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

Physician: Doctor, Example

Patient: Patient, Example

DOB	4/28/1971
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Multiple Endocrine Neoplasia Type 2 (MEN2), RET Sequencing

ARUP test code 3004572

MEN2 Specimen	Whole Blood
MEN2 Interp	Positive

RESULT
One pathogenic variant was detected in the RET gene.

PATHOGENIC VARIANT
Gene: RET (NM_020975.6)
Nucleic Acid Change: c.2671T>G; Heterozygous
Amino Acid Alteration: p.Ser891Ala
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.2671T>G; p.Ser891Ala, was detected in the RET gene by massively parallel sequencing. This variant has been associated with multiple endocrine neoplasia type 2A (MEN2A) and/or familial medullary thyroid carcinoma (FMTC); therefore, this individual is predicted to be affected.

Molecular testing results should be combined with clinical findings and family history information for the most accurate determination of MEN2 subtype. National Comprehensive Cancer Network (NCCN) guidelines are available for 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 RET c.2671T>G; p.Ser891Ala variant (rs75234356) is reported in the literature in individuals and families with medullary thyroid carcinoma, pheochromocytoma and hyperparathyroidism (Elisei 2019, Hofstra 1997, Qi 2021, Shulte 2010). This variant is also reported as pathogenic by multiple laboratories in ClinVar (Variation ID: 13951). This variant is only observed on three alleles in the Genome Aggregation Database, indicating it is not a common polymorphism. Functional analyses of the variant protein show that it has low transforming activity (Colombo 2015, Iwashita 1999, Plaza Menacho 2005). Additionally, according to the American Thyroid Association, this variant is classified as a moderate risk variant for aggressive medullary thyroid carcinoma with a low incidence of pheochromocytoma or hyperparathyroidism (Wells 2015). Computational analyses predict that this variant is deleterious (REVEL: 0.733). Based on available information, this variant is considered to be pathogenic.

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

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 RET 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
Colombo C et al. The modifier role of RET-G691S polymorphism in hereditary medullary thyroid carcinoma: functional characterization and expression/penetrance studies. Orphanet J Rare Dis. 2015 Mar 1;10:25. PMID: 25887804.
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Hofstra RM et al. A novel point mutation in the intracellular domain of the ret protooncogene in a family with medullary thyroid carcinoma. J Clin Endocrinol Metab. 1997 Dec;82(12):4176-8. PMID: 9398735.
Iwashita T et al. Biological and biochemical properties of Ret with kinase domain mutations identified in multiple endocrine neoplasia type 2B and familial medullary thyroid carcinoma. Oncogene. 1999 Jul 1;18(26):3919-22. PMID: 10445857.
National Comprehensive Cancer Network. Thyroid Carcinoma (4.2023): https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf
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Qi XP et al. Spectrum of Germline RET variants identified by targeted sequencing and associated Multiple Endocrine Neoplasia type 2 susceptibility in China. BMC Cancer. 2021 Apr 7;21(1):369. PMID: 33827484.
Schulte KM et al. The clinical spectrum of multiple endocrine neoplasia type 2a caused by the rare intracellular RET mutation S891A. J Clin Endocrinol Metab. 2010 Sep;95(9):E92-7. PMID: 20554711.
Wells SA et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015 Jun;25(6):567-610. PMID: 25810047.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Multiple Endocrine Neoplasia Type 2 (MEN2), RET Sequencing

CHARACTERISTICS: Multiple endocrine neoplasia type 2 (MEN2) is a hereditary syndrome caused by pathogenic variants in the RET gene. MEN2 is classified into subtypes MEN2A, MEN2B, and familial medullary thyroid cancer (FMTC). All MEN2 subtypes have an increased risk of medullary thyroid cancer (MTC). MEN2A is also associated with benign parathyroid adenomas/hyperplasia and pheochromocytoma (PCC). MEN2B is associated with more aggressive MTC that can occur during childhood, PCC, neuromas, eye anomalies, and distinctive physical features. FMTC is considered a disease variant of MEN2A and is characterized as multiple cases of MTC in a family, typically without the presence of PCC or hyperparathryoidism.

EPIDEMIOLOGY: One in 35,000 individuals are estimated to have MEN2. Approximately 25-30 percent of all individuals with MTC have a germline RET pathogenic variant.

CAUSE: Pathogenic germline variants in the RET gene

INHERITANCE: Autosomal dominant

PENETRANCE: The penetrance of MTC in MEN2A is 95 percent, and in MEN2B and FMTC is 100 percent.

CLINICAL SENSITIVITY: MEN2A: >95 percent; MEN2B: >98 percent; FMTC: >88-95 percent

GENE TESTED: RET (NM_020975)

METHODOLOGY: Probe hybridization-based 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 to confirm reported variants that do not meet acceptable quality metrics. 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. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a diagnosis of MEN2. This test only detects variants within the coding regions and intron-exon boundaries of the RET gene. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants, deep intronic variants, and large deletions/duplications will not be identified. 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.

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.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
MEN2 Specimen	23-229-133102	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
MEN2 Interp	23-229-133102	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