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

MODY and Neonatal Diabetes Panel, Sequencing

ARUP test code 3001593

Monogenic Diabetes Specimen	Whole Blood

Monogenic Diabetes Interp

Positive

RESULT
One pathogenic variant was detected in the HNF1A gene.

PATHOGENIC VARIANT
Gene: HNF1A (NM_000545.8)
Nucleic Acid Change: c.787C>T; Heterozygous
Amino Acid Alteration: p.Arg263Cys
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.787C>T; p.Arg263Cys, was detected in the HNF1A gene by massively parallel sequencing. Pathogenic HNF1A variants are inherited in an autosomal dominant manner, and are associated with maturity-onset diabetes of the young (MODY) type 3 (MIM: 600496). Therefore, this individual is predicted to have a predisposition for MODY. 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 a list of the genes analyzed, methodology and limitations of this test.

Evidence for variant classification:
The HNF1A c.787C>T; p.Arg263Cys variant (rs771108132) is reported in the literature in multiple individuals and one family affected with maturity-onset diabetes of the young (MODY) (Bjorkhaug 2003, Delvecchio 2014, Groopman 2019, Huang 2018, Iwasaki 1997). Functional analyses of the variant protein show that DNA binding is abrogated and transcriptional activity is reduced by up to 85% (Najmi 2017, Yang 1999). This variant is also reported in ClinVar (Variation ID: 562367). This variant is only observed on one allele in the Genome Aggregation Database, indicating it is not a common polymorphism. Additionally, other variants at this codon (c.788G>A, p.Arg263His; c.788G>T, p.Arg263Leu) have been reported in individuals with MODY and are considered pathogenic (Balamurugan 2016, Groopman 2019, Kim 2003). The arginine at codon 263 is highly conserved, and computational analyses predict that this variant is deleterious (REVEL: 0.948). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic and endocrinology consultations are indicated, including a discussion of medical screening and management. At-risk family

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

members should be offered testing for the identified pathogenic HNF1A variant (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
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Bjorkhaug L et al. Hepatocyte nuclear factor-1 alpha gene mutations and diabetes in Norway. J Clin Endocrinol Metab. 2003 Feb;88(2):920-31. PMID: 12574234.
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Groopman EE et al. Diagnostic Utility of Exome Sequencing for Kidney Disease. N Engl J Med. 2019 Jan 10;380(2):142-151. PMID: 30586318.
Huang X ET AL. Lower Circulating miR-122 Level in Patients with HNF1A Variant-Induced Diabetes Compared with Type 2 Diabetes. J Diabetes Res. 2018 Aug 1;2018:7842064. PMID: 30155490.
Iwasaki N et al. Mutations in the hepatocyte nuclear factor-1alpha/MODY3 gene in Japanese subjects with early- and late-onset NIDDM. Diabetes. 1997 Sep;46(9):1504-8. PMID: 9287053.
Kim KA et al. Identification and functional characterization of a novel mutation of hepatocyte nuclear factor-1alpha gene in a Korean family with MODY3. Diabetologia. 2003 May;46(5):721-7. PMID: 12712243.
Najmi LA et al. Functional Investigations of HNF1A Identify Rare Variants as Risk Factors for Type 2 Diabetes in the General Population. Diabetes. 2017 Feb;66(2):335-346. PMID: 27899486.
Yang Q et al. Structure/function studies of hepatocyte nuclear factor-1alpha, a diabetes-associated transcription factor. Biochem Biophys Res Commun. 1999 Dec 9;266(1):196-202. PMID: 10581189.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: MODY and Neonatal Diabetes Panel, Sequencing

CHARACTERISTICS: Maturity-onset diabetes of the young (MODY) is a group of inherited disorders that cause nonautoimmune diabetes mellitus with a typical onset before age 35. Most affected individuals have features that are atypical for type 1 and type 2 diabetes, including a lack of pancreatic islet autoantibodies, normal weight, triglycerides, and HDL, no acanthosis nigricans, low insulin requirements, and no ketoacidosis when insulin is omitted from treatment. Individuals with neonatal diabetes (ND) mellitus have complete or partial insulin deficiency and develop hyperglycemia by 6 months of age. Affected individuals often have intrauterine growth restriction, glucosuria, osmotic polyuria, severe dehydration, and failure to thrive.

EPIDEMIOLOGY: MODY accounts for 1-3 percent of all cases of diabetes with no ethnic predilection; prevalence of ND is 1 in 160,000 in Austria and 1 in 215,000 in Slovakia.
CAUSE: Pathogenic germline variants in numerous genes.

INHERITANCE: Autosomal dominant or autosomal recessive, depending on the causative gene.

CLINICAL SENSITIVITY: Greater than 70 percent for MODY and greater than 73 percent for ND.

GENES TESTED: ABCC8*, APPL1, BLK, CEL*, EIF2AK3, FOXP3, GATA4, GATA6, GCK, HNF1A, HNF1B, HNF4A, INS, KCNJ11, KLF11, NEUROD1, NEUROG3, PAX4, PDX1, RFX6, SLC19A2, WFS1, ZFP57
* - One or more exons are not covered by sequencing for the indicated gene; see limitations section below.

METHODOLOGY: Targeted 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 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 MODY or ND mellitus. 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 unless specifically targeted for their clinical relevance. Deletions/duplications/insertions of any size may not be detected by massively 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 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:
CEL (NM_001807) exons 1, 8, 9, 11
ABCC8 (NM_001351295) partial exon 14 (Chr11:17449973-17450018)

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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Monogenic Diabetes Specimen	22-307-112060	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Monogenic Diabetes Interp	22-307-112060	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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