Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: TEST,

Patient: THYCAN, POS

DOB	
Sex:	Male
Patient Identifiers:	46547
Visit Number (FIN):	46876
Collection Date:	2/21/2023 07:48

Hereditary Thyroid Cancer Panel, Sequencing and Deletion/Duplication

ARUP test code 3005944

THYCAN Specimen	Whole Blood
THYCAN Interp	Positive

RESULT
One pathogenic variant was detected in the RET gene.

PATHOGENIC VARIANT
Gene: RET (NM_020630.4)
Nucleic Acid Change: c.1901G>C; Heterozygous
Amino Acid Alteration: p.Cys634Ser
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.1901G>C; p.Cys634Ser, was detected in the RET gene by massively parallel sequencing. Pathogenic RET variants are inherited in an autosomal dominant manner and are associated with multiple endocrine neoplasia (MEN) IIA (MEN2A; MIM: 171400), MEN2B (MIM: 162300), pheochromocytoma (MIM: 171300), medullary thyroid carcinoma (MIM: 155240), Hirschsprung disease (MIM: 142623), and congenital central hypoventilation syndrome (MIM: 209880). This individuals 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 RET c.1901G>C; p.Cys634Ser variant (rs75996173), also known as Cys380Ser, is reported in the literature in multiple individuals and families affected with MEN2 (Elisei, 2019; Mulligan, 1993; Romei, 2010). In addition, another variant (c.1900T>A; p.Cys634Ser) giving rise to the same amino acid alteration has been reported in affected individuals and is considered pathogenic (Mahesh, 2014). This variant is reported in ClinVar (Variation ID: 13910). It is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. Additionally, other amino acid substitutions at this codon (Arg, Gly, Phe, Trp, Tyr, Thr, Val) have been reported in individuals with MEN2 and are considered pathogenic (Mulligan, 1993; Romei, 2010). This variant lies within a cysteine rich domain; pathogenic variants resulting in the loss of a cysteine residue are common in these repeats and are predicted to disrupt protein structure, resulting in aberrant activation of the RET protein (Amoresano, 2005; Chappuis-Flament, 1998; Ito, 1997). The cystine at codon 634 is highly conserved, and computational analyses predict that this variant is deleterious (REVEL: 0.902). 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; reportable variants are confirmed by Sanger sequencing:
NONE

REFERENCES
Amoresano A, et al. Direct interactions among Ret, GDNF and GFRalpha1 molecules reveal new insights into the assembly of a functional three-protein complex. Cell Signal. 2005;17(6):717-27. PMID: 15722196.

Chappuis-Flament S, et al. Dual effect on the RET receptor of MEN 2 mutations affecting specific extracytoplasmic cysteines. Oncogene. 1998;17(22):2851-61. PMID: 9879991.

Elisei R, et al. Twenty-five years experience on RET genetic screening on hereditary MTC: an update on the prevalence of germline RET mutations. Genes (Basel). 2019;10(9):698. PMID: 31510104.

Ito S, et al. Biological properties of Ret with cysteine mutations correlate with multiple endocrine neoplasia type 2A, familial medullary thyroid carcinoma, and Hirschsprung's disease phenotype. Cancer Res. 1997;57(14):2870-2. PMID: 9230192.

Mahesh DM, et al. RET mutations in a large Indian family with medullary thyroid carcinoma. Indian J Endocrinol Metab. 2014;18(4):516-20. PMID: 25143909.

Mulligan LM, et al. Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. Nature. 1993;363(6428):458-60. PMID: 8099202.

Romei C, et al. Multiple endocrine neoplasia type 2 syndromes (MEN 2): results from the ItaMEN network analysis on the prevalence of different genotypes and phenotypes. Eur J Endocrinol. 2010;163(2):301-8. Erratum in Eur J Endocrinol. 2010;163(6):963. PMID: 20516206.

BACKGROUND INFORMATION: Hereditary Thyroid Cancer Panel, Sequencing and Deletion/Duplication
CHARACTERISTICS: Pathogenic germline variants in multiple genes have been implicated in hereditary thyroid cancer. Hereditary thyroid cancer syndromes are often characterized by early age of onset (typically before 50 years of age), the presence of any number of related thyroid cancers (pheochromocytoma, medullary thyroid carcinoma, C-cell hyperplasia, etc.), and/or similar cancers in a closely related family member(s).

EPIDEMIOLOGY: Approximately 5 percent of thyroid cancers are associated with a hereditary cause.

CAUSE: Pathogenic germline variants in genes associated with hereditary thyroid cancer

INHERITANCE: Autosomal dominant

GENES TESTED: APC*; DICER1; MEN1*; PRKAR1A; PTEN*; RET; TP53

*One or more exons are not covered by sequencing and/or

deletion/duplication analysis for the indicated gene; see limitations section below.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes, (including selected PTEN promoter variants), 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. Testing of selected exons (and exon/intron boundaries) of PTEN was performed by bidirectional Sanger sequencing.

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 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 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 heritable form of thyroid cancer or other cancer. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. 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 2 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) variants, 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.

The following regions are not sequenced due to technical limitations of the assay:
APC (NM_001354896) exon 12
APC (NM_001354898, NM_001354904) exon 2
APC (NM_001354900) exon 11
MEN1 (NM_001370251) exon 8

Deletions/duplications will not be called for the following exons:
APC (NM_001354896) 12; APC (NM_001354898, NM_001354904) 2; APC (NM_001354900) 11; MEN1 (NM_001370251) 8; PTEN (NM_000314, NM_001304718) 9; PTEN (NM_001304717) 1,10

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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
THYCAN Specimen	23-052-100857	2/21/2023 7:48:00 AM	2/21/2023 7:49:35 AM	2/21/2023 7:51:00 AM
THYCAN Interp	23-052-100857	2/21/2023 7:48:00 AM	2/21/2023 7:49:35 AM	2/21/2023 7:51:00 AM

END OF CHART

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