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

Physician: Doctor, Example

Patient: Patient, Example

DOB	10/15/1952
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Birt-Hogg-Dube Syndrome (FLCN) Sequencing and Deletion/Duplication

ARUP test code 3005703

FLCN Specimen	Whole Blood
FLCN Interp	Positive

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

RESULT
One pathogenic variant was detected in the FLCN gene.

PATHOGENIC VARIANT
Gene: FLCN (NM_144997.7)
Nucleic Acid Change: c.296del; Heterozygous
Amino Acid Alteration: p.Asp99ValfsTer31
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.296del; p.Asp99ValfsTer31, was detected in the FLCN gene by massively parallel sequencing. This result is consistent with a diagnosis of Birt-Hogg-Dube syndrome (MIM: 135150; OMIM (R)). National Comprehensive Cancer Network (NCCN) guidelines are available for renal cancer risk management in heterozygous individuals. This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

Please refer to the background information included in this report for the methodology and limitations of this test.

Evidence for variant classification:
The FLCN c.296del; p.Asp99ValfsTer31 variant (rs398124534), also published as c.751delA, is reported in the literature in multiple individuals and families affected with Birt-Hogg-Dube syndrome and has been reported to segregate with disease (Mahtani 2021, Schmidt 2005, Toro 2008). This variant is also absent from the Genome Aggregation Database (v2.1.1), 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. Based on available information, this variant is considered to be 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 pathogenic FLCN 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
Mahtani K et al. Importance of Family History in the Era of Exome Analysis: A Report of a Family with Multiple Concurrent Genetic Diseases. Hum Hered. 2021;86(1-4):28-33. PMID: 34706366.
National Comprehensive Cancer Network. Kidney Cancer (3.2025): www.nccn.org/professionals/physician_gls/pdf/kidney.pdf
Schmidt LS et al. Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dube syndrome. Am J Hum Genet. 2005 Jun;76(6):1023-33. PMID: 15852235.
Toro JR et al. BHD mutations, clinical and molecular genetic investigations of Birt-Hogg-Dube syndrome: a new series of 50 families and a review of published reports. J Med Genet. 2008 Jun;45(6):321-31. PMID: 18234728.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Birt-Hogg-Dube Syndrome (FLCN) Sequencing and Deletion/Duplication
CHARACTERISTICS: Birt-Hogg-Dube syndrome (BHDS) is characterized by cutaneous manifestations, pulmonary cysts (typically with history of pneumothorax), and various renal tumors.

EPIDEMIOLOGY: Approximately two individuals per million in the general population are estimated to have BHDS.

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

CAUSE: BHDS is caused by heterozygous pathogenic germline variants in the FLCN gene.

INHERITANCE: Autosomal dominant

PENETRANCE: Approximately 90-95 percent of individuals with a single pathogenic FLCN variant will develop at least one feature of BHDS.

CLINICAL SENSITIVITY: Approximately 96 percent

GENE TESTED: FLCN (NM_144997)

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the FLCN gene, 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 diagnosis of Birt-Hogg-Dube syndrome or FLCN-associated tumors. This test only detects variants within the coding regions and intron-exon boundaries of the FLCN gene. 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.

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
FLCN Specimen	25-077-401545	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
FLCN Interp	25-077-401545	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