

Genetic Testing for Germline Variants of the RET Proto-Oncogene

Policy Number: AHS – M2078 – Genetic Testing for Germline Variants of the RET Proto-Oncogene	Policy Revision Date: 04/01/2025 Initial Policy Effective Date: 12/01/2024
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I. Policy Description

The rearranged during transfection (Elisei et al.) proto-oncogene encodes a transmembrane receptor tyrosine kinase (Takahashi et al., 1985) that regulates a complex network of signal transduction pathways during development, survival, proliferation, differentiation, and migration of the enteric nervous system progenitor cells (Hedayati et al., 2016). Disruption of RET signaling by mutation, gene rearrangement, overexpression or transcriptional up-regulation of the *RET* gene is implicated in several human cancers (Plaza-Menacho et al., 2014), most commonly thyroid cancer, but also chronic myelomonocytic leukemia, acute myeloid leukemia, and lung, breast, pancreatic, and colon cancers (Gordon et al., 2018). Mutation of the *RET* gene in a germline cell results in an autosomal dominant hereditary cancer syndrome, multiple endocrine neoplasia type 2 (MEN2), characterized by medullary thyroid carcinoma (MTC), pheochromocytoma (PHEO), and primary parathyroid hyperplasia (PPTH) (Figlioli et al., 2013).

This policy covers genetic testing for germline variants in the *RET* gene. For information on testing of tumors for *RET* variants for guiding chemotherapy, see AHS-M2030 Testing for Targeted Therapy of Non-Small-Cell Lung Cancer, AHS-M2108 Molecular Markers in Fine Needle Aspirates of the Thyroid, and AHS-M2171 Esophageal Pathology Testing.

II. Related Policies

Policy Number	Policy Title
AHS-M2030	Testing for Targeted Therapy of Non-Small-Cell Lung Cancer
AHS-M2108	Molecular Markers in Fine Needle Aspirates of the Thyroid
AHS-M2171	Esophageal Pathology Testing

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the “Applicable State and Federal Regulations” section of this policy document.

- 1) Genetic testing for *RET* proto-oncogene variants **MEETS COVERAGE CRITERIA** when any of the following conditions are met:
 - a) For individuals who are a member of a family with defined *RET* gene mutations.

- b) For individuals who are a member of a family that is known to be affected by inherited medullary thyroid cancer but whose family has not previously been evaluated for *RET* mutations.
- c) For individuals who are a first-degree relative (see Note 1) of individuals with MTC.
- d) For individuals with a diagnosis of MTC, a clinical diagnosis of multiple endocrine neoplasia type 2 (MEN2), or primary C-cell hyperplasia.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

- 2) For all other situations not discussed above, genetic testing for germline variants in the *RET* gene **DOES NOT MEET COVERAGE CRITERIA.**

NOTES:

Note 1: First-degree relatives include parents, full siblings, and children of the individual.

IV. Table of Terminology

Term	Definition
A750T	Alanine-750-threonine
A883F	Alanine-883-phenylalanine
AKT	<i>AKT serine/threonine kinase 1</i>
ALK	<i>ALK receptor tyrosine kinase</i>
AMP	Association for Molecular Pathology
ATA	American Thyroid Association
BTA	British Thyroid Association
C634R	Cysteine-634-arginine
C634Y	Cystine-634-tyrosine
CAP	College of American Pathologists
CDKN2A	<i>Cyclin dependent kinase inhibitor 2A</i>
CLA	Cutaneous lichen amyloidosis
CLIA'88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid Services
DNA	Deoxyribonucleic acid
EGFR	<i>Epidermal growth factor receptor</i>
ESMO	European Society for Medical Oncology
ETA	European Thyroid Association
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FISH	Fluorescent in situ hybridization
FLT3	<i>Fms related receptor tyrosine kinase 3</i>
FMTC	Familial medullary thyroid carcinoma

HD	Hirschsprung disease
HPTH	Primary hyperparathyroidism
HSCR	Hirschsprung's disease
IASLC	International Association for the Study of Lung Cancer
IHC	Immunohistochemistry
L790F	Leucine-790-phenylalanine
LDTs	Laboratory developed tests
M918T	Methionine-918-threonine
MAPK	<i>Mitogen-activated protein kinase</i>
MEN	Multiple endocrine neoplasia
MEN2	Multiple endocrine neoplasia type 2
MEN2A	Multiple endocrine neoplasia type 2A
MEN2B	Multiple endocrine neoplasia type 2B
MTC	Medullary thyroid carcinoma
NAT2	<i>N-acetyltransferase 2</i>
NCCN	National Comprehensive Cancer Network
NGS	Next-generation sequencing
NHS	National Health Services
NSCLC	Non-small cell lung cancer
PTH	Parathyroid hyperplasia
PHEO	Pheochromocytoma
PPTH	Primary parathyroid hyperplasia
QOE	Quality of evidence
Q-PCR	Quantitative polymerase chain reaction
R387Q	Arginine-387-glutamine
R693H	Arginine-693-histidine
RET	Rearranged during transfection
ROS1	<i>ROS proto-oncogene 1, receptor tyrosine kinase</i>
RT-PCR	Real-time polymerase chain reaction
SNP	Single nucleotide polymorphism
SOR	Strength of recommendation
V292M	Valine-292-methionine
V804M	Valine-804-methionine
VUS	Variants of unknown significance

V. Scientific Background

The *RET* gene encodes a receptor tyrosine kinase that transduces growth and differentiation signals from the glial cell-derived neurotrophic factor family of ligands (Saarma, 2001). *RET* is expressed in the neuroendocrine parafollicular C-cells of the thyroid gland, adrenal medulla, neurons, and other tissues (Takaya et al., 1996). Unlike loss of function mutations that inactivate tumor suppressor proteins, oncogenic *RET* mutations result in a gain-of-function, inducing ligand-independent autophosphorylation of the RET receptor (Santoro et al., 1995), uncontrolled activation of MAPK and phosphoinositide 3-

kinase pathways, and ultimately uncontrolled growth and cell dedifferentiation (Hansford & Mulligan, 2000; Raue & Frank-Raue, 2018).

Oncogenic activation of the *RET* gene can result from either somatic or germline alterations. Activating germline point mutations in *RET* with autosomal dominant heritability have been identified as the primary initiating events causative of malignancy in C-cells of the thyroid gland (MTC) and other clinical presentations of MEN2 (Hansford & Mulligan, 2000; Mulligan, 2014). These mutations are identified in 98-100% of MEN2 cases (Raue & Frank-Raue, 2018; Romei et al., 2016), which are responsible for 25% of MTC cases overall (Raue & Frank-Raue, 2015). An estimated 64,000 individuals are diagnosed with thyroid cancer in the United States annually, and 1-2% of these cases are due to MTC. The most common alterations in the *RET* proto-oncogene are missense gain-of-function mutations mainly located in the extracellular domain of the *RET* gene (exons 10 or 11) and in the *RET* tyrosine kinase domain (exons 13, 14, 15 and 16) (ATA, 2016).

Germline *RET* mutations are associated with clear genotype-phenotype correlations (Plaza-Menacho et al., 2014). These clinical phenotypes can be divided into two subclasses of MEN2: multiple endocrine neoplasia type 2A (MEN2A) including familial medullary thyroid carcinoma (FMTC) and MEN type 2B (MEN2B) (Jasim et al., 2011). Over 100 *RET* point mutations, duplications, insertions, deletions, and fusions have been identified in individuals with MEN2A, with the C634R mutation in exon 11 being the most common mutation, whereas only two *RET* mutations have been identified in individuals with MEN2B (mainly M918T, and rarely A883F) (Giani et al., 2020; Romei et al., 2018). New variants continue to be reported (Paragliola et al., 2018; Qi et al., 2018). For example, in a case study of a 7-year-old girl in Italy, a “de novo” new germline *RET* deletion in exon 11 was found to cause features of both MEN2B without PHEO (pheochromocytoma), but “with a pelvic plexiform neurofibroma and with HPTH (primary hyperparathyroidism), which is typical of MEN2A” (Giani et al., 2020).

The MEN2A subclass is characterized by MTC and variable rates of PHEO, PPTH or both, with *RET* mutations in codons 609, 611, 618, or 620 of exon 10 and codon 634 of exon 11. Subtypes of classical MEN2A include development of cutaneous lichen amyloidosis and Hirschsprung disease. Absence of any clinical finding other than MTC in at least four family members is classified as FMTC (Wells et al., 2015).

The MEN2B subclass is characterized by highly aggressive MTC, usually PHEO, but not PPTH, and may exhibit musculoskeletal abnormalities and developmental defects with *RET* mutations in codons 918 and 883 of exon 15 (Wells et al., 2015).

Figure 1: *RET* point mutations in MEN2A, MEN2B, and FMTC (Wells et al., 2013).

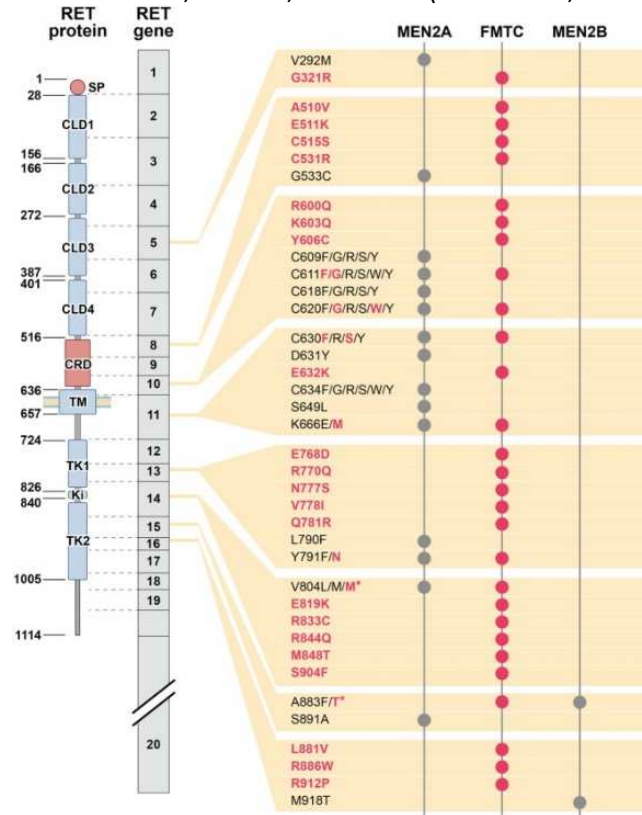


Table 1: Clinical expression of familial MTC-associated syndromes (Links et al., 2015).

	FMTC (%)	MEN2A (%)	MEN2B (%)
MTC	100	100	100
Pheochromocytoma	0	10-60	50
Hyperparathyroidism	0	10-30	0
Marfanoid habitus	0	0	100
Intestinal ganglioneuromatosis	0	0	60-90
Mucosal neuromas	0	0	70-100

Clinical Utility and Validity

The development of tyrosine kinase inhibitors that specifically target *RET* (Suyama & Iwase, 2018) has allowed for genetic analysis of *RET* germline mutations to become the standard of care in the initial workup for detecting germline mutations and familial risk and identifying targeted therapy in MTC (Ernani et al., 2016; Wells et al., 2015). Further, somatic *RET* rearrangements have recently been implicated in a variety of cancers, including chronic myelomonocytic leukemia; acute myeloid leukemia; and lung, breast, pancreatic, and colon cancers; an individual previously diagnosed with lung cancer underwent genomic profiling, and the identification of a *RET* point mutation associated with MTC allowed researchers to determine that this lung cancer diagnosis was incorrect (Gordon et al., 2018). A change in treatments proved to be very helpful for this individual. Other researchers have reported *RET* translocations in lung cancer cases, but they state that this is extremely rare (Zhao et al., 2016).

Guan et al. (2020) identified *RET* mutations in human epithelial ovarian cancer, providing another area of benefit from genetic testing of the *RET* gene for developing targeted therapies. Results showed that R693H and A750T mutants, in the juxtamembrane region and intracellular kinase domain, respectively, could promote the MAPK and AKT signaling pathway in ovarian cancer, and that the *RET* inhibitor vandetanib could decrease signal transduction and inhibit cancer growth (Guan et al., 2020).

Though activating variants in the receptor tyrosine kinase rearranged during transfection are known to be associated with MEN 2, not all variants are created equal. Hansen et al. (2021) explored the pathogenic role of the variant c.166C>A, p.Leu56Met in *RET*, which was identified in individuals presenting short segment HSCR and more recently in two individuals with MTC. Seven unrelated *RET* Leu56Met carriers from a Danish cohort were evaluated in the study, none of whom displayed evidence of MEN 2 or MTC based on the authors' predefined criteria for MEN2B (“(i) the individual demonstrates more than one MEN 2 manifestation, including histologically verified MTC, histologically verified pheochromocytoma, histologically verified gastrointestinal or mucosal neuromas, histologically verified HSCR, biochemically verified PHPT, and clinically or histologically verified cutaneous lichen amyloidosis, or (Martins-Costa et al.) the individual has one MEN 2 manifestation and a relative with MTC and the *RET* Leu56Met variant”). Moreover, while known causative variants of MEN 2 such as p.Cys634Tyr and p.Met918Thr boast allele frequencies below 0.001%, the allele frequency for the Leu56Met variant computed from the in-house diagnostic cohort was much higher at 0.59%. These considerations, combined with the lack of family history for MEN 2, suggest that Leu56Met is “a common variant without clinical significance in the Danish population” and “is most likely a benign variant” (Hansen et al., 2021).

Researchers have also found in two *RET* L790F index individuals that somatic *RET* variants were not responsible for the early onset and aggressiveness of MTC in a *RET* germline mutation carrier. Normally, variations in MTC presentation could be attributed to *RET* germline variants (Mathiesen et al., 2020). However, Mathiesen et al. (2020) found an *FLT3* R387Q variant - *FLT3* being a protein commonly found in hematopoietic malignancies - that could have been a genetic modifier instead.

The strong genotype-phenotype correlation of *RET* mutations makes genetic screening of significant value in diagnosis, prognosis, and management of MEN2 (Eng et al., 1996; Frank-Raue et al., 2010; Romei et al., 2015) and resultant MTC (Machens, Lorenz, et al., 2018), PHEO (Kimura et al., 2018), and PPTH. Each specific *RET* mutation correlates with MEN2 presentation, age at onset of MTC, and MTC aggressiveness (Brandi et al., 2001). Screening and early treatment of the manifestations of MEN2 can prevent metastasis of MTC and the morbidity and mortality caused by PHEO (Gagel et al., 1988; Makri et al., 2018). Moreover, screening has been associated with improved survivorship and outcomes (Raue et al., 2018). Based upon these genotype-phenotype correlations, *RET* mutations have been stratified into three risk levels based on the penetrance and aggressiveness of the MTC (Brandi et al., 2001; Wells et al., 2015). Consequently, mutation type should guide major management decisions, such as whether and when to perform thyroidectomy (Machens, Elwerr, et al., 2018; Machens, Lorenz, et al., 2018). Children in the highest risk category should undergo thyroidectomy in their first year of life, and perhaps even in their first months of life (Machens, Elwerr, et al., 2018; Machens, Lorenz, et al., 2018). Those with mutations in the high-risk category (codon 634 mutations) “should undergo thyroidectomy before reaching the age of 5 years” (Larouche et al., 2019). Annual biochemical screening in individuals with a family history of FMTC or MEN2 can also be stopped in those individuals who test negative for mutations (Wells et al., 2015).

Martins-Costa et al. (2018) performed *RET* genetic sequencing on exons 8, 10, 11, and 13-16 in 247 individuals with MTC or who are at risk of developing MTC due to family history. Before genetic testing,

54 of the individuals were diagnosed with sporadic disease and six were diagnosed with hereditary disease; after genetic testing, 31 individuals were diagnosed with sporadic disease and 29 with hereditary disease (Martins-Costa et al., 2018). *RET* screening allowed several individuals to be classified as hereditary who were initially diagnosed with sporadic MTC; 73 at-risk relatives were identified as mutation carriers, which will assist in long-term life and reproductive decisions (Martins-Costa et al., 2018).

A meta-analysis consisting of 438 Indian individuals with MTC and 489 healthy controls of similar ages and genders was completed; all participants received molecular genetic testing including *RET* gene sequencing and SNP genotyping (Mishra et al., 2019). This study identified *RET* SNPs as a significant risk factor for developing hereditary MTC; *CDKN2A* and *NAT2* SNPs with a significant risk of developing sporadic MTC (Mishra et al., 2019).

Genetic screening for *RET* was also provided to a total of 2031 Italian subjects; this included 1264 individuals with sporadic MTC symptoms, 117 individuals with hereditary MTC symptoms, and 650 relatives (Elisei et al., 2019). The researchers state, “A *RET* germline mutation was found in 115/117 (98.3%) hereditary and in 78/1264 (6.2%) apparently sporadic cases: in total, 42 distinct germline variants were found” (Elisei et al., 2019). This thereby underscores the significance of genetic screening in unsuspected MEN2 families. Sporadic MTC cases were present most commonly with a V804M mutation, and all M918T mutations were *de novo* “and exclusively associated with MEN2B” (Elisei et al., 2019). These researchers also identified several variants of unknown significance (VUS).

A paper by Milićević et al. (2021) focused on examining the crude annual incidence rate of MTC and *RET* mutation frequency. The study involved Slovenian individuals at the Institute of Oncology Ljubljana from 1995 to 2015 and involved their family members who participated in genetic counseling and testing there. It was found that among 143 individuals with MTC, 37 (25.9%) harbored a germline *RET* mutation, and said mutations were uncovered in exons 10, 11, 13, 14, and 16. Also, the researchers noted that “*RET* germline mutations are quite commonly discovered even in the apparently sporadic form of the disease”, such that 14.2% of individuals with a negative family history were presented with them. It was also reported that the most frequent *RET* germline mutations were found on codons 634 and 618 (30.0%) and exon 11 was the most frequently altered, though mutations of codons 790, 804, and 918 were observed in smaller but noticeable percentages (25.0%, 10.0%, and 5.0%, respectively). However, despite the low compliance of family members resulting in a smaller pool of participants, the authors extol the use of genetic counseling in this case, as “Annual incidence increase and nation-specific frequency of discovered *RET* mutations justify the continuation of gene counseling and testing of MTC individuals in Slovenia” (Milićević et al., 2021).

A study by Fussey et al. (2021) aimed to lend their perspective on the diagnostic potential of *RET* genetic testing. Between 1997 and 2018, the Exeter Genomics Laboratory at the Royal Devon and Exeter NHS Foundation Trust collected information on 1058 index individuals with MTC and other MEN2-related clinical features. They found that in total, 92 of the 766 UK individuals with MTC were harboring a germline *RET* pathogenic variant, and that variants in 10, 11, and 14 comprised its bulk, with codons 634 in exon 11 and 804 in exon 14 being most often affected. As such, the researchers believe that “the use of somatic *RET* analysis to confirm the diagnosis of sporadic MTC in individuals with no identified germline *RET* variants may be a useful adjunct both in terms of reassuring family members about the lack of a heritable pathogenic germline variant, and risk-stratifying sporadic tumours based on somatic variants” (Fussey et al., 2021).

Genetic screening for *RET* could also disclose new variants with their respective phenotypes. Yang et al. (2020) described a compound C634Y/V292M transmutation in a northern Chinese family that was associated with a more aggressive clinical presentation. Carriers of this variant had bilateral MTC with PHEO or lymph node metastasis with faster cell growth (cell growth speed identified *in vitro*). On the other hand, carriers of the V292M variant were asymptomatic, and carriers of the C634Y mutation only had elevated calcitonin (Yang et al., 2020). This has demonstrated the striking variability in MTC clinical presentation based on *RET* gene variants, making it critical to aid in any future potential treatment regimen.

Though activating variants in the receptor tyrosine kinase rearranged during transfection are known to be associated with MEN 2, not all variants are created equal. Hansen et al. (2021) explored the pathogenic role of the variant c.166C>A, p.Leu56Met in *RET*, which was identified in individuals presenting short segment HSCR and more recently in two individuals with MTC. Seven unrelated *RET* Leu56Met carriers from a Danish cohort were evaluated in the study, none of whom displayed evidence of MEN 2 or MTC based on the authors' predefined criteria for MEN2B (“(i) the individual demonstrates more than one MEN 2 manifestation, including histologically verified MTC, histologically verified pheochromocytoma, histologically verified gastrointestinal or mucosal neuromas, histologically verified HSCR, biochemically verified PHPT, and clinically or histologically verified cutaneous lichen amyloidosis, or (Martins-Costa et al.) the individual has one MEN 2 manifestation and a relative with MTC and the *RET* Leu56Met variant”). Moreover, while known causative variants of MEN 2 such as p.Cys634Tyr and p.Met918Thr boast allele frequencies below 0.001%, the allele frequency for the Leu56Met variant computed from the in-house diagnostic cohort was much higher at 0.59%. These considerations, combined with the lack of family history for MEN 2, suggest that Leu56Met is “a common variant without clinical significance in the Danish population” and “is most likely a benign variant” (Hansen et al., 2021).

Bhandari et al. (2023) studied the testing patterns for *RET* in the United States for people with advanced or metastatic medullary thyroid cancer. The authors completed a retrospective analysis of 203 individuals being cared for by 75 oncologists. Here, “A total of 59.6% (121 of 203) of patients underwent testing for *RET*, and 37.2% (45 of 121) had a *RET* mutation, of which 55.6% were identified as *RET* mutation-positive before initial diagnosis.” The authors also note that “90 (44.3%) patients were tested for biomarkers on or after initial diagnosis, with *RET* being the most tested (95.6%) biomarker.” The authors conclude that there is opportunity to improve testing rates (Bhandari et al., 2023).

VI. Guidelines and Recommendations

European Society for Medical Oncology (ESMO)

The ESMO has published clinical practice guidelines on diagnosis, treatment, and follow-up of thyroid cancer, stating that “All patients with MTC should be offered genetic counselling and screened for germline *RET* mutations” (Filetti et al., 2020). Filetti et al. (2020) also stated that “screening for somatic *RET* mutations is only recommended if *RET* inhibitor therapy is planned.”

In 2021, ESMO Translational Research and Precision Medicine Working Group expanded upon the algorithm to identify individuals eligible for anti-*RET* therapy across three scenarios based on the malignancies. The recommendations are captured below:

“Scenario A: Patients affected by NSCLC, non-MTC or other solid tumours, with available formalin-fixed, paraffin-embedded (FFPE) specimen need to be screened for detection of *RET* fusion. If NGS is not

available, FISH or RT-PCR is indicated in NSCLC and non-MTC, depending on local availability, cost and/or amount of tumour cells. In case of a negative test result, it is recommended to perform an NGS panel. It should be noted, however, that the recent ESMO recommendations suggest using multigene NGS to assess NSCLC level I alterations, including *RET* fusions.

In addition to *RET* fusion testing, patients affected by other solid tumours may need to be tested also for *RET* mutation according to the results of pending clinical trials. This can be done preferably by NGS; if this is not available, Q-PCR can be used. In none of the above cases is RET IHC testing recommended.

Scenario B: For patients affected by NSCLC, non-MTC or other solid tumours whose FFPE specimens are not available or are exhausted, we suggest performing a liquid biopsy (cell-free nucleic acid NGS panel) to test for *RET* alteration.

It is important to notice that if an *RET* alteration is not detected by liquid biopsy, then tumour tissue testing is still required to definitively exclude the possibility of an RET fusion.

Scenario C: Patients affected by MTC need to be screened for detection of *RET* mutation. They should be referred to genetic counselling in order to study the presence of MEN syndrome or FMTC. Mutations in the *RET* gene, in fact, are canonical in hereditary MTC, but can be found also in sporadic MTC. A Q-PCR or NGS can be carried out on sputum or blood of the patient. In case of known familial *RET* mutation, a simple Sanger test can be carried out on blood leukocyte DNA. If a germline *RET* mutation is present, family counselling is indicated. In case of absence of germline *RET* mutations, if the patient with MTC becomes metastatic, a Q-PCR or NGS analysis on FFPE tissue specimens from metastatic site of disease should be carried out in order to confirm or reject the presence of this alteration.

In none of the above cases is RET IHC testing recommended” (Belli et al., 2021).

American Thyroid Association (ATA)

The ATA published revised guidelines (Wells et al., 2015) which state that:

- “Initial testing for patients with MEN2A phenotype is either a single or multi-tiered analysis to detect *RET* mutations in exon 10 (codons 609, 611, 618, and 620), exon 11 (codons 630 and 634), and exons 8, 13, 14, 15, and 16. Grade B Recommendation”
- Initial testing for patients with MEN2B phenotype should be tested for the *RET* codon M918T mutation (exon 16), and if negative, the *RET* codon A883F mutation (exon 15).
- “Sequencing of the entire coding region should be reserved for situations in which no *RET* mutation is identified or there is a discrepancy between the MEN2 phenotype and the expected genotype. Grade B Recommendation
- Patients with the MEN2B phenotype should be tested for the *RET* codon M918T mutation (exon 16), and if negative, the *RET* codon A883F mutation (exon 15). If there are no mutations identified in these two exons the entire *RET* coding region should be sequenced. Grade B Recommendation
- Patients with presumed sporadic MTC should have genetic testing to detect a germline *RET* mutation. If a *RET* mutation is found the patient should have genetic testing. Grade B Recommendation

- In very rare families who meet the clinical criteria for MEN2A or 2B, despite negative sequencing of the entire *RET* coding region, the relatives at risk should be periodically screened by conventional methods for MTC, PHEO, and HPTH. After the initial evaluation, screening should continue at 1- to 3-year intervals. Grade C Recommendation
- Genetic counseling and genetic testing for *RET* germline mutations should be offered to
 - First-degree relatives of patients with proven hereditary MTC,
 - Parents whose infants or young children have the classic phenotype of MEN2B,
 - Patients with CLA [cutaneous lichen amyloidosis], and
 - Infants or young children with HD and exon 10 *RET* germline mutations, and adults with MEN2A and exon 10 mutations who have symptoms suggestive of HD” (Wells et al., 2015).

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for neuroendocrine and adrenal tumors (NCCN, 2024b) recommends that for diagnosis of or clinical suspicion of MEN2, genetic counseling and *RET* genetic testing should be offered in the following cases:

- “Individuals with MTC or primary C-cell hyperplasia or a clinical diagnosis of MEN2.”
- “At-risk relative of an individual with a known germline *RET* mutation at a very young age.”
- “All patients with MTC should be tested for germline mutation of the *RET* oncogene even if the family history is not suggestive of a hereditary syndrome, because about 50% of patients with presumed sporadic MTC have a *de novo* germline mutation” (NCCN, 2024b).

NCCN Guidelines for Thyroid Carcinoma (NCCN, 2024c) stated that as part of the additional workup after medullary thyroid carcinoma is identified by initial thyroid surgery, a “Screen for germline *RET* PV (exons 10, 11, 13-16); genetic counseling may be indicated” and “Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling” (NCCN, 2024c).

The FDA has approved several targeted therapeutic agents for use in esophageal and EGJ cancers. NCCN guidelines for Esophageal and Esophagogastric Junction Cancers (NCCN, 2024a) lists *RET* gene fusion as a targeted biomarker for NGS. “Immunohistochemistry/in situ hybridization/targeted PCR should be considered first for the identification of biomarkers, followed by NGS testing” (NCCN, 2024a).

The College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP)

The 2013 guidelines from CAP, IASLC and AMP for molecular testing in lung cancer individuals have been updated in 2018; new recommendations state that *RET* testing is approved in lung cancer specimens “as part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, and *ROS1* testing are negative” because “*RET* molecular testing is not recommended as a routine stand-alone assay outside the context of a clinical trial” (Lindeman et al., 2018).

The British Thyroid Association (BTA)

Regarding MTC, the BTA has stated that “In all confirmed cases of MTC, *RET* mutation analysis to establish the possible genetic basis for the disease within an individual or kindred, should be performed

even in the absence of a positive family history.” Other key recommendations to consider before genetic testing are listed below.

- “Because of the possibility of heritable disease, every case of MTC should be offered genetic testing”
- “Testing should always begin with the affected individual, if they are available”
- “If the affected individual is not available, the decision and strategy for testing should be discussed with the clinical genetics service”
- “Before blood is taken, a clear explanation must be given of the nature of the test, the possible outcomes, and of the implications of a positive or negative result for the individual and the family. This explanation should be recorded in the case notes for each individual” (Perros et al., 2014).

European Thyroid Association (Giani et al.)

The ETA Executive Committee in 2012 issued guidelines specifically devoted to *RET* genetic screening for individuals affected by MTC with reference to three different phenotypes: multiple endocrine neoplasia types 2A and 2B and familial MTC (FMTC) (Elisei et al., 2013). In their attempt to improve the quality of care for individuals and families with MTC, they made recommendations with varying valences, grading their own recommendations by the quality of evidence (QOE), which is indicated by plus signs at three levels, and the strength of recommendation (SOR) score, indicated by a 1 (strong recommendation for or against) or a 2 (“weak recommendation or a suggestion that may not be appropriate for every patient, depending on the context, patient values, and preferences”). The relevant parts of the guidelines are

From Recommendation 4:

“(a) Exons 5, 8, 10, 11, 13, 14, 15, and 16 should always be analyzed starting from the most likely involved in the presenting syndrome (i.e. exon 10 in MEN 2A, exon 16 in MEN 2B, etc.). DNA from MTC individuals with a strong suggestion of familial disease should also be analyzed for all other uncommonly mutated exons when those listed above are negative... (QOE = +++; SOR = score 1).”

(b) Subjects belonging to the few families (2–5% of all MEN 2/FMTC families) with clinically evident MEN 2/FMTC features but lacking evidence of an associated germline *RET* mutation should be followed up annually by measurement of basal serum Ct, metanephrines, calcium, and PTH. Neck and abdomen ultrasound could also be useful although not absolutely required if biochemical tests are still negative (QOE = ++; SOR = score 1).

(c) Once a germline *RET* mutation has been identified, all first-degree relatives and other relevant family members should be screened for the specific causative mutation (QOE = +++; SOR = score 1).

(d) Once a germline *RET* mutation has been discovered, further sequencing adds little, although some cases of double or triple *RET* mutations have been reported. These peculiar cases would likely be missed if *RET* screening was stopped when the first mutation was identified. The completeness of *RET* gene analysis is particularly indicated when the first identified mutation is rare and with a low or null transforming ability. These rare cases should be referred to specialized tertiary centers for a complete characterization of the mutation and its relationship with the disease (QOE = ++; SOR = score 2).

(e) Family members negative for the mutation are not at risk for the development of MTC and their children are not at risk either. Such individuals should be reassured and do not require further investigation or follow-up (QOE = +++; SOR = score 1)” (Elisei et al., 2013).

From Recommendation 5:

“(a) All patients with either apparently sporadic or familial MTC should be screened for germline *RET* mutations (QOE = +++; SOR = score 1).”

From Recommendation 6:

“(a) Patients with bilateral PHEO [pheochromocytoma] should be considered for *RET* genetic screening when other MEN 2A endocrinopathies (MTC and/or PHPT [primary hyperparathyroidism]) or CLA are present in the same subject or if a family history of MEN 2A or 2B is present. The screening becomes mandatory if the basal serum Ct is above the normal range, independently of the presence of other MEN 2A endocrinopathies (QOE = ++; SOR = score 1).

(b) Patients with multiple adenomatosis of the parathyroid glands and PHPT should be considered for *RET* genetic screening if other MEN 2A endocrinopathies (MTC and/or PHEO) or CLA are present in the same subject or if a family history of MEN 2A is present. Also in this case, *RET* genetic screening must be performed if basal serum Ct levels are above the normal range, even if no other MEN 2A endocrinopathies are diagnosed (QOE = ++; SOR = score 1).

(c) Subjects with CLA should be investigated clinically and should undergo genetic testing for MEN 2A. In particular *RET* codon 634 in exon 11 should be analyzed (QOE = +++; SOR = score 1).

(d) Patients with Hirschsprung disease should have *RET* genetic screening for mutations involved in Hirschsprung disease, but analyses performed specifically to investigate an association with MEN 2 should be limited to exon 10 (QOE = +++; SOR = score 1)” (Elisei et al., 2013).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81404	Molecular pathology procedure, Level 5 Gene:

	RET (ret proto-oncogene) (eg, multiple endocrine neoplasia, type 2B and familial medullary thyroid carcinoma), common variants (eg, M918T, 2647_2648delinsTT, A883F)
81405	Molecular pathology procedure, Level 6 Gene: RET (ret proto-oncogene) (eg, multiple endocrine neoplasia, type 2A and familial medullary thyroid carcinoma), targeted sequence analysis (eg, exons 10, 11, 13-16)
81406	Molecular pathology procedure, Level 7 Gene: MUTYH (mutY homolog [E.coli]) (eg, MYH-associated polyposis), full gene sequence
S3840	DNA analysis for germline mutations of the ret proto-oncogene for susceptibility to multiple endocrine neoplasia type 2

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Evidence-based Scientific References

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X. Review/Revision History

Effective Date	Summary
04/01/2025	<p>Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following edits were made for clarity and consistency:</p> <p>Title changed from “Genetic Testing for Germline Mutations of the RET Proto-Oncogene” to “Genetic Testing for Germline Variants of the RET Proto-Oncogene” to reflect appropriate nomenclature for genetic changes that are germline vs somatic.</p> <p>In addition to the title change to reflect appropriate nomenclature, CC1 and CC2 were edited to change “point mutations” to “variants”.</p> <p>Removed CC1.c.: “c) For individuals with apparently sporadic medullary thyroid carcinoma (MTC).” which was in conflict with former CC1.e., now CC1.d.: “d) For individuals with a diagnosis of MTC, a clinical diagnosis of multiple endocrine neoplasia type 2 (MEN2), or primary C-cell hyperplasia.”</p> <p>Removed “sporadic” from former CC1.d., now CC1.c.</p>
12/01/2024	Initial Policy Implementation