Estimated at 87 percent for ADPKD.

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.

ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.

LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Large deletions/duplications, regulatory region mutations and deep intronic mutations in PKD1 or PKD2 will not be detected. Mosaic mutations in PKD1 or PKD2 may not be detected. Mutations in genes other than PKD1 and PKD2 are not assessed by this assay.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
ADPKD Sequencing Specimen	20-329-111969	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
ADPKD Sequencing Interpretation	20-329-111969	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