

**Multiple Endocrine Neoplasia Type 2B (MEN2B)
 via Targeted *RET* Gene Sequencing (Test #794)**

Brief Description of Clinical Features: Multiple endocrine neoplasia type 2 (MEN2) is characterized by medullary thyroid carcinoma (MTC) and classified into three subtypes: MEN2A, FMTC and MEN2B. MEN2B (OMIM#162300) is characterized by the early development of an aggressive form of MTC, pheochromocytoma in association with a "Marfanoid" body habitus and mucosal neuromas of the lips and tongue (Morrison & Nevin. *J Med Genet* 33:779-782, 1996). MEN2A/FMTC is described under Test #792-793.

Genetics: MEN2B is inherited in an autosomal dominant manner with complete penetrance. Approximately 50% of cases are due to *de novo* mutations. The disorder is caused by constitutively activating (gain-of-function) mutations of the *RET* proto-oncogene. Over 95% of MEN2B patients have the same germline mutation in the tyrosine kinase domain of *RET*: p.Met918Thr in exon 16 (Eng et al. *JAMA* 276:1575-1579, 1996). Somatic mutations at this codon are frequently observed in individuals with sporadic MTC. Another mutation (p.Ala883Phe) in exon 15 has been reported in 2-4% of cases. MEN2B comprises about 5% of cases of MEN2. The *RET* proto-oncogene is one of the receptor tyrosine kinases, cell-surface molecules that transduce signals for cell growth and differentiation. RET interacts with the glial-derived neurotrophic factor (GDNF) family of ligands: GDNF, neurturin, persephin, and artemin. Formation of a complex containing two RET protein molecules leads to RET autophosphorylation and intracellular signaling (Santoro et al. *Endocrinology* 145:5448-5451, 2004).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of selected exons (exons 15, 16) of the *RET* gene plus ~50 bp of flanking non-coding DNA on each side. As indicated, we will also sequence any single exon (Test #100) in family members of patients with a known mutation, or to confirm research results (\$190). This test is specifically designed for heritable germline mutations and is not appropriate for the detection of somatic mutations in tumor tissue.

Reference Sequences: Genomic: NC_000010.10 mRNA: NM_020975.4
 Protein: NP_066124.1 mRNA and Protein: CCDS 7200.1

Indications for Test: Candidates for this test are patients with clinical features consistent with MEN2B and family members of patients who have known *RET* mutations.

Sensitivity of Test: This test is predicted to detect disease mutations in >98% of cases with MEN2B (American Thyroid Association Guidelines Task Force 2009).

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Prices: Sequencing of *RET* gene, Exons 15 and 16 \$ 340

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x2	83898 \$ 70	Sequencing x2	83904 \$100
Separation x1	83894 \$ 30	Interpretation/Report x1	83912 \$ 70

Accreditation: CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12).

Contact: Ying Wang, MD, PhD, ying.wang@preventiongenetics.com, www.preventiongenetics.com