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

Physician: Doctor, Example

Patient: Patient, Example

DOB	3/9/1987
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

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

RESULT
One pathogenic variant was detected in the VHL gene.

PATHOGENIC VARIANT
Gene: VHL (NM_000551.4)
Nucleic Acid Change: Deletion of exons 2-3; Heterozygous
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, deletion of exons 2-3, was detected in the VHL gene by massively parallel sequencing-based deletion/duplication analysis and confirmed by exon-level microarray. This result is consistent with a diagnosis of von Hippel-Lindau (VHL) syndrome. Clinical manifestations of VHL syndrome are variable and age dependent. National Comprehensive Cancer Network (NCCN) guidelines are available for cancer risk management in heterozygous individuals. Other genetic/environmental factors may influence an individual's risk of developing cancer. Because this deletion includes the last exon of the VHL gene and the breakpoints of the deletion cannot be determined, the deletion may extend downstream of the VHL gene. This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

No additional pathogenic variants were identified in the targeted genes. 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 VHL deletion of exons 2-3 has been previously described in the medical literature in individuals and families affected with Von-Hippel Lindau syndrome type 1 (Boedeker 2009, Franke 2009, Hes 2007, McNeill 2009). Similar deletions are also reported in ClinVar (Variation ID: 456563, 659603). Based on available information, this variant is classified as 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 variant.

COMMENTS
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS

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

with sufficient confidence in this sample due to technical limitations: None

REFERENCES
Boedeker CC et al. Head and neck paragangliomas in von Hippel-Lindau disease and multiple endocrine neoplasia type 2. J Clin Endocrinol Metab. 2009 Jun;94(6):1938-44. PMID: 19336503.

Franke G et al. Alu-Alu recombination underlies the vast majority of large VHL germline deletions: Molecular characterization and genotype-phenotype correlations in VHL patients. Hum Mutat. 2009 May;30(5):776-86. PMID: 19280651.

Hes FJ et al. Frequency of Von Hippel-Lindau germline mutations in classic and non-classic Von Hippel-Lindau disease identified by DNA sequencing, Southern blot analysis and multiplex ligation-dependent probe amplification. Clin Genet. 2007 Aug;72(2):122-9. PMID: 17661816.

McNeill A et al. Genotype-phenotype correlations in VHL exon deletions. Am J Med Genet A. 2009 Oct;149A(10):2147-51. PMID: 19764026.

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. Hereditary cancer predisposition is often characterized by early age of onset (typically before age 50) and multiple, multifocal, and/or related cancers in a single individual or in closely related family member(s). Pathogenic variants in the genes analyzed by this panel cause variable phenotypes and cancer risks, including nonrenal cancers.

EPIDEMIOLOGY: Approximately 3-5 percent of renal cancers are associated with a hereditary cause.

CAUSE: Pathogenic germline variants in genes associated with hereditary renal cancer

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.

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

* - One or more exons are not covered by sequencing and/or deletion/duplication analysis for the indicated gene; see limitations section below.

** - Deletion/duplication analysis of EPCAM (NM_002354) exon 9 only, sequencing is not available for this gene.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes (including selected PTEN promoter variants), 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. Testing of selected exons (and exon/intron boundaries) of PMS2, PTEN, and MSH2 was performed by bidirectional Sanger sequencing. Deletion/duplication testing of PMS2 was performed by multiplex ligation-dependent probe amplification (MLPA).

ANALYTICAL SENSITIVITY: 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. The analytical sensitivity for MLPA is greater than 99 percent.

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. 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.

The following regions are not sequenced due to technical limitations of the assay:
FLCN (NM_001353229) exon 7
SDHA (NM_004168) exon 14
SDHA (NM_001294332) exon 13
SDHA (NM_001330758) exon 12
SDHC (NM_001035511) partial exon 5 (Chr1:161332225-161332330)
SDHC (NM_001278172) partial exon 4 (Chr1:161332225-161332330)
SDHD (NM_001276506) exon 4
VHL (NM_001354723) exon 2

Deletions/duplications will not be called for the following exons:
FLCN (NM_001353229) 7; PTEN (NM_000314, NM_001304718) 9; PTEN(NM_001304717) 1,10; SDHA (NM_004168) 1,10-15; SDHA (NM_001294332) 1,9-14; SDHA (NM_001330758) 1,10-13; SDHD (NM_001276506) 4; VHL (NM_001354723) 2

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
Renal Hereditary Cancer Panel Specimen	23-317-143456	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Renal Hereditary Cancer Panel Interp	23-317-143456	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