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Corporate Medical Policy

Genetic Testing for Germline Mutations of the RET Proto-Oncogene AHS - M2078

File Name:	genetic_testing_for_germline_mutations_of_the_ret_proto-oncogene
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Description of Procedure or Service

The RET (rearranged during transfection) proto-oncogene encodes a transmembrane receptor tyrosine kinase (Takahashi, Ritz, & Cooper, 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, Zarif Yeganeh, Sheikholeslami, & Afsari, 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, Mologni, & McDonald, 2014), most commonly thyroid, 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, Landi, Romei, Elisei, & Gemignani, 2013).

This policy covers genetic testing for germline variants in the RET gene. For information on testing of tumors for RET variants to guide chemotherapy.

Related Policies

M2109 Molecular Panel Testing of Cancers to Identify Targeted Therapy
M2030 Testing for Targeted Therapy of Non-Small-Cell Lung Cancer
M2108 Molecular Markers in Fine Needle Aspirates of the Thyroid.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for genetic testing for germline mutations of the RET proto-oncogene when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Germline Mutations of the RET Proto-Oncogene is covered

Genetic Testing for Germline Mutations of the RET Proto-Oncogene AHS - M2078

Genetic testing for RET proto-oncogene point mutations is considered **medically necessary** in any of the following situations:

A. Individual is a member of a family with defined RET gene mutations

B. Individual is a member of a family known to be affected by inherited medullary thyroid cancer, but not previously evaluated for RET mutations

C. Individual with apparently sporadic medullary thyroid carcinoma (MTC)

D. Individual is a first-degree relative of individuals with sporadic medullary thyroid cancer

E. Individual with a diagnosis of MTC or a clinical diagnosis of MEN2 (multiple endocrine neoplasia type 2) or primary C-cell hyperplasia.

When Genetic Testing for Germline Mutations of the RET Proto-Oncogene is not covered

Genetic testing for germline point mutations of the RET gene is **investigational** in all other situations.

Policy Guidelines

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, Ciampi, & Elisei, 2016), which are responsible for 25% of MTC cases overall (Raue & Frank-Raue, 2015). An estimated 64,000 patients 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 patients with MEN2A, with the C634R mutation in exon 11 being the most common mutation, whereas only two *RET* mutations have been identified in patients 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).

MEN2A 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).

MEN2B 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, Pacini, Robinson, & Santoro, 2013).

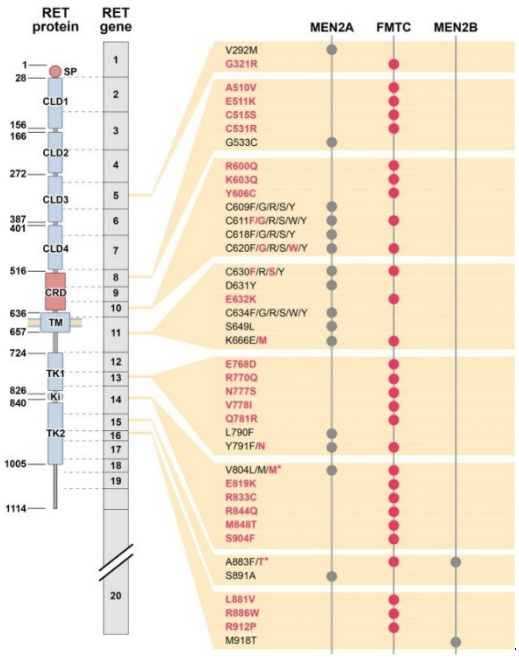

Table 1: Clinical expression of familial MTC-associated syndromes (Links, Verbeek, Hofstra, & Plukker, 2015).

	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 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,Kumar,Chen,&Owonikoko,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; a patient 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 patient. 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).

Researchers have also found in two *RET* L790F index patients 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.

Clinical Utility

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, Rondot, & Raue, 2010; Romei et al., 2015) and resultant MTC (Machens, Lorenz, Weber, & Dralle, 2018), PHEO (Kimura, Takekoshi, & Naruse, 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, Dralle, Machens, Bruckner, & Frank-Raue, 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, Lorenz, Weber, & Dralle, 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, Akirov, Thomas, Krzyzanowska, & Ezzat, 2019). Annual biochemical screening in patients with a family history of FMTC or MEN2 can also be stopped in those patients 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 patients with MTC or who are at risk of developing MTC due to family history. Before genetic testing, 54 of these patients were diagnosed with sporadic disease and six were diagnosed with hereditary disease; after genetic testing, 31 patients were diagnosed with sporadic disease and 29 with hereditary disease (Martins-Costa et al., 2018). *RET* screening allowed several patients 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 patients 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, Kowtal, Rane, & Sarin, 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).

RET genetic screening was also provided to a total of 2031 Italian subjects; this included 1264 patients with sporadic MTC symptoms, 117 patients 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).

RET genetic screening 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.

Guidelines and Recommendations

European Society for Medical Oncology (ESMO) (Filetti et al., 2019, 2020)
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."

American Thyroid Association (ATA) (Wells et al., 2015)

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, 2020a, 2020b)

NCCN guidelines for neuroendocrine and adrenal tumors (NCCN, 2020a) recommends that for diagnosis of or clinical suspicion of MEN2, genetic counseling and *RET* genetic testing should be offered to:

- "An individual with a diagnosis of MTC or clinical diagnosis of MEN2 or primary C-cell hyperplasia;
- An at-risk relative of an individual with a known germline *RET* mutation.
    - Genetic testing of at-risk family members at a very early age"
- Genetic testing of at-risk family members at a very early age"
- "50% of cases have *de novo RET* mutations; therefore, even if a family history is not suggestive of a hereditary syndrome, genetic testing for *RET* mutations should still be performed on the affected individual
- 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, 2020a)

NCCN Guidelines for Thyroid Carcinoma (NCCN, 2020b) stated the following:

- Medullary thyroid carcinoma on fine needle aspiration (FNA) should be screened for *RET* proto-oncogene mutations (exons, 10,11,13-16)
- Medullary thyroid carcinoma diagnosed after initial thyroid surgery should be screened for germline *RET* proto-oncogene mutations (exons 10, 11, 13-16) with genetic counseling
- "Genetic testing for *RET* proto-oncogene mutations is recommended for all patients with newly diagnosed clinically apparent sporadic MTC, and for screening children and adults in known kindreds with inherited forms of MTC; genetic counseling should be considered" (NCCN, 2020b)

The College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) (Lindeman et al., 2018)

The 2013 guidelines from CAP, IASLC and AMP for molecular testing in lung cancer patients 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, 2014)

The BTA has stated, in regards to MTC, that "In all confirmed cased 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 (BTA, 2014)."

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81404, 81405, 81406, S3840

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Policy Implementation/Update Information

For Policy Titled: Genetic Testing for Germline Mutations RET Proto-Oncogene Medullary Carcinoma Thyroid

1/1/2019 New policy developed. BCBSNC will provide coverage for genetic testing for germline mutations RET proto-oncogene medullary carcinoma of the thyroid when it is determined to be medically necessary and criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)

For Policy Re-Titled: Genetic Testing for Germline Mutations of the RET Proto-Oncogene

4/16/19 Reviewed by Avalon 4th Quarter 2018 CAB. Policy title changed from "Genetic Testing for Germline Mutations RET Proto-Oncogene Medullary Carcinoma Thyroid" to "Genetic Testing for Germline Mutations of the RET Proto-Oncogene." Under "When Covered" section: added bullet F. "individual with a clinical diagnosis of MEN2 (multiple endocrine neoplasia type 2) or primary C-cell hyperplasia." Medical Director review 4/2019. (lpr)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)

2/11/20 Reviewed by Avalon Q4 2019 CAB. No changes to policy. (lpr)

3/31/20 Specialty Matched Consultant Advisory Panel review 3/18/2020.No change to policy statement. (lpr)

2/9/21 Reviewed by Avalon 4th Quarter 2020 CAB. Under When Covered section: removed item C. (as an alternative to annual biochemical testing for C cell hyperplasia); added MTC to statement D.; added "diagnosis of MTC" to statement F. All revisions for clarification and due to 2020 NCCN guidelines. Added CPT codes 81406 and S3840 to Billing/Coding section. Extensive revisions to Policy Guidelines. Add related policies section. References updated. Medical Director review 1/2021. (lpr)

4/6/21 Specialty Matched Consultant Advisory Panel review 3/17/2021. No change to policy statement. (lpr)

and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.