



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Genetic Testing for RET Proto-Oncogene Germline Point Mutations

Effective Date 11/15/2009
Next Review Date 11/15/2011
Coverage Policy Number 0224

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Hyperlink to Related Coverage Policies

Genetic Counseling
Genetic Testing of Heritable Disorders

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2009 CIGNA

Coverage Policy

CIGNA covers genetic testing for RET (rearranged during transfection) proto-oncogene germline point mutations as medically necessary when ANY of the following criteria are met:

- For diagnostic testing with ANY of the following:
 - multiple endocrine neoplasia type 2 (MEN 2) subtypes (i.e., MEN 2A and MEN 2B)
 - familial medullary thyroid carcinoma (FMTC) or sporadic (nonfamilial) medullary thyroid cancer
 - sporadic pheochromocytoma
- For predictive testing when the individual has a first- or second-degree relative* in whom a disease causing RET germline mutation has been identified

*A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.

*A second-degree relative is defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces, and half-siblings.

All individuals undergoing genetic testing for any reason should have both pre- and post-test genetic counseling with a physician or a licensed or certified genetic counselor.

CIGNA does not cover genetic testing for the susceptibility to RET proto-oncogene germline mutations in the general population because it is considered not medically necessary or of unproven benefit.

General Background

Multiple endocrine neoplasia type 2 (MEN2) is a genetic disorder caused by germline (i.e., inherited) mutations in the RET (rearranged during transfection) proto-oncogene. MEN2 is classified into two sub-types: MEN 2A and MEN 2B (Perry, 2006). The MEN 2 subtypes along with familial medullary thyroid carcinoma (FMTC) are associated with a high lifetime risk of medullary thyroid carcinoma (MTC) which arises from the parafollicular calcitonin secreting cells of the thyroid glands. The MEN 2 subtypes, MEN 2A and MEN 2B, carry an increased risk for pheochromocytoma. MEN 2A carries an increased risk for parathyroid adenoma or hyperplasia. Additional features in MEN 2B include mucosal neuromas of the lips and tongue, distinctive facies with enlarged lips, ganglioneuromatosis of the gastrointestinal tract, and tall, thin (Marfanoid) body type. The onset of MTC is usually in early childhood in MEN 2B, early adulthood in MEN 2A and middle age in FMTC (Wiesner, et al., 2005).

The diagnosis of the MEN 2 subtypes and FMTC rely on a combination of clinical findings, family history, and molecular genetic testing of the RET gene. The RET proto-oncogene is the gene responsible for these three conditions (Wiesner, et al., 2005; Perry, 2006), which are inherited in an autosomal dominant manner. The probability of a de novo gene mutation is 5% or less in index cases with MEN 2A and 50% in index cases with MEN 2B. Molecular genetic testing identifies disease-causing mutations in 95% of individuals with MEN 2A and MEN 2B and in about 88% of families with FMTC. Such testing is available and may be for presymptomatic identification of at-risk individuals in order to reduce morbidity and mortality through early intervention. Molecular genetic testing of the RET gene has become a standard of care as an integral part of clinical management of MEN 2A, MEN 2B and FMTC (NCI, 2009; NCCN, 2009a).

MEN 2 and FMTC carrier determination is an example of a genetic test that mandates a highly effective clinical intervention (Brandi, et al., 2001). Consensus was reached at the MEN 97 Workshop that the decision to perform thyroidectomy in MEN 2 should be based predominately on the result of RET mutation testing, rather than on computed tomography (CT) testing. Several unique features of MEN 2 support this recommendation. Early detection and intervention can alter the clinical course of MTC. Treatment of early MTC by thyroidectomy is well-tolerated, even by most infants. The use of abnormal CT tests to dictate thyroidectomy led to a low, but still problematic, incidence (as high as 5–10%) of false-positive tests, with lower incidence in some current immunometric CT assays; false positivity was determined by retrospective testing for RET mutation. The testing for RET mutations has a higher rate of true-positives and lower rates of false-negatives than the CT tests, thereby facilitating earlier thyroidectomy (Brandi, et al., 2001).

RET gene molecular genetic testing is offered to probands with either of the MEN 2 subtypes and FMTC and to all at-risk individuals in whom a germline RET mutation has been identified in an affected family member. In individuals with an identified germline RET mutations prophylactic thyroidectomy with autotransplantation of the parathyroid is the primary preventive measure for all subtypes of MEN 2. The surgery is considered safe for all age groups. The timing of the surgery is described in a consensus guideline developed by an international group of endocrinologists (Brandi, et al., 2001). Genetic testing of unaffected relatives is most useful when a germline mutation has been identified in the affected family member.

The probability of a RET germline mutation in a patient with an apparently sporadic MTC is 1-7% (Brandi, et al., 2001). A RET germline mutation is more likely if there is an early age of onset or multiplicity within the thyroid. Due to the critical implications of finding a RET mutation, it is recommended that all cases of sporadic MTC should be tested for germline RET mutation (Brandi, et al., 2001).

Several studies have been published that indicate that molecular analysis of RET gene may offer early identification of those patients at high risk to develop MTC and may provide the opportunity for early intervention (Bugalho, et al., 2007; Moore, et al., 2007; Frank-Raue, et al., 2006; Jimenez, et al., 2006; Szinnai, et al., 2003; Neumann, et al., 2002; Janeschewicz, et al., 2000).

Pheochromocytoma is a potentially life-threatening disease and a rare cause of hypertension. While most are sporadic (nonfamilial) tumors, pheochromocytoma is also associated with a group of susceptibility genes which include: the RET proto-oncogene, the von Hippel-Lindau gene (VHL), succinate dehydrogenase subunit D (SDHD) and succinate dehydrogenase subunit B (SDHB) (Neumann, et al., 2002). If the pheochromocytoma has an autosomal dominant pattern of inheritance, it can be an early manifestation of unsuspected MEN 2. Due to the importance of an abnormal mutation finding there is support for genetic testing for MEN2 (Brandi, et al., 2001).

Professional Societies/Organizations

In a policy statement on genetic testing for cancer susceptibility, the American Society of Clinical Oncologists (ASCO) identified MEN2 as a Group 1 disorder. This group includes conditions in which testing for either a positive or negative result will change medical care, and for which genetic testing may be considered part of the standard management of affected families (ASCO, 2003).

The National Comprehensive Cancer Network (NCCN) guidelines for neuroendocrine tumors contain the recommendations (NCCN, 2009a):

- All patients with medullary thyroid cancer (MTC) should be screened by genetic testing for a mutation in RET proto-oncogene
- Family members of all patients with MTC should receive genetic counseling and testing for germline RET mutation.

Summary

Genetic testing for RET (rearranged during transfection) proto-oncogene germline point mutations offers opportunity for early identification of those patients at high risk to develop multiple endocrine neoplasia type 2 (MEN 2) and familial medullary thyroid carcinoma (FMTC) providing an opportunity for early intervention.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT [®] * Codes	Description
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA)
83894	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide), each nucleic acid preparation
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
83904	Molecular diagnostics; mutation identification by sequencing, single segment, each segment
83909	Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis), each nucleic acid preparation
83912	Molecular diagnostics; interpretation and report

HCPCS Codes	Description
S3840	DNA analysis for germline mutations of the ret Proto-oncogene for susceptibility to multiple endocrine neoplasia type 2

ICD-9-CM Diagnosis Codes	Description
193	Malignant neoplasm of thyroid gland
194.0	Malignant neoplasm; adrenal gland

194.6	Malignant neoplasm; aortic body and other paraganglia
227.0	Benign neoplasm; adrenal gland
227.6	Benign neoplasm; aortic body and other paraganglia
237.2	Neoplasm of uncertain behavior; adrenal gland
237.3	Neoplasm of uncertain behavior; paraganglia

***Current Procedural Terminology (CPT®) ©2008 American Medical Association: Chicago, IL.**

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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	11/15/2007	0224	Genetic Testing for RET Proto-Oncogene Germline Point Mutations

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