

MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	GENETIC TESTING FOR GERMLINE MUTATIONS OF THE RET PROTO ONCOGENE IN MEDULLARY CARCINOMA OF THE THYROID
Policy Number	2.02.07
Category	Laboratory Test
Effective Date	10/18/01
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Product Disclaimer	<ul style="list-style-type: none"> • If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply. • If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit. • If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.

POLICY STATEMENT

Based upon our criteria and review of the peer-reviewed literature, genetic testing for germline point mutations in the RET gene has been medically proven to be effective and therefore, is **medically appropriate** only when done by a qualified laboratory in settings with adequately trained health care providers to provide appropriate pre- and post-test counseling for the following situations:

- I. Members of families with defined RET gene mutations;
- II. Members of families known to be affected by medullary thyroid carcinoma but not previously evaluated for RET mutations; or
- III. Patients with apparently sporadic medullary thyroid carcinoma.

Refer to Corporate Medical Policy #2.02.03 regarding Genetic Testing for Specific Diseases.

Refer to Corporate Medical Policy #11.01.12 regarding Screening Tests.

POLICY GUIDELINES

- I. The Health Plan and its employees adhere to all state and federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test.
- II. Laboratories performing clinical tests must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).
- III. Genetic assays for RET mutations must be ordered by a geneticist. (If there is no participating geneticist then adequately trained health care practitioners may provide counseling and request testing.)
- IV. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.
- V. If the genetic test is being done for knowledge only and that knowledge will not alter management or treatment of the patient or family member then the testing is **not medically appropriate**. However, testing of a patient who may become the “index” patient in a family is medically appropriate, since family history of the mutation may begin with

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that individual.

VI. If there is a high clinical likelihood that the patient has a specific disease and the treatment will not be modified based on the genetic testing results then the testing is **not medically appropriate**.

DESCRIPTION

Thyroid cancer is the most common malignancy of endocrine tissues, although it accounts for only 1.1% of all non-skin cancers detected annually in the United States. Up to 9% of thyroid cancer is medullary carcinoma. Three distinct but related familial cancer syndromes together are responsible for about one fourth of the incidence of medullary carcinoma of the thyroid; the remaining three fourths of cases are sporadic. From 90 to 95% of the inherited medullary thyroid carcinoma can be attributed to specific RET (rearranged during transfection) point mutations (multiple endocrine neoplasia - MEN 2A, MEN 2B - or familial medullary thyroid cancer - FMTC). All three of the syndromes (MEN 2A, MEN 2B and FMTC) exhibit an autosomal dominant pattern of inheritance with nearly complete penetrance. Thus, over their lifetime, more than 95% of those who inherit a mutated gene will develop medullary thyroid carcinoma if the gland is not removed before the disease is diagnosed by clinical symptoms.

Medullary thyroid carcinoma is surgically curable if detected before it has spread to regional lymph nodes. However, lymph node involvement at diagnosis may be found in up to 75% of patients for whom a thyroid nodule is the first sign of disease. Medullary thyroid carcinoma often recurs and/or spreads despite complete thyroidectomy in those with positive lymph nodes. Thus, early detection and intervention in affected families is critical.

The development of invasive medullary thyroid cancer usually is preceded by C-cell hyperplasia, which can be detected by hypersecretion of calcitonin in response to a chemical challenge. Surveillance by annual biochemical monitoring (pentagastrin testing) has been used to identify those with the inherited disease before it progresses beyond the earliest stages.

Genetic assays for RET mutations are used as an alternative to biochemical monitoring to test individuals from families affected by MEN 2A, MEN 2B or FMTC. Annual biochemical screening can be stopped in those individuals 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 are also used to determine if new cases of medullary thyroid carcinoma in individuals with no family history of the disease 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.

RATIONALE

The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with a high positive predictive value of the occurrence of a disease. Analytical sensitivity and specificity of a genetic test must be of such a level that the tests results can and will be used in making treatment decisions. DNA based testing of the RET gene identifies disease-causing mutations in about 95% of individuals with MEN 2A and 2B, and in about 85% of individuals with FMTC.

Information on the risks and benefits of genetic testing must be presented fully and objectively without coercion to persons contemplating genetic testing.

The American Society of Clinical Oncologists (ASCO) identifies MEN 2 as a Group 1 disorder, meaning that genetic testing (in this case, for mutations in the RET gene) is considered part of standard management of first-degree relatives of affected individuals. Persons who are mutation-positive may undergo thyroidectomy as a preventive measure, followed by biochemical screening for the other endocrine tumors. Genetic testing of unaffected relatives is most useful when a germline mutation has been identified in the affected family member.

There is sufficient evidence to conclude that genetic tests for germline point mutations in the RET gene can identify individuals with an inherited susceptibility for medullary thyroid cancer earlier and more definitively than is possible with

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biochemical tests. 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.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

CPT Codes

Code	Description
81404	Molecular pathology procedure level 5
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HCPCS Codes

Code	Description
S3840	DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2

ICD10 Codes

Code	Description
C73	Malignant neoplasm of thyroid gland
C79.89-C79.9	Secondary malignant neoplasm of other and unspecified digestive organs and of other and unspecified sites (code range)
D09.3-D09.8	Carcinoma in situ of thyroid and other endocrine glands and other specified sites (code range)
Z80.8	Family history of malignant neoplasm of other organs or systems
Z85.850	Personal history of malignant neoplasm of thyroid

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*Key Article

KEY WORDS

Familial thyroid cancer, Medullary thyroid cancer, RET proto-oncogene, Thyroid cancer.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ver=59&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=All&bc=AggAAAIAIAAAA%3d%3d&