



Disease Information

Multiple endocrine neoplasia type 2 (MEN2), also known as Sipple syndrome, is characterized by benign or malignant tumors of the endocrine system. The most common malignancy associated with MEN2 is medullary thyroid carcinoma (MTC). MEN2 is caused by mutations that result in the activation of the *RET* proto-oncogene and is inherited in an autosomal dominant manner. Tumors generally occur in the endocrine system, but may also occur in non-endocrine tissues. Depending on the tissues involved, MEN2 can be further subdivided into three subtypes: MEN2A, MEN2B, and familial medullary thyroid carcinoma (FMTC).¹

MEN2A is characterized by MTC in 95% of cases, hyperparathyroidism in up to 30% of cases, and unilateral or bilateral pheochromocytomas in up to 50% of cases.^{1,2} Co-segregation of *RET*-related Hirschsprung's disease and MEN2A has also been reported.³

MEN2B is the rarer but most aggressive of the MEN2 subtypes, causing up to 10% of MEN2 cases. Clinical manifestations consist of: MTC (100%) and pheochromocytoma (50%). MEN2B can be differentiated from MEN2A by a lack of hyperparathyroidism. Individuals affected with MEN2B also exhibit a marfanoid habitus, bumpy lips and tongues as a result of neuromas,^{1,2} as well as intestinal ganglioneuromas in children.⁴

FMTC is the mildest of the subtypes and comprises about 5%-35% of MEN2 cases. Individuals are only affected with medullary thyroid carcinoma and do not exhibit any of the other MEN2 findings.^{1,2} However, papillary thyroid carcinoma has been reported in patients with mutations in three specific codons of the *RET* gene.⁵

Testing Benefits & Indications

Genetic testing is an especially useful diagnostic tool to differentiate sporadic medullary thyroid carcinoma (MTC) cases from those affected with multiple endocrine neoplasia type 2 (MEN2). According to Brandi et al (2001), it is beneficial if an individual is identified to be a carrier of a *RET* mutation before they reach adulthood as there are screening and surgical interventions that help diminish their mortality rate. For example, individuals with an undiagnosed pheochromocytoma have a high risk of death due to untreated hypertension and there are clearly established guidelines for thyroidectomy depending on MEN2 subtype. It is recommended that even sporadic cases of MTC be tested for *RET* mutations to improve prognosis. For example, early thyroidectomy can lower mortality from MTC to less than 5%.⁶

Test Description

The Ambry Sequence: Multiple Endocrine Neoplasia Type 2 (MEN2) begins with double-stranded automated sequencing in sense and antisense directions of exons 10, 11, and 13-16 of *RET* plus at least 20 bases into the 5' and 3' ends of the corresponding introns. If no mutation is detected, testing continues automatically with sequencing of the remaining exons plus at least 20 bases into the 5' and 3' ends of the corresponding introns.

Mutation Detection Rate

Mutations in the *RET* gene account up to 98% of individuals affected with MEN2.⁷ The Ambry Sequence: MEN2 is capable of detecting >99% of described mutations in *RET*.

Turn-Around-Time

Gene sequence analysis	14 – 21 days
Step 1 only:	10 – 21 days
Step 2 only:	10 – 21 days
Specific mutation analysis	10 – 14 days

Specimen Requirements

Blood: Collect 3-5 cc from adult or 2 cc minimum from child into EDTA purple-top tube (first choice) or ACD yellow-top tube (second choice). Store at room temperature or refrigerate. Ship at room temperature.

Blood Spot: Call for availability.

Saliva: Collect 2 ml into Oragene™ DNA Self-Collection container. Store and ship at room temperature.

DNA: Send 20 µg in TE at 50-100 ng/µl. Store frozen and ship on ice or dry ice.

Prenatal: Prenatal testing is available. Please call an Ambry Genetic Counselor to discuss your case.

CPT Codes

Gene sequence or specific mutation analysis83891, 83894x21, 83898x 20, 83904x35, 83909x35, 83912

References

- ¹Eng C et al. *JAMA*. 1996; 276(19): 1575-1579.
- ²Fraue F et al. *Horm*. 2009; 8(1): 23-23.
- ³Moore SW et al. *Pediatr Surg Int*. 2008; 24:521-530.
- ⁴Lora M et al. *J Clin Endocrinol Metab*. 2005; 90(7): 4383-4387.
- ⁵Brauckhoff M et al. *Thyroid*. 2002; 12(7): 557-61.
- ⁶Brandi ML et al. *J Clin Endocrinol Metab*. 2001; 86: 5658-5671.
- ⁷Lodish MB et al. *Expert Rev Anticancer Ther*. 2009; 8(4): 625-632.