

Overview

Useful For

Confirmation of suspected clinical diagnosis of multiple endocrine neoplasia type A or B, Hirschsprung disease, or congenital central hypoventilation syndrome

Identification of familial pathogenic or likely pathogenic *RET* mutation to allow for predictive or diagnostic testing in family members

Genetics Test Information

This test includes next-generation sequencing of exons 1-20 to evaluate for mutations in the *RET* gene. Sanger sequencing may be performed to confirm detected variants. Testing can be ordered for multiple endocrine neoplasia types 2A (MEN2A) and 2B (MEN2B), and familial medullary thyroid carcinoma (FMTC). If an interpretation is desired specific to Hirschsprung disease (HSCR) or congenital central hypoventilation syndrome (CCHS), call 800-533-1710 and ask for the Genomics Genetic Counselor oncall.

Highlights

Full sequencing of the *RET* gene including all exons 1-20

Mutations in the *RET* gene are the most common cause of multiple endocrine neoplasia type 2 and Hirschsprung disease

Special Instructions

- [Molecular Genetics: Inherited Cancer Syndromes Patient Information](#)
- [Molecular Genetics: Congenital Inherited Diseases Patient Information](#)
- [Informed Consent for Genetic Testing](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)

Method Name

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

NY State Available

Yes

Specimen

Specimen Type

Varies

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. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

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 specimen in original tube.

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 in Special Instructions:

-[Informed Consent for Genetic Testing](#) (T576)

-[Informed Consent for Genetic Testing-Spanish](#) (T826)

2. [Molecular Genetics: Inherited Cancer Syndromes Patient Information](#) (T519) in Special Instructions

3. If not ordering electronically, complete, print, and send an [Oncology Test Request Form](#) (T729) with the specimen.

Specimen Minimum Volume

1 mL

Reject Due To

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

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Frozen		
	Refrigerated		

Clinical and Interpretive**Clinical Information**

[Mutations in the RET proto-oncogene are associated with 3 distinct, and in rare cases, overlapping clinical syndromes.](#)

Multiple endocrine neoplasia type 2 (MEN2):

MEN2 is an autosomal dominant cancer syndrome that has classically been divided into 3 subtypes: MEN 2A, MEN 2B, and familial medullary thyroid carcinoma (FMTC). The characteristic features of MEN 2A include medullary thyroid carcinoma (MTC), pheochromocytoma, and primary hyperparathyroidism. MEN 2B is characterized by early-onset MTC, pheochromocytoma, mucosal neuromas, and distinctive facies with enlarged lips. Other features of MEN 2B include enlarged nerves of the gastrointestinal tract (ganglioneuromatosis), marfanoid habitus, hypotonia, and corneal nerve thickening. FMTC has traditionally been diagnosed in families with 4 or more cases of MTC in the absence of pheochromocytoma or parathyroid involvement. Early diagnosis of thyroid cancer and appropriate surgical intervention can prevent metastatic MTC and can reduce the morbidity and mortality associated with MTC. All MEN2 subtypes are inherited in an autosomal dominant inheritance pattern. The majority of MEN2-related mutations occur at conserved cysteine residues within exons 10 and 11. Additional mutations in exons 13, 14, 15, and 16 account for the majority of other MEN2-related *RET* mutations.

Hirschsprung disease (HSCR):

HSCR is a congenital disorder of impaired intestinal motility, also known as aganglionic megacolon. Variable lengths of the colon may be affected, resulting in either total aganglionosis, long-segment HSCR, or short-segment HSCR. HSCR affects approximately 1 in 5,000 live births and is resolved via surgical intervention.

Hirschsprung disease can result from chromosome abnormalities, single gene disorders (both syndromic and non-syndromic), a combination of mutations in multiple genes, and unknown causes. Pathogenic *RET* variants are considered the most common cause of HSCR cases, though, particularly in families with multiple cases of HSCR and long segment disease. It has been reported that up to 50% of familial cases of HSCR and 3% to 10% of single HSCR cases are due to *RET* germline mutations.

While gain of function mutations in *RET* are typically associated with MEN2, loss of function mutations have been reported in patients with Hirschsprung disease (HSCR) including full or partial *RET* gene deletions. In addition to clearly pathogenic *RET* variants that cause HSCR, additional benign variants in *RET* (which may not be causative in themselves) confer increased susceptibility to HSCR.

Congenital central hypoventilation syndrome (CCHS):

CCHS is a congenital disorder of autonomic nervous system dysfunction in which individuals hypoventilate during sleep, and less commonly while awake. While not the primary etiology of disease, *RET* mutations have been associated with CCHS; in addition, *RET* mutations may be modifiers of CCHS development in individuals with HSCR.

Co-occurrence of HSCR and CCHS is more commonly observed than the co-occurrence of MEN2 with either HSCR or CCHS.

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.⁽¹⁾ Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Some individuals who have a diagnosis of multiple endocrine neoplasia type A or B, Hirschsprung disease, or congenital central hypoventilation syndrome and/or involvement of *RET* may have a mutation that is not identified by

this method (eg, large genomic deletions or duplications, promoter mutations, deep intronic mutations). The absence of a mutation, therefore, does not eliminate the possibility of a diagnosis of multiple endocrine neoplasia type A or B, Hirschsprung disease, or congenital central hypoventilation syndrome. Note that while full or partial gene RET deletions have been described in cases of Hirschsprung disease (HSCR), multiple endocrine neoplasia (MEN)/familial medullary thyroid carcinoma (FMTC2) occurs through a gain of function mechanism, [gene-targeted deletion/duplication analysis](#) to detect intragenic deletions or duplications is not indicated for assessment of MEN2 and FMTC.

For predictive testing of asymptomatic individuals, it is important to first document the presence of an *RET* gene mutation in an affected family member.

In some cases, DNA alterations of undetermined significance may be identified.

Technical limitations:

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

Evaluation tools:

Multiple in-silico evaluation tools were used to assist in the interpretation of these results. These tools are updated regularly; therefore, changes to these algorithms may result in different predictions for a given alteration. Additionally, the predictability of these tools for the determination of pathogenicity is currently unvalidated.

Unless reported or predicted to cause disease, alterations in protein coding genes that do not result in an amino acid substitution are not reported. These and common polymorphisms identified for this patient are available upon request.

Reclassification of Variants-Policy:

All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. At this time, it is not standard practice for the laboratory to systematically review likely pathogenic alterations or variants of uncertain significance that have been previously detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in our interpretation of results may occur if information given is inaccurate or incomplete.

Clinical Reference

1. 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 May;17(5):405-424
2. American Thyroid Association Guidelines Task Force, Kloos RT, Eng C, Evans DB, et al: Medullary thyroid cancer: management guidelines of the American Thyroid Association. 2009;19(6):565-612
3. Moline J, Eng C: Multiple endocrine neoplasia type 2: an overview. *Genet Med* 2011;13(9):755-764
4. Ruiz-Ferrer M, Fernandez RM, Antinolo G, et al: A complex additive model of inheritance for Hirschsprung disease is supported by both RET mutations and predisposing RET haplotypes. *Genet Med* 2006;8(11):704-710

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5. de Pontual L, Pelet A, Trochet D, et al: Mutations of the RET gene in isolated and syndromic Hirschsprung's disease in human disclose major and modifier alleles at a single locus. *J Med Genet* 2006 May;43(5):419-423
 6. Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, et al: An official ATS clinical policy statement: Congenital central hypoventilation syndrome: genetic basis, diagnosis, and management. *Am J Respir Crit Care Med* 2010 Mar 15;181(6):626-644
 7. Marquard J, Eng C. Multiple Endocrine Neoplasia Type 2-In GeneReviews-NCBI Bookshelf. Updated 2015 Jun 25. Edited by RA Pagon, MP Adam, HH Ardinger, et al: University of Washington,. Seattle WA. 1993-2018. Accessed January 2019. Available at www.ncbi.nlm.nih.gov/books/NBK1257/
 8. Parisi M. Hirschsprung Disease Overview. In -GeneReviews-NCBI Bookshelf. Updated 2015 Oct 1. Edited by RA Pagon, MP Adam, HH Ardinger, et al: University of Washington,. Seattle WA. 1993-2017. Accessed January 2019. Available at www.ncbi.nlm.nih.gov/books/NBK1439/

Performance

Method Description

Next-generation sequencing is used to test for the presence of a mutation in all coding regions and intron/exon boundaries of the *RET* gene. Sanger sequencing is used to confirm alterations detected by next-generation sequencing when appropriate.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Varies

Report Available

14 to 20 days

Specimen Retention Time

Whole Blood: 2 weeks (if available) Extracted DNA: 3 months

Performing Laboratory Location

Rochester

Fees and 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 Regional Manager. 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. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81406-RET (ret proto-oncogene) (eg, Hirschsprung disease), full gene sequence

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
RETZ	RET Gene, Full Gene Analysis	94224-3

Result ID	Test Result Name	Result LOINC Value
53108	Result Summary	50397-9
53109	Result	82939-0
53110	Interpretation	69047-9
53111	Additional Information	48767-8
53112	Specimen	31208-2
53113	Source	31208-2
53114	Released By	18771-6