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

Physician: Doctor, Example

Patient: Patient, Example

DOB	12/9/1967
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Hereditary Renal Cancer Panel, Sequencing and Deletion/Duplication

ARUP test code 2010214

Renal Hereditary Cancer Panel Specimen	Whole Blood

Renal Hereditary Cancer Panel Interp

Positive

INDICATION FOR TESTING
Family history of Birt-Hogg-Dube syndrome.

RESULT
One pathogenic variant was detected in the FLCN gene.

PATHOGENIC VARIANT
Gene: FLCN (NM_144997.5)
Nucleic Acid Change: c.1177-5_1177-3delCTC Heterozygous
Inheritance: Autosomal Dominant

INTERPRETATION
One pathogenic variant, c.1177-5_1177-3delCTC, was detected in the FLCN gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic FLCN variants are associated with Birt-Hogg-Dube Syndrome (BHDS) (MIM: 135150) and are inherited in an autosomal dominant manner. Thus, this individual is predicted to be at increased risk for the manifestations associated with BHDS which include cutaneous findings, pulmonary cysts, pneumothorax and various types of renal tumors. Offspring of this individual have a 50 percent chance of inheriting the causative variant.

No additional pathogenic variants were identified in the other targeted genes by massively parallel sequencing or deletion/duplication analysis. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant classification:
The FLCN c.1177-5_1177-3delCTC variant (rs767671406) is reported in the literature in individuals with BHDS (Bartram 2017, Furuya 2016, Johannesma 2014, Kunogi Okura 2013, Kunogi 2010), and it has been shown to co-segregate with disease (Kunogi Okura 2013). Functional analyses demonstrate that this intronic variant causes exon skipping ultimately leading to a truncated and destabilized protein (Bartram 2017). This variant is reported by multiple laboratories in ClinVar (Variation ID: 228691). It is found in the general population with a low overall allele frequency of 0.001% (3/243776 alleles) in the Genome Aggregation Database. Computational algorithms also predict that the variant has an impact on the nearby canonical splice acceptor (Alamut v.2.10), consistent with functional studies. Based on available information, this variant is considered pathogenic.

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

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At risk adult family members should be offered testing for the identified pathogenic FLCN variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Benign variants are not included in this report, but are available upon request.

REFERENCES
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This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Hereditary Renal Cancer Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Pathogenic variants in multiple genes have been implicated in hereditary renal cancer. Germline variants in genes associated with hereditary renal cancer may also confer

risk for other non-renal cancers. Variants in genes analyzed in this panel cause variable phenotypes including Birt-Hogg-Dube (BHD) syndrome, Cowden syndrome/ PTEN Hamartoma Tumor Syndrome (PHTS), DICER1-Related Disorders, Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC), Hereditary Papillary Renal Carcinoma (HPRC), Hereditary Paraganglioma-Pheochromocytoma (PGL/PCC) syndrome, Li-Fraumeni Syndrome (LFS), Lynch syndrome/Hereditary Non-Polyposis Colorectal Cancer (HNPCC), Malignant Mesothelioma, Rhabdoid Tumor Predisposition Syndrome (RTPS), Tuberous Sclerosis Complex (TSC), Von Hippel-Lindau (VHL) syndrome, and WT1-Related Disorders.

EPIDEMIOLOGY: Approximately 65,000 new cases of renal cancer are diagnosed in the U.S. per year.

CAUSE: Approximately 5 percent of renal cancers are associated with a hereditary cause.

INHERITANCE: Autosomal dominant, with the exception of the SDHD gene which is autosomal dominant with parent-of-origin effect. Additionally, some genes are also associated with autosomal recessive childhood cancer predisposition or other syndromes.

PENETRANCE: Varies, depending on the gene and specific variant.

GENES TESTED: BAP1, DICER1, FH, FLCN, MET, MLH1, MSH2, MSH6, PMS2, PTEN, SDHB, SDHC*, SDHD*, SMARCA4**, SMARCB1, TP53, TSC1, TSC2, VHL, WT1**

* - One or more exons are not covered by sequencing for the indicated gene; see limitations section below.
** - Deletion/duplication detection is not available for this gene.

METHODOLOGY: Targeted capture of all coding exons and exon-intron junctions of the targeted genes, including the PTEN promoter region, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. A custom tiled comparative genomic hybridization array (aCGH) was used to detect large deletions or duplications in the indicated subset of genes. Analysis of the PMS2 gene was performed by bidirectional Sanger sequencing of coding regions and their respective exon intron boundaries as well as multiplex ligation-dependent probe amplification (MLPA). Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a heritable form of cancer. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants and deep intronic variants will not be identified and breakpoints of large deletions/duplications will not be determined. Single exon deletions/duplications or deletions/duplications less than 1kb may not be detected. Deletions/duplications/insertions of any size may not be detected by massive parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
SDHC(NM_001035511) exon(s) 5
SDHD(NM_001276506) exon(s) 4

Single exon deletions/duplications will not be called for the following exons:
BAP1(NM_004656) 1;FH(NM_000143) 1; FLCN(NM_144997) 8;MSH2(NM_000251) 1;MSH2(NM_001258281) 2;MSH6(NM_000179) 10;PTEN(NM_000314) 8,9;PTEN(NM_001304717) 1;SDHD(NM_001276506) 4;SMARCB1(NM_003073) 5;TP53(NM_001126113) 10;TP53(NM_001126114) 10;TSC2(NM_000548) 17,29,41;VHL(NM_000551) 1

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Renal Hereditary Cancer Panel Specimen	18-344-106684	12/10/2018 11:33:00 AM	12/10/2018 12:15:06 PM	12/10/2018 4:49:00 PM
Renal Hereditary Cancer Panel Interp	18-344-106684	12/10/2018 11:33:00 AM	12/10/2018 12:15:06 PM	12/10/2018 4:49:00 PM

END OF CHART

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