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
Origination: 1/2019
Last CAP Review: 3/2020
Next CAP Review: 3/2021
Last Review: 3/2020

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 in order to guide chemotherapy see M2109 Molecular Panel Testing of Cancers to Identify Targeted Therapy, M2030 Testing for Targeted Therapy of Non-Small-Cell Lung Cancer, and 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 RET proto-oncogene point mutations is considered medically necessary in any of the following situations:
Genetic Testing for Germline Mutations of the RET Proto-Oncogene
AHS - M2078

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. As an alternative to annual biochemical testing for C-cell hyperplasia
D. Individual with apparently sporadic medullary thyroid carcinoma
E. Individual is a first-degree relative of individuals with sporadic medullary thyroid cancer
F. Individual with 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

Per SEER (Surveillance, Epidemiology, and End Results) data, medullary thyroid carcinoma (MTC) accounts for 1–2% of thyroid cancers in the United States, which is a lower range than the 3-5% often cited, primarily because of the increased incidence of papillary thyroid carcinoma (American Thyroid Association, 2015). Thyroid cancer is traditionally seen as a largely curable disease: thyroidectomy, suppression of thyroid stimulating hormone (TSH), and administration of radioactive iodine confers overall survival rates of 71% at 10 years and 55% at 20 years (Emami V et al, 2016).

Yet these survival rates are only true for the 90% of differentiated thyroid cancers that originate in the follicular cells, comprising papillary, follicular, and Hürthle cell thyroid carcinomas. Medullary thyroid cancer (MTC), which represents approximately 4% of cases, tends to present at late stages and does not respond to TSH suppression or iodine, making it difficult to manage and conferring worse outcomes overall.

MTC originates from calcitonin-secreting neuroendocrine parafollicular or C cells of the thyroid. These cells lack TSH receptors and do not concentrate radioactive iodine. Approximately 50% of patients present with stage III/IV disease and 5-year survival rates range from 73% for patients with stage III disease to 40% for patients with stage IV disease (Machens A et al, 2013).

It is estimated that 20% of MTCs are associated with one of three inherited endocrine syndromes caused by germline mutations of the RET gene (Santoro M and Carlomagno F, 2013). The remaining 80% of MTCs are sporadic, although somatic mutations in RET can be seen in 40% to 50% of sporadic cases. Each of the syndromes can be distinguished by a unique cluster of clinical findings.

Multiple endocrine neoplasia (MEN) 2A is associated with RET mutations in codons 609, 611, 618, and 620 in exon 10, as well as in codon 634 in exon 11. Patients with MEN2A typically have MTC, pheochromocytoma, and primary hyperparathyroidism (PHPT) (Opsahi EM et al, 2016).

MEN2B is associated with RET mutations in codons 918 in exon 16 (> 95% of cases) and codon 883 in exon 15. These patients present with the most aggressive type of MTC. They typically have pheochromocytoma but not PHPT, and, unlike in the other syndromes, also exhibit musculoskeletal abnormalities and other developmental defects.

Finally, familial medullary thyroid cancer (FMTC) is associated with mutations in codons 609, 611, 618, and 620 in exon 10, as well as codon 768 in exon 13 and codon 804 in exon 14. In these patients, MTC
Genetic Testing for Germline Mutations of the RET Proto-Oncogene
AHS - M2078

is often the only clinical finding, i.e., patients do not necessarily have either pheochromocytoma or PHPT. The diagnosis of FMTC is therefore made after demonstrating MTC in at least 4 family members.

As in MEN2B, the most common mutation in patients with sporadic MTC is in codon 918 in exon 16. Patients with sporadic MTC typically have decreased survival compared with the inherited forms, and often demonstrate lymph node metastases at presentation.

Medullary thyroid cancer (MTC) is a rare tumor (3–5% of all thyroid cancers) arising from the calcitonin-producing parafollicular C cells of the thyroid gland (Wells et al., 2015, Hadoux et al., 2016). MTC occurs either sporadically or (in approximately one-third of cases) in a hereditary form as a component of the type 2 multiple endocrine neoplasia (MEN) syndromes MEN2A and 2B and the related syndrome familial MTC (FMTC) associated with germline RET (rearranged during transfection) mutations (Wells et al., 2015, Hadoux et al., 2016). The RET protooncogene is located in chromosome 10q11.2, encodes a single-pass transmembrane tyrosine kinase receptor, and is known to play a central role in the tumorigenesis of sporadic and hereditary MTC (Wells et al., 2015, Hadoux et al., 2016). While RET germline mutations can be detected in almost 100% of hereditary MTC cases, sporadic MTCs reveal somatic RET mutations in 50–60% of cases (Wells et al., 2015, Hadoux et al., 2016). RET/PTC rearrangements, which were previously believed to be exclusive to PTC, have now been found in some other human cancers, including MTC, but at a very low prevalence (Romei, Ciampi, & Elisei, 2016).

Currently, most patients with either FMTC or MEN2 are identified by genetic testing of at-risk family members. Patients with a positive family history of germline mutation of the RET gene have a 50% chance of inheriting the same mutation. Once identified as genetic carriers, there is a nearly 100% lifetime risk of developing malignancy (Roy et al., 2013).

FMTC

FMTC is similar to MEN2A with a strong predisposition to MTC in various family members without pheochromocytoma or hyperparathyroidism. In FMTC, there must not be any diagnosis of either pheochromocytoma or hyperparathyroidism in >10 carriers, and presentation must be after the age of 50 in multiple family members affected by the disease. Once a family is labeled as FMTC, there is a higher chance of missing a pheochromocytoma because these patients are not screened for the disease. If there is any uncertainty, it is much safer to label the family as MEN2 instead of FMTC (Roy et al., 2013).

Molecular Pathogenesis

MTC in MEN2 is inherited in an autosomal dominant pattern with very high penetrance. The genetic defect in these disorders involves the RET proto-oncogene on chromosome 10q11.2. Currently known RET mutations account for >95% of cases of hereditary MTC.

Understanding of candidate initiating and driving events in oncogenic transformation of thyroidal C cells has been facilitated by the discovery of activating germline mutations of the RET gene in the early 1990s as the genetic basis for hereditary forms of MTC (Wells et al., 2015). RET is located on chromosomal band 10q11.2 and encodes a single-pass transmembrane receptor tyrosine kinase. The RET protein has an extracellular ligand-binding domain composed of a cadherin-like region, and a highly conserved
Genetic Testing for Germline Mutations of the RET Proto-Oncogene
AHS - M2078

cysteine-rich domain. The intracellular region is composed of two tyrosine kinase domains. Upon ligand binding, the extracellular cysteine-rich domain facilitates receptor dimerization leading to autophosphorylation and tyrosine kinase activation triggering parallel downstream signaling pathway activation including RAS/RAF/MAPK, PI3K/AKT, and JAK-STAT pathways (Mulligan 2014). More than 80 different germline RET mutations have been identified in hereditary MTC. Most are single-nucleotide missense mutations resulting in constitutive activation of the RET tyrosine kinase (Wells et al. 2015).

Recently, genetic assays for RET mutations have been used as an alternative to annual biochemical testing for C-cell hyperplasia, in patients with a known family history of MEN 2A, 2B, or FMTC. Annual biochemical screening can be stopped in those patients who test negative for mutations. Patients who test positive may undergo immediate thyroidectomy or postpone thyroidectomy until biochemical tests suggest evolving medullary cancer. Genetic assays have also been used to determine if new cases of medullary thyroid cancer without a family history are truly sporadic in origin. A positive test in this setting should initiate evaluation of family members. In addition, a positive test may prompt screening for pheochromocytoma, a component of MEN 2A and 2B, in the affected patient.

Common Mutations in Sporadic MTC

<table>
<thead>
<tr>
<th>Most Common Mutation(s)</th>
<th>Typical Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN2A</td>
<td>MTC, pheochromocytoma, and PHPT</td>
</tr>
</tbody>
</table>
| • Codons 609, 611, 618, and 620 in exon 10  
• Codon 634 in exon 11 | |
| MEN2B                   | Most aggressive MTC  
• Pheochromocytoma, not PHPT  
• Musculoskeletal abnormalities and developmental defects |
| • Codon 918 in exon 16 (> 95% of cases)  
• Codon 883 in exon 15 | |
| FMTC                    | MTC present in at least 4 family members  
• Pheochromocytoma and PHPT not necessarily present |
| • Codons 609, 611, 618, and 620 in exon 10  
• Codon 768 in exon 13  
• Codon 804 in exon 14 | |
| Sporadic                | Decreased survival  
• Lymph nodes metastases at presentation |

Applicable Federal Regulations
N/A

Guidelines and Recommendations

Currently, most patients with either FMTC or MEN2 are identified by genetic testing of at-risk family members. Patients with a positive family history of germline mutation of the RET gene have a 50% chance of inheriting the same mutation. Once identified as genetic carriers, there is a nearly 100% lifetime risk of developing malignancy.

2009 ATA guidelines for MTC recommend that all patients with C-cell hyperplasia or MTC be offered germline RET testing. It is important to provide appropriate genetic counseling to patients prior to screening for RET mutations. The risks and benefits of genetic testing must be discussed with patients and their families. In addition, once a positive RET mutation is detected, the patient must be carefully
Genetic Testing for Germline Mutations of the RET Proto-Oncogene
AHS - M2078

advised regarding the risks for other members of the family. Other clinical presentations such as Hirschsprung disease and CLA should also prompt genetic testing for RET mutations (Kloos et al., 2009). Ideally, in the event that a RET mutation is identified, at-risk family members should be offered a prophylactic thyroidectomy prior to the development of MTC. On occasion, a germline RET mutation may not be detected in a family with a clinical diagnosis of MEN2. In these at-risk relatives, periodic screening for MTC should be performed with neck U/S and serum calcitonin levels, screening for pheochromocytoma should be done by measurement of plasma or 24-hour urine metanephrines and normetanephrines, and hyperparathyroidism should be screened with albumin-corrected calcium or ionized calcium and parathyroid hormone levels (Kloos et al., 2009).

Data provide very strong support for the hypothesis that genetic tests for germline point mutations in the RET gene can identify those with an inherited susceptibility for medullary thyroid cancer earlier and more definitively than is possible with biochemical tests. For example, of 365 asymptomatic family members at risk for the inherited disease, 115 tested positive for RET gene mutations. Evidence of disease was subsequently found in all 115 with mutations and in none of the 250 without mutations. Test results affect patient management by prompting thyroidectomy or continued biochemical monitoring in affected patients, and by prompting discontinuation of monitoring in patients who test negative.

NCCN Guidelines for both Medullary Thyroid Carcinoma and Neuroendocrine tumors include screening for Screen for RET protooncogene mutations (exons, 10,11,13-16). Germline mutation should prompt family testing of first-degree relatives and genetic counseling (NCCN, 2017a, 2017b).

**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*

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**

American Thyroid Association Guidelines for management of Medullary Thyroid Carcinoma; Thyroid, 2015 June 25 (6):567-610 [link]


Christine Spitzweg· John C Morris· and Keith C Bible Endocr Relat Cancer June 1, 2016 23 R287-R297 doi: 10.1530/ERC-16-0104
Genetic Testing for Germline Mutations of the RET Proto-Oncogene
AHS - M2078


Emami V, Kumar M, Chen AY, Owonikoko TK; Systemic treatment and management approaches for medullary thyroid cancer; Cancer Treat Rev. 2016 Sep 10.50.89–98; link


Figlioli G, Stefano Landi, Cristina Romei, Rossella Ellisei, Federica Gemignani, Medullary Thyroid Carcinoma (MTC) and RET proto-oncogene: Mutation Spectrum in the Familial cases and a meta-analysis of Studies on the sporadic form. Mutation research 752 (2013)36-44.


Machen A, Lorenz K, Dralle H; Progression of Medullary Thyroid Cancer in RET Carriers of ATA class A and C Mutations; J Clin Endocrinol Metab. 2013 Dec 2

Madhuchhanda Roy, Herbert Chen and Rebecca S. Sippel, Current Understanding and Management of Medullary Thyroid Cancer The Oncologist October 2013 vol. 18 no. 10 1093-1100


Genetic Testing for Germline Mutations of the RET Proto-Oncogene

AHS - M2078


Opsahl EM, Brauckhoff M, Schichting E, Helset K, Svartberg J, Brauckhoff K, et al; A Nationwide study of multiple endocrine neoplasia type 2A in Norway: prognostic and predictive factors for the clinical course of medullary thyroid carcinoma; Thyroid 2016 Sep 26(9): 1225-38


Santoro M, Carломagno F; Central Role of RET in Thyroid Cancer; Cold Spring Harb Perspect Biol, 2013 Dec 1.5(12)


Medical Director review 4/2019
Genetic Testing for Germline Mutations of the RET Proto-Oncogene
AHS - M2078

Medical Director review 3/2020

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)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.