MAYO CLINIC LABORATORIES

Test Definition: THYRP

Hereditary Thyroid Cancer Panel, Varies

Overview

Useful For

Evaluating patients with a personal or family history suggestive of a hereditary thyroid cancer syndrome

Establishing a diagnosis of a hereditary thyroid cancer syndrome, allowing for targeted surveillance based on associated risks

Identifying genetic variants associated with increased risk for thyroid and other cancers, allowing for predictive testing and appropriate screening of at-risk family members

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 7 genes associated with hereditary thyroid cancer syndromes: *APC* (including promoters 1A and 1B), *DICER1*, *PRKAR1A*, *PTEN* (including promoter), *RET*, *TP53*, and *WRN*. For more information see Method Description and Gene Selection Table.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for hereditary thyroid cancer syndromes.

Special Instructions

- Molecular Genetics: Inherited Cancer Syndromes Patient Information
- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)

Method Name

Sequence Capture and Targeted Next-Generation Sequencing (NGS) followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

Customization of this panel and single gene analysis for any gene present on this panel are available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on

this panel. For more information see FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. For instructions for testing patients who have received a bone marrow transplant, call 800-533-1710.
Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Green top (Sodium heparin)
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot**.
Specimen Stability Information: Ambient 4 days/Refrigerated 4 days/Frozen 4 days
Additional Information:
1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for samples received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.
2. To ensure minimum volume and concentration of DNA is met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate.

Specimen Type: Saliva
Patient Preparation: Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.
Supplies:
DNA Saliva Kit High Yield (T1007)
Saliva Swab Collection Kit (T786)
Container/Tube:
Preferred: High-yield DNA saliva kit
Acceptable: Saliva swab
Specimen Volume: 1 Tube if using T1007 or 2 swabs if using T786
Collection Instructions: Collect and send specimen per kit instructions.
Specimen Stability Information: Ambient (preferred) 30 days/Refrigerated 30 days
Additional Information: Saliva specimens are acceptable but not recommended. Due to lower quantity/quality of DNA yielded from saliva, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be required to complete testing.

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing-Spanish (T826)
2. Molecular Genetics: Inherited Cancer Syndromes Patient Information (T519)
3. If not ordering electronically, complete, print, and send a Oncology Test Request (T729) with the specimen.

Specimen Minimum Volume

Whole blood: 1 mL; Saliva: See Specimen Required

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

The lifetime risk to develop thyroid cancer is approximately 1.2%.(1) Rarely, a predisposition to thyroid cancer may be inherited in families with certain genetic alterations. Most of these genetic alterations are syndromic, meaning individuals who inherit them are usually at risk for other types of cancers or features, in addition to thyroid cancer.

Papillary thyroid cancers are typically sporadic but can be seen in individuals or families with familial adenomatous polyposis (FAP) syndrome, caused by variants within the *APC* gene (cribriform morular variant). Individuals with FAP are at also very high risk for colonic polyposis and colorectal cancer.

Follicular or papillary thyroid cancers may be seen in families with *PTEN* hamartoma tumor syndrome (PHTS*)*. Individuals with disease-causing *PTEN* variants have a 70-fold increased incidence of thyroid cancer compared to the general population and are at increased risk to develop breast and endometrial cancer.(2)

Thyroid cancers with follicular or papillary features can also be seen in individuals with disease-causing *DICER1* variants, as well as individuals with Carney complex, which is caused by disease-causing variants within the *PRKAR1A* gene.(3,4)

Approximately 25% of cases of medullary thyroid cancer (MTC) are caused by an inherited *RET* variant.(5) Some disease-causing *RET* variants are associated with only isolated, familial MTC, while others cause a syndrome called multiple endocrine neoplasia type 2 (MEN2). Individuals with MEN2 have a high risk for MTC and may also have other tumors of the endocrine/neuroendocrine system, including paragangliomas, mucosal neuromas, pheochromocytomas, and parathyroid tumors.(6)

The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with hereditary thyroid cancer syndromes.(7)

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(8) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact the Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

Deletion/Duplication Analysis:
This analysis targets single and multi-exon deletions/duplications; however, in some instances, single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

Deletion/duplication events that extend past the genes included on the panel may occur. In these instances, genes included in the ordered test are provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. However, copy number variants for genes not listed in the Method Description are typically not reported or interpreted for haploinsufficiency/triplosensitivity. CMACB / Chromosomal Microarray, Congenital, Blood; WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies; or WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies is recommended for a full interpretation of deletions/duplications predicted to extend past the genes included on the panel.

This test is not designed to detect low levels of mosaicism or differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. For detailed information regarding gene specific

performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

Reclassification of Variants:
Currently, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time.

Variant Evaluation:
Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(8) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Clinical Reference

1. Surveillance Epidemiology and End Results Program: Cancer Stat Facts: Thyroid cancer. National Cancer Institute; 2018. Accessed April 25, 2024. Available at http://seer.cancer.gov/statfacts/html/thyro.html
2. Ngeow J, Mester J, Rybicki LA, Ni Y, Milas M, Eng C. Incidence and clinical characteristics of thyroid cancer in prospective series of individuals with Cowden and Cowden-like syndrome characterized by germline PTEN, SDH, or KLLN alterations. J Clin Endocrinol Metab. 2011;96(12):E2063-E2071
3. Stratakis CA, Raygada M. Carney complex. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2003. Updated September 21, 2023. Accessed April 25, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1286/
4. Schultz KAP, Stewart DR, Kamihara J, et al. DICER1 tumor predisposition. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2014. Updated April 30, 2020. Accessed April 25, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK196157/
5. Shepet K, Alhefdhi A, Lai N, Mazeh H, Sippel R, Chen H. Hereditary medullary thyroid cancer: age-appropriate thyroidectomy improves disease-free survival. Ann Surg Oncol. 2013;20(5):1451-1455
6. Eng C. Multiple endocrine neoplasia type 2. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1999. Updated August 10, 2023. Accessed April 25, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1257/
7. Haddad RI, Nasr C, Bischoff L, et al. NCCN Guidelines Insights: Thyroid carcinoma, Version 2.2018. J Natl Compr Canc Netw. 2018;16(12):1429-1440
8. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletions-insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. For details regarding the targeted genes analyzed and specific gene regions not routinely covered see Gene Selection Table.(Unpublished Mayo method)

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Genes analyzed: *APC* (including promoters 1A and 1B), *DICER1*, *PRKAR1A*, *PTEN* (including promoter), *RET*, *TP53*, and *WRN*

PDF Report

No

Day(s) Performed

Varies

Report Available

14 to 21 days

Specimen Retention Time

Whole blood: 2 weeks (if available); Saliva: 1 month; Extracted DNA: 3 months

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

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Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81437

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
THYRP	Hereditary Thyroid Cancer Panel	106780-0

Result ID	Test Result Name	Result LOINC® Value
614863	Test Description	62364-5
614864	Specimen	31208-2
614865	Source	31208-2
614866	Result Summary	50397-9
614867	Result	82939-0
614868	Interpretation	69047-9
614869	Resources	99622-3
614870	Additional Information	48767-8
614871	Method	85069-3
614872	Genes Analyzed	48018-6
614873	Disclaimer	62364-5
614874	Released By	18771-6