Medical Policy

**Genetic Testing for Germline Mutations of the RET Proto-Oncogene in Medullary Carcinoma of the Thyroid**

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**Policy Number:** 564

BCBSA Reference Number: 2.04.05A

NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

**Related Policies**

None

**Policy**

**Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity**

Genetic testing for RET proto-oncogene point mutations may be considered MEDICALLY NECESSARY in the following situations:
- Among symptomatic members of families with defined RET gene mutations;
- Among members of families known to be affected by inherited medullary thyroid cancer, but not previously evaluated for RET mutations; and
- Among patients with sporadic medullary thyroid cancer.

**Medicare HMO BlueSM and Medicare PPO BlueSM Members**

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

**Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)**

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at [https://www.cms.gov](https://www.cms.gov).

**Prior Authorization Information**

**Inpatient**
- For services described in this policy, precertification/preauthorization IS REQUIRED for all products if the procedure is performed inpatient.

**Outpatient**
For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.

<table>
<thead>
<tr>
<th>Coverage Type</th>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>Prior authorization is not required.</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
<td>Prior authorization is not required.</td>
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<tr>
<td>Medicare HMO BlueSM</td>
<td>Prior authorization is not required.</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
<td>Prior authorization is not required.</td>
</tr>
</tbody>
</table>

**CPT Codes / HCPCS Codes / ICD Codes**

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

**CPT Codes**

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81404</td>
<td>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)</td>
</tr>
<tr>
<td>81405</td>
<td>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, regionally targeted cytogenomic array analysis)</td>
</tr>
<tr>
<td>81406</td>
<td>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)</td>
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**HCPCS Codes**

<table>
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<tr>
<th>HCPCS codes:</th>
<th>Code Description</th>
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<tr>
<td>S3840</td>
<td>DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2</td>
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**Description**

Medullary carcinoma of the thyroid is an uncommon type of thyroid cancer that arises from the parafollicular or C cells thyroid, which produces the hormone calcitonin. (Papillary thyroid cancer, arising from the glandular cells, is the most common type of thyroid cancer.) Three distinct but related familial cancer syndromes together are responsible for approximately one-fourth of the incidence of medullary carcinoma of the thyroid; the remaining three-fourths are sporadic. The 3 inherited syndromes include multiple endocrine neoplasia (MEN) types 2A and 2B and familial medullary thyroid cancer (FMTC). MEN 2A and MEN 2B differ from each other (and from MEN 1) in the spectrum and frequency of accompanying endocrine malignancies and other disorders. In contrast, FMTC is defined as being in a family with the repeated occurrence of medullary thyroid cancer in the absence of other endocrine malignancies or disorders. MEN 2A, MEN 2B, and FMTC are all dominantly inherited. Point mutations of the germline RET gene, located on chromosome 10, are associated with inheritance of MEN 2A, MEN 2B, or FMTC.

Medullary thyroid cancer is curable surgically 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. Surveillance by annual biochemical monitoring has been used to identify those with the inherited disease before it progresses beyond the earliest stages. 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. 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.

Policy History

<table>
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<th>Date</th>
<th>Action</th>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines