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 Targeted Genes and Methodology Details for Hereditary Thyroid Cancer Panel.

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)
- Targeted Genes and Methodology Details for Hereditary Thyroid Cancer Panel

### Method Name

Sequence Capture and Targeted Next-Generation Sequencing 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.

## Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

## 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:** Any anticoagulant
**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 (preferred) 4 days/Refrigerated
**Additional Information**: 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.

## 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

1 mL

## 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.

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, Everman DB, 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, Everman DB, 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, Everman DB, 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 Targeted Genes and Methodology Details for Hereditary Thyroid Cancer Panel.(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
Supplemental

### Day(s) Performed
Varies

### Report Available
14 to 21 days

### Specimen Retention Time
Whole Blood: 2 weeks (if available); Extracted DNA: 3 months

### Performing Laboratory Location
Rochester

## 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.

### 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
81201
81321
81406
81351
81479
81479 (if appropriate for government payers)

### LOINC® Information

| Test ID | Test Order Name | Order LOINC® Value |
|---|---|---|
| THYRP | Hereditary Thyroid Cancer Panel | In Process |

| 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 |