

Multiple Endocrine Neoplasia Type 2

Indications for Ordering

Diagnostic and predictive testing for multiple endocrine neoplasia type 2A (MEN2A), multiple endocrine neoplasia type 2B (MEN2B), and familial medullary thyroid carcinoma (FMTC)

Test Description

Polymerase chain reaction and bidirectional sequencing of *RET* proto-oncogene

- Exons 5, 8, 10, 11, 13-16

Tests to Consider

Primary tests

[Multiple Endocrine Neoplasia Type 2 \(MEN2\), *RET* Gene Mutations by Sequencing 0051390](#)

- Diagnostic test for MEN2

[Familial Mutation, Targeted Sequencing 2001961](#)

- Useful when a pathogenic familial variant identifiable by sequencing is known

Related test

[Cancer Panel, Hereditary, Sequencing and Deletion/Duplication, 47 Genes 2012032](#)

- Confirm diagnosis of a hereditary cancer syndrome with personal or family history consistent with features of more than one cancer syndrome

Disease Overview

Prevalence – 1/35,000

Symptoms

MEN2 has 3 defined subtypes

- MEN2A – 70-80% of cases
 - Early onset MTC – typically prior to 35 years
 - Pheochromocytoma
 - Parathyroid adenoma/hyperplasia
- MEN2B – ~5% of cases
 - Early onset MTC – childhood
 - Pheochromocytoma
 - Mucosal abnormalities
 - Gastrointestinal ganglioneuromatosis
 - Eye abnormalities – eg, corneal nerve thickening
 - Skeletal abnormalities – eg, marfanoid body
- FMTC – 10-20% of cases
 - Considered as a variant of MEN2A with decreased penetrance of pheochromocytoma and hyperparathyroidism

Genetics

Gene – *RET*

Inheritance – autosomal dominant

Penetrance

- Clinical course differs between subtypes
- Penetrance of MTC (Raue, 2012)
 - 95% for MEN2A
 - Nearly 100% for FMTC and MEN2B

Structure/function

- Receptor tyrosine-protein kinase involved in cell proliferation, neuronal navigation, cell migration, and cell differentiation
- Regulates cell death/survival balance
- Required for intestinal and renal organogenesis, development of enteric nervous system
- Involved in the development of neural crest

De novo pathogenic variants

- 5% of MEN2A
- 50% of MEN2B pathogenic variants

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity
 - MEN2A – 95% (Kloos, 2009; Mulligan, 1995)
 - MEN2B – 98% (Kloos, 2009; Moline 2011)
 - FMTC – 88% (Kloos, 2009; Mulligan, 1995)
- Analytical sensitivity/specificity – 99%

Results

- Positive – one *RET* pathogenic variant detected
 - Confirms diagnosis and etiology
- Negative – no *RET* pathogenic variant detected
 - MEN2A, MEN2B, or FMTC is unlikely, but not excluded
- Inconclusive – *RET* variant detected, but whether variant is benign or pathogenic is unknown

Limitations

- Not evaluated
 - Regulatory region variants
 - Deep intronic variants
 - Large deletions/duplications
 - *RET* exons other than 5, 8, 10, 11, 13-16
- Diagnostic errors can occur due to rare sequence variations

References

- Kloos RT, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid*. 2009;19(6):565-612
- Moline J, Eng C. Multiple endocrine neoplasia type 2: an overview. *Genetics in Medicine*. 2011;13(9):755-64
- Mulligan LM et al, Genotype-phenotype correlation in multiple endocrine neoplasia type 2: report of the International RET Mutation Consortium. *J Intern Med*. 1995;238:343-6a
- Raue F, Frank-Raue K. Genotype-phenotype correlation in multiple endocrine neoplasia type 2. *Clinics*. 2012;67(S1):69-75