Cigna Medical Coverage Policy

Subject  Genetic Testing for RET Proto-Oncogene and Hereditary Paraganglioma- Pheochromocytoma (PGL/PCC) Syndrome

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Hyperlink to Related Coverage Policies
Genetic Counseling
Genetic Testing for von Hippel-Lindau Disease
Genetic Testing of Heritable Disorders
Preimplantation Genetic Diagnosis

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Coverage Policy

Please refer to the applicable benefit plan document to determine benefit availability and the terms, conditions and limitations of coverage. Under some benefit plans, coverage for genetic screening and/or testing may be excluded or restricted. If coverage for genetic testing is available, the following conditions of coverage apply.

RET (rearranged during transfection) Proto-Oncogene Germline Point Mutations

Cigna covers genetic testing for RET proto-oncogene germline point mutations with targeted mutation analysis as medically necessary for ANY of the following indications:

- confirmatory testing for multiple endocrine neoplasia type 2 (MEN 2) subtypes (i.e., MEN 2A and MEN 2B) and familial medullary thyroid carcinoma (FMTC)
- diagnostic testing with ANY of the following:
  - primary C cell hyperplasia
  - sporadic (nonfamilial) medullary thyroid cancer
  - Hirschsprung disease consistent with monogenic nonsyndromic etiology
  - pheochromocytoma with ANY of the following
    - family history of medullary thyroid carcinoma
    - bilateral pheochromocytoma
unilateral pheochromocytoma, with a negative evaluation and genetic testing for von Hippel-Lindau syndrome and/or hereditary pheochromocytoma/paraganglioma syndrome

Cigna covers genetic testing for RET proto-oncogene germline point mutations with full sequence analysis as medically necessary when the criteria listed above for genetic testing for RET proto-oncogene germline point mutations are met, targeted mutation analysis is negative and clinical suspicion for these conditions remains high.

Cigna covers predictive testing for the known familial mutation (i.e., testing for the known familial variant) for RET proto-oncogene germline point mutations as medically necessary for EITHER of the following indications:

- when the individual has a blood relative in whom a disease causing RET germline mutation has been identified
- prenatal testing of a fetus (i.e., amniocentesis or chorionic villus sampling [CVS]) or preimplantation genetic diagnosis (PGD) when the disease-causing mutation has been identified in one member of the reproductive couple

**Hereditary Paraganglioma-Pheochromocytoma (PGL/PCC) Syndrome**

Cigna covers confirmatory (i.e., diagnostic) genetic testing with full sequence analysis as medically necessary for hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndrome (genes SDHB, SDHC, and SDHD) when ALL of the following criteria are met:

- pheochromocytoma or paraganglioma
- other syndromes and causes of PGL/PCC have been ruled out (e.g., von Hippel-Lindau disease, multiple endocrine neoplasia [MEN])
- stepwise testing of the PGL/PCC genes is planned based on clinical features

Cigna covers genetic testing for the known familial mutation (i.e., testing for the known familial variant) for PGL/PCC syndrome as medically necessary for EITHER of the following indications:

- predictive testing when the individual has a blood relative in whom a disease causing germline mutation has been identified
- prenatal testing of a fetus (i.e., amniocentesis or chorionic villus sampling [CVS]) or preimplantation genetic diagnosis (PGD) when the disease-causing mutation has been identified in one member of the reproductive couple

Any individual undergoing genetic testing for RET proto-oncogene germline mutations or hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndrome should have both pre-and post-test genetic counseling completed by ONE of the following:

- an independent Board-Certified or Board-Eligible Medical Geneticist
- an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory (Genetic counselors are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).
- a genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory (Genetic nurses are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).
Cigna does not cover genetic testing for the susceptibility to RET proto-oncogene germline mutations or hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndrome in the general population because it is considered not medically necessary.

General Background

**Multiple endocrine neoplasia type 2 (MEN2)**

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. 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.

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 (Moline, et al., 2013), 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 of the RET gene identifies disease-causing mutations in 98% of individuals with MEN 2A, more than 98% of individuals with MEN 2B, and in about 95% of families with FMTC (Moline, et al., 2013). 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 (National Cancer Institute [NCI], 2013a, 2013c; National Comprehensive Cancer Network® (NCCN®), 2013/2014).

RET molecular genetic testing is indicated in all individuals with a diagnosis of MTC and a clinical diagnosis of MEN 2 or primary C-cell hyperplasia (Moline, et al., 2013; American Thyroid Association, et al., 2009). RET gene molecular genetic testing is offered to probands with either of the MEN 2 subtypes and FMTC 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).

Predictive testing for at-risk asymptomatic family members requires prior identification of the disease-causing mutation in the family. RET gene molecular genetic testing should be offered to probands with any of the MEN 2 subtypes and to all at-risk members where a germline RET mutation has been identified in an affected family member. Consideration of molecular genetic testing of at-risk family members is appropriate for surveillance (Moline, et al., 2013).

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 is 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).
Hirschsprung disease, or congenital intestinal aganglionosis, is a birth defect characterized by complete absence of neuronal ganglion cells from a portion of the intestinal tract. The aganglionic segment includes the distal rectum and a variable length of contiguous proximal intestine. The condition may occur as an isolated finding or as part of a multisystem disorder. Affected infants frequently present in the first two months of life with symptoms of impaired intestinal motility (e.g., failure to pass meconium within the first 48 hours of life, constipation, emesis, abdominal pain or distention, and occasionally diarrhea) Nonsyndromic Hirschsprung is when is where the condition occurs without other anomalies and has been associated with mutations in at least six genes (Parisi, 2011).

Germline mutations in RET have also been implicated in 10–40% of cases of Hirschsprung disease, with higher frequencies associated with familial cases. While most individuals with MEN 2A do not have aganglionosis, and vice versa, in some series an estimated 2.5%-5% of individuals with Hirschsprung disease have a MEN 2A-associated RET mutation. As Hirschsprung disease may be the initial finding in such individuals, molecular genetic testing could lead to recognition of RET mutations associated with MEN 2A and a cancer predisposition, with significant impact on care of the affected individual and family members (Parisi, 2011; American Thyroid Association, et al., 2009).

When monogenic, nonsyndromic Hirschsprung disease is confirmed or likely, then molecular genetic testing of RET should be considered. Hirschsprung disease-associated mutations have been described in each of the 20 RET exons and no single specific defect is particularly common. If a RET mutation is not identified, molecular genetic testing of genes EDN3 and/or EDNRB may be considered (Parisi, 2011).

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; Janeszewicz, et al., 2000).

**Paraganglioma-Pheochromocytoma (PGL/PCC) Syndrome**

Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes are characterized by paragangliomas (tumors that arise from neuroendocrine tissues symmetrically distributed along the paravertebral axis from the base of the skull to the pelvis) and by pheochromocytomas (paragangliomas that are confined to the adrenal medulla). Approximately 80-90% of pheochromocytomas arise in the adrenal medulla and the remaining are ectopic/extra-aortic sympathetic ganglia called paragangliomas (NCCN, 2014; Kirmani, et al., 2012). PCCs and PGLs are relatively rare tumors.

The hereditary PGL/PCC syndromes are inherited in an autosomal dominant manner. It is estimated that 25% of pheochromocytomas and paragangliomas occur in the setting of a hereditary syndrome (NCI, 2013c). The genes associated with PGL/PCC include:

- **SDHD**: Formerly referred to as familial pheochromocytoma-paraganglioma syndrome type 1
- **SDHAF2 (SDH5)**: Formerly referred to as familial pheochromocytoma-paraganglioma syndrome type 2
- **SDHC**: Formerly referred to as familial pheochromocytoma-paraganglioma syndrome type 3
- **SDHB**: Formerly referred to as familial pheochromocytoma-paraganglioma syndrome type 4
- **SDHA**
- **MAX**

Hereditary PGL/PCC syndromes should be considered in all individuals with paragangliomas and/or pheochromocytomas, in particular should be considered with the following findings (Kirmani, et al., 2012; Pacak, et al., 2007):

- multiple tumors (i.e., more than one paraganglioma or pheochromocytoma), including bilateral adrenal pheochromocytoma and including multiple tumors in a single adrenal gland and may not occur simultaneously
- multifocal with multiple synchronous or metachronous tumors
- recurrent tumors
- early onset of tumors (i.e., age <45 years)
- a family history of such tumors
Sequence analysis of the coding regions of SDHB, SDHC, and SDHD, and associated intron-exon junctions detects approximately 70% of familial cases of skull base and neck paraganglioma. There is no universally agreed-upon consensus or standard protocol regarding a diagnostic approach to individuals with hereditary PGL/PCC. The strategy employed should use all available clinical data (family history, physical exam, tumor location, presence of metastases and biochemical phenotype) to make the best clinical judgment with regard to the most likely genetic etiology in each affected individual or family. The decision can then be made for pursuing genetic testing in a step-wise fashion, and multiple algorithms have been suggested using this approach.

Genetic testing is often recommended for PGL/PCC in the following situations (NCI, 2013c):

- a personal or family history of clinical features suggestive of a hereditary pheochromocytoma-paraganglioma syndrome
- bilateral or multifocal tumors
- sympathetic or malignant extra-adrenal paragangliomas
- diagnosed before age 40 years

Since early diagnosis and treatment is very likely to change the outcome for individuals, it is recommended that relatives at risk be offered genetic testing as early as possible when the family mutation is known. Molecular genetic testing will assist in clarifying genetic status to improve diagnostic certainty and reduce the need for screening procedures in those who have not inherited the disease-causing mutation (Kirmani, et al., 2012).

Prioritizing the gene-specific testing for pheochromocytoma and paraganglioma patients should be completed based on patient-specific information including patient and family history and clinical features (Erlic, et al., 2009). The First International Symposium on Pheochromocytoma noted that consideration of tumor location, presence of multiple tumors or metastases, and type of catecholamine produced could be useful in deciding which genes to test (Pacak, et al., 2007).

A predisposition to pheochromocytoma may be associated with MEN 2 and von Hippel-Lindau disease (VHL) syndrome. Von Hippel-Lindau (VHL) disease or syndrome is an inherited multisystem disorder characterized by abnormal growth of blood vessels. VHL is characterized by hemangioblastomas of the brain, spinal cord and retinas; renal cysts and clear cell renal cell carcinomas; pheochromocytomas; and endolymphatic sac tumors. The VHL gene is a tumor suppressor that is the only gene known to be associated with the disease and is inherited in an autosomal dominant manner (Frantzen, et al., 2012).

Genetic testing should be undertaken only after independent genetic counseling has been provided to patients in order to assist in complex medical decision-making. Post genetic testing counseling should be planned. The genetic counseling should be provided by an independent specialty-trained professional such as a medical geneticist or a genetic counselor who is an American Board of Medical Genetics or American Board of Genetic Counseling certified genetic counseling professional who is unaffiliated with the genetic testing lab performing the test(s).

Prenatal Testing and Preimplantation Genetic Testing

The optimal time for determination of genetic risk and availability of prenatal testing is before pregnancy. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk. Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family (Moline, et al., 2013). Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15 to 18 weeks’ gestation or chorionic villus sampling (CVS) at about ten to 12 weeks’ gestation. The disease-causing allele of a family member must be identified or linkage established in the family before prenatal testing or PGD can be performed.

Professional Societies/Organizations

American Thyroid Association published management guidelines for medullary thyroid cancer. The guidelines include the following recommendations regarding genetic testing (American Thyroid Association, et al., 2009):

- All patients with a personal medical history of primary C cell hyperplasia, MTC, or MEN 2 should be offered germline RET testing
• All people with a family history consistent with MEN 2 or FMTC, and at risk for autosomal dominant inheritance of the syndrome should be offered RET testing. For MEN 2B this should be done shortly after birth. For MEN 2a and FMTC this should be done before five years of age.

• Testing of exon 10 should be considered in individuals with Hirschsprung disease. Although mutations are distributed throughout the gene, and some prefer sequencing of all exons in this setting, the most important clinical decision for Hirschsprung disease is whether they also have an activating exon 10 mutation which would confer risk of MEN 2.

• Pre- and post-test genetic counseling by a genetics counselor, or other qualified professional, should be offered to all patients undergoing RET testing

• Once a germline mutation has been identified in a family, RET mutation analysis should be offered to all first-degree relatives of known mutation carriers which should be done before the age of recommended prophylactic thyroidectomy whenever possible.

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; Robson, et al., 2010).

The National Cancer Institute (NCI) notes that MEN 2 is a well-defined hereditary cancer syndrome for which genetic testing is considered an important part of the management for at-risk family members. At-risk individuals are defined as first-degree relatives of a person known to have MEN 2. Testing allows the identification of people with asymptomatic MEN 2 who can be offered risk-reducing thyroidectomy and biochemical screening as preventive measures. A negative mutation analysis in at-risk relatives, however, is useful only after a disease-causing mutation has been identified in an affected relative. Since early detection of at-risk individuals affects medical management, testing of children who have no symptoms is considered beneficial. Germline DNA testing for RET mutations is generally recommended to all individuals with a diagnosis of MTC, regardless of whether there is a personal or family history suggestive of MEN 2. Approximately 95% of patients with MEN 2A or MEN 2B will have an identifiable germline RET mutation. For FMTC the detection rate is slightly lower at 88%. In addition, 1%–7% of apparently sporadic cases of MTC will carry a germline RET mutation, underscoring the importance of testing all cases (NCI, 2013a).

The National Comprehensive Cancer Network Guidelines™ (NCCN Guidelines™ ) for neuroendocrine tumors and medullary thyroid cancer contain the recommendations (NCCN, 2013/2014):

• 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.
• Patients with pheochromocytoma/paraganglioma should be offered genetic counseling, and genetic testing when appropriate.

Use Outside of the US
No relevant information found.

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.

Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes are characterized by paragangliomas (tumors that arise from neuroendocrine tissues symmetrically distributed along the paravertebral axis from the base of the skull to the pelvis) and by pheochromocytomas (paragangliomas that are confined to the adrenal medulla). Genetic testing may be used for confirmatory, predictive, and prenatal testing. Since early diagnosis and treatment is very likely to change the outcome for individuals, it is recommended that relatives at risk be offered genetic testing as early as possible when the family mutation is known.

Coding/Billing Information
**Coverage Policy Number: 0224**

**Note:** 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

**Covered when medically necessary:**

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<th>CPT® Codes</th>
<th>Description</th>
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| 81403      | Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)  
- Known familial variant, not otherwise specified, for gene listed in Tier 1 or Tier 2, DNA sequence analysis, each variant exon |
| 81404      | Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)  
- RET (ret proto-oncogene) (eg, multiple endocrine neoplasia, type 2B and familial medullary thyroid carcinoma), common variants (eg, M918T, 2647_2648delinsTT, A883F)  
- SDHD (succinate dehydrogenase complex, subunit D, integral membrane protein) (eg, hereditary paragangioma), full gene sequence  
- SDHC (succinate dehydrogenase complex, subunit C, integral membrane protein, 15kDa) (eg, hereditary paraganglioma-pheochromocytoma syndrome), duplication/deletion analysis  
- SDHD (succinate dehydrogenase complex, subunit D, integral membrane protein) (eg, hereditary paraganglioma), full gene sequence |
| 81405      | Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons)  
- RET (ret proto-oncogene) (eg, multiple endocrine neoplasia, type 2A and familial medullary thyroid carcinoma), targeted sequence analysis (eg, exons 10, 11, 13-16)  
- SDHB (succinate dehydrogenase complex, subunit B, iron sulfur) (eg, hereditary paragangioma), full gene sequence  
- SDHC(succinate dehydrogenase complex, subunit C, integral membrane protein, 15kDa) (eg, hereditary paraganglioma-pheochromocytoma syndrome), full gene sequence |
| 81406      | Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)  
- RET (ret proto-oncogene) (eg, Hirschsprung disease ), full gene sequence |

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<th>HCPCS Codes</th>
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<tr>
<td>S3840</td>
<td>DNA analysis for germline mutations of the ret Proto-oncogene for susceptibility</td>
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References


http://www.cancer.gov/cancertopics/pdq/treatment/pheochromocytoma/HealthProfessional/page1#Secti
on_33


