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Tracy I. George, MD, Chief Medical Officer

Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108-
USA

Provider: 68912 -arup,arup

Patient: **Test Cert, MEN2 NGS**
DOB:
Sex: Female
Patient Identifiers: 33903
Visit Number (FIN): 34211
Client Supplied ID:

Specimen Collected: 21-Jan-22 10:48

MEN2 by NGS | **Received: 21-Jan-22 10:52** **Report/Verified: 21-Jan-22 11:16**

Procedure	Result	Units	Reference Interval
MEN2 Specimen	Whole Blood		
MEN2 Interp	Positive [f1 i1]		

Result Footnote

f1: MEN2 Interp

RESULT
One pathogenic variant was detected in the RET gene.

PATHOGENIC VARIANT
Gene: RET (NM_020975.6)
Nucleic Acid Change: c.1858T>C; Heterozygous
Amino Acid Alteration: p.Cys620Arg
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.1858T>C; p.Cys620Arg, 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 detected pathogenic variant.

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

Evidence for variant classification: The RET c.1858T>C; p.Cys620Arg variant (rs77316810) is reported in the literature in multiple individuals affected with multiple endocrine neoplasia type 2A (MEN2A) and/or familial medullary thyroid carcinoma (FMTC) (Donis-Keller, 1993; Boedeker, 2009; Hedayati, 2011; Vaclavikova, 2012). This variant is also reported in ClinVar (Variation ID: 13915), but is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. The cysteine at residue 620 is highly conserved, and computational analyses predict that this variant is deleterious (REVEL: 0.897). 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 RET variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

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

*=Abnormal, #=Corrected, C=Critical, f=Result Footnote, H-High, i-Test Information, L-Low, t-Interpretive Text, @=Performing lab

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f1: MEN2 Interp

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;94(6):1938-44. PMID: 19336503.

Donis-Keller Ht, et al. Mutations in the RET proto-oncogene are associated with MEN 2A and FMTC. Hum Mol Genet. 1993;2(7):851-6. PMID: 8103403.

Hedayati M, et al. Predominant RET Germline Mutations in Exons 10, 11, and 16 in Iranian Patients with Hereditary Medullary Thyroid Carcinoma. J Thyroid Res. 2011:264248. PMID: 21765987.

National Comprehensive Cancer Network. Thyroid Carcinoma (3.2021): https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf

Vaclavikova E, et al. Hirschsprung's disease and medullary thyroid carcinoma: 15-year experience with molecular genetic screening of the RET proto-oncogene. Pediatr Surg Int. 2012;28(2):123-8. PMID: 21986619.

Test Information

i1: MEN2 Interp

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.

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Test Information

i1: MEN2 Interp

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.