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

Primary Ciliary Dyskinesia Panel, Sequencing

ARUP test code 3001621

Primary Ciliary Dyskinesia Specimen	Whole Blood

Primary Ciliary Dyskinesia Interp	Positive

RESULT
Two pathogenic variants were detected in the DNAH5 gene.

PATHOGENIC VARIANT
Gene: DNAH5 (NM_001369.3)
Nucleic Acid Change: c.4348C>T; Heterozygous
Amino Acid Alteration: p.Gln1450Ter
Inheritance: Autosomal recessive

PATHOGENIC VARIANT
Gene: DNAH5 (NM_001369.3)
Nucleic Acid Change: c.6763C>T; Heterozygous
Amino Acid Alteration: p.Arg2255Ter
Inheritance: Autosomal recessive

INTERPRETATION
Two pathogenic variants, c.4348C>T; p.Gln1450Ter, and c.6763C>T; p.Arg2255Ter, were detected in the DNAH5 gene by massively parallel sequencing. Pathogenic variants in DNAH5 are associated with autosomal recessive primary ciliary dyskinesia 3, with or without situs inversus (MIM: 608644). This result is consistent with a diagnosis of primary ciliary dyskinesia if the two pathogenic variants occur on opposite chromosomes.

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 classifications:
The DNAH5 c.4348C>T; p.Gln1450Ter variant (rs771663107) is reported in the literature in the homozygous or compound heterozygous state in multiple individuals and families affected with primary ciliary dyskinesia (Failly 2009, Ferkol 2013). This variant is reported in ClinVar (Variation ID: 208992), and is only observed on one allele in the 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. Based on available information, this variant is considered to be pathogenic.

The DNAH5 c.6763C>T; p.Arg2255Ter variant (rs745918507) is reported in the literature in individuals affected with primary ciliary dyskinesia, including at least one individual with a different pathogenic DNAH5 variant on the opposite chromosome

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

(Boaretto 2016, Quinlan-Jones 2019). This variant is reported in ClinVar (Variation ID: 454795), and is only observed on four alleles in the 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. 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 targeted testing for the identified pathogenic DNAH5 variants (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics. 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
Boaretto F et al. Diagnosis of Primary Ciliary Dyskinesia by a Targeted Next-Generation Sequencing Panel: Molecular and Clinical Findings in Italian Patients. J Mol Diagn. 2016;18(6):912-922.
Failly M et al. Mutations in DNAH5 account for only 15% of a non-preselected cohort of patients with primary ciliary dyskinesia. J Med Genet. 2009;46(4):281-286.
Ferkol TW et al. Primary ciliary dyskinesia-causing mutations in Amish and Mennonite communities. J Pediatr. 2013;163(2):383-387.
Quinlan-Jones E et al. Molecular autopsy by trio exome sequencing (ES) and postmortem examination in fetuses and neonates with prenatally identified structural anomalies. Genet Med. 2019;21(5):1065-1073.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Primary Ciliary Dyskinesia Panel, Sequencing

CHARACTERISTICS: Primary ciliary dyskinesia (PCD, also known as Kartagener syndrome) is a rare inherited condition that results from an underlying defect in the structure or function of motile cilia, impacting multiple body systems. Patients with PCD typically first present with neonatal respiratory distress, chronic oto-sinopulmonary disease, and year-round wet coughing. Approximately half of patients with PCD will have a laterality defect such as situs inversus totalis or heterotaxy. PCD is also associated with infertility and ectopic pregnancy due to ciliary dysfunction.

PREVALENCE: Approximately 1 in 16,000

CAUSE: Pathogenic germline variants in genes associated with structure and function of the motile cilia

INHERITANCE: Autosomal recessive; rare X-linked recessive forms have been reported

PENETRANCE: 100 percent

GENES TESTED: ARMC4*, CCDC103*, CCDC114*, CCDC151, CCDC39, CCDC40*, CCDC65, CCNO, CFAP298*, DNAAF1, DNAAF2, DNAAF3, DNAAF4, DNAAF5*, DNAH1, DNAH11, DNAH5, DNAI1, DNAI2*, DNAL1, DRC1, GAS8, LRRC6, MCIDAS, NME8, PIH1D3, RSPH1, RSPH3, RSPH4A, RSPH9, SPAG1*, ZMYND10
*One or more exons are not covered by sequencing for the indicated gene; see limitations section below.

METHODOLOGY: Capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity of sequencing 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 diagnosis of primary ciliary dyskinesia. 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.
Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. 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 mosaic or somatic variants associated with disease. 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:
ARMC4(NM_001290020) exon(s) 9
ARMC4(NM_001290021) exon(s) 13
ARMC4(NM_001312689) exon(s) 4
ARMC4(NM_018076) exon(s) 9
CCDC103(NM_001258397) exon(s) 4
CCDC114(NM_001364171) exon(s) 3
CCDC114(NM_001364171) partial exons(s) 4(Chr19:48822049-48822069)
CCDC40(NM_001243342) exon(s) 18
CFAP298(NM_001350335) partial exons(s) 5(Chr21:33975399-33975450)
CFAP298(NM_001350337) partial exons(s) 6(Chr21:33974534-33974561)
DNAAF5(NM_017802) exon(s) 1
DNAI2(NM_001353167) exon(s) 13
SPAG1(NM_001374321) partial exons(s) 11(Chr8:101225456-101225529)
SPAG1(NM_003114) partial exons(s) 11(Chr8:101225456-101225529)
SPAG1(NM_172218) partial exons(s) 11(Chr8:101225456-101225529)

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US 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.

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VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Primary Ciliary Dyskinesia Specimen	22-311-110883	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Primary Ciliary Dyskinesia Interp	22-311-110883	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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