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

Physician: Doctor, Example

Patient: Patient, Example

DOB	11/13/2021
Sex:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Multiple Endocrine Neoplasia Type 1 (MEN1) Sequencing and Deletion/Duplication

ARUP test code 3004437

MEN1 Specimen	Whole Blood
MEN1 Interp	Positive

RESULT
One pathogenic variant was detected in the MEN1 gene.

PATHOGENIC VARIANT
Gene: MEN1 (NM_130799.2)
Nucleic Acid Change: c.784-9G>A; heterozygous
Inheritance: Autosomal dominant

INTERPRETATION
One copy of a pathogenic variant, c.784-9G>A, was detected in the MEN1 gene by massively parallel sequencing and confirmed by Sanger sequencing. This result is consistent with a diagnosis of multiple endocrine neoplasia type 1. Clinical manifestations are variable. National Comprehensive Cancer Network (NCCN) guidelines are available for tumor risk management (NCCN, 2021). This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

No additional pathogenic variants were identified in the MEN1 gene by massively parallel sequencing or deletion/duplication analysis. Please refer to the background information included in this report for the clinical sensitivity and limitations of this test.

Evidence for variant classification: The MEN1 c.784-9G>A variant (rs794728625) (also described as nt5168G>A, 5178-9G>A, 894-9G>A, c.799-9G>A, and IVS4-9G>A, for alternative transcripts or reference sequences), is reported in the literature in multiple individuals with MEN1, and is reported to cosegregate with disease in some of these families (Gortz, 1999; Hai, 1999; Kishi, 1999; Komminoth, 2000; Lemos, 2008; Mutch, 1999; Pard,i 2017; Pieterman, 2012; Turner, 2002). This variant is reported in ClinVar (Variation ID: 200981). This variant is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. Computational algorithms predict this variant introduces a strong cryptic acceptor splice site upstream the canonical acceptor of intron 4 (Alamut v.2.10). In support of this, functional studies have shown this variant causes aberrant splicing by adding 7 extra nucleotides in intron 4, ultimately leading to a frameshift in the coding sequence of exon 5 (Kishi, 1999; Komminoth, 2000; Mutch, 1999). Based on available information, this variant is considered 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 (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Likely benign and benign variants are not included in this report.

REFERENCES
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Lemos MC, et al. Multiple endocrine neoplasia type 1 (MEN1): analysis of 1336 mutations reported in the first decade following identification of the gene. Hum Mutat. 2008;29(1):22-32.

Mutch MG, et al. Germline mutations in the multiple endocrine neoplasia type 1 gene: evidence for frequent splicing defects. Hum Mutat. 1999;13(3):175-85.

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Pieterman CR, et al. Primary hyperparathyroidism in MEN1 patients: a cohort study with longterm follow-up on preferred surgical procedure and the relation with genotype. Ann Surg. 2012;255(6):1171-8.

Turner JJ, et al. Frequent occurrence of an intron 4 mutation in multiple endocrine neoplasia type 1. J Clin Endocrinol Metab. 2002;87(6):2688-93.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Multiple Endocrine Neoplasia Type 1 (MEN1) Sequencing and Deletion/Duplication

CHARACTERISTICS: Multiple endocrine neoplasia type 1 (MEN1) syndrome can include multiple endocrine and nonendocrine tumors. Common MEN1-related endocrine tumors include parathyroid, pancreatic islets, and pituitary. Nonendocrine tumors include facial angiofibroma, collagenoma, lipoma, meningioma, ependymoma, and leiomyoma. Primary hyperparathyroidism is the most common and often the first manifestation of MEN1. High mortality rates occur in individuals with gastrinoma and carcinoid tumors.

EPIDEMIOLOGY: 1/10,000 to 1/100,000.

CAUSE: Pathogenic germline variants in the MEN1 gene.

INHERITANCE: Autosomal dominant.

PENETRANCE: Greater than 50 percent by age 20 and 95 percent by age 40.

CLINICAL SENSITIVITY: A pathogenic MEN1 variant is identified in 80 to 90 percent of individuals who meet clinical criteria for MEN1 syndrome and have a family history of related cancers.

GENE TESTED: MEN1 (NM_130799)

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted 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 two exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of three 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 MEN1. A negative result does not exclude all genetic diagnoses. This test only detects variants within the coding regions and intron-exon boundaries of the MEN1 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 two 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) mutations, 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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
MEN1 Specimen	21-319-104675	11/15/2021 11:20:00 AM	11/15/2021 2:51:31 PM	11/15/2021 3:28:00 PM

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

MEN1 Interp	21-319-104675	11/15/2021 11:20:00 AM	11/15/2021 2:51:31 PM	11/15/2021 3:28:00 PM

END OF CHART

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