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

Archived Medical Policy

Archived medical policies are no longer subject to periodic review, are maintained for reference, and may be returned to active status if the need is identified.

Policy # 00202
Original Effective Date: 05/17/2006
Archived Date: 05/16/2012

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider genetic testing for RET proto-oncogene point mutations to be eligible for coverage 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 (MTC), but not previously evaluated for RET mutations; and
- Among patients with sporadic MTC.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for RET proto-oncogene point mutations for any other situation that is not listed above to be investigational.*

Background/Overview
RET Mutations - RET is an abbreviation for "rearranged during transfection". The RET gene provides instructions for producing a protein that is involved in signaling within cells. This protein appears to be essential for the normal development of several kinds of nerve cells, including nerves in the intestine (enteric neurons) and the portion of the nervous system that controls involuntary body functions such as heart rate (the autonomic nervous system). The RET protein is also necessary for normal kidney development and the production of sperm (spermatogenesis).

The RET protein spans the cell membrane, so that one end of the protein remains inside the cell and the other end projects from the outer surface of the cell. This positioning of the protein allows it to interact with specific factors outside the cell and to receive signals that help the cell respond to its environment. When molecules that stimulate growth and development (growth factors) attach to the RET protein, a complex

©2013 Blue Cross and Blue Shield of Louisiana
An independent licensee of the Blue Cross and Blue Shield Association
No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.
Genetic Testing for Germline Mutations of the RET Proto-Oncogene in Medullary Carcinoma of the Thyroid

Archived Medical Policy

Archived medical policies are no longer subject to periodic review, are maintained for reference, and may be returned to active status if the need is identified.

Policy # 00202
Original Effective Date: 05/17/2006
Archived Date: 05/16/2012

cascade of chemical reactions inside the cell is triggered. These reactions instruct the cell to undergo certain changes, such as dividing or maturing to take on specialized functions. Mutations in the RET gene are the most common genetic cause of many disorders.

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 MTC; the remaining three-fourths are sporadic. The three 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 MTC 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 MTC 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 MTC 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Genetic tests are currently regulated at the federal level through three mechanisms:

1. The Clinical Laboratory Improvement Amendments (CLIA);
2. The Federal Food, Drug, and Cosmetic Act; and
3. During investigational phases of test development, under applicable regulations for the protection of human subjects.

Centers for Medicare and Medicaid Services (CMS)
In 2000, the Centers for Disease Control and Prevention (CDC), as a scientific advisor to the FDA, and the CMS in development of requirements for clinical laboratories under the CLIA, issued a proposal to change current CLIA regulations to specifically recognize a genetic testing specialty. These proposed new regulations would address issues such as the accuracy and reliability of test results, and related issues, such as informed consent, confidentiality, counseling and the clinical appropriateness of a genetic test.

Under current CLIA requirements, laboratories are required to have a qualified clinical consultant to evaluate the appropriateness of the testing ordered and to interpret test results. The consultant must be available to assist in ensuring that appropriate tests are ordered to meet clinical expectations that reports of test results include pertinent information required for specific patient interpretation, and that matters related to the quality of test results are communicated. The laboratory must provide any additional information relevant and necessary to a specific test on the requisition or test authorization to ensure accurate and timely testing and reporting.

At the present time, the FDA does not regulate tests developed by research and commercial laboratories that are conducted in those laboratories. In 1997, the FDA issued its final rule on the topic of “analyte specific reagents” (ASRs, the “active ingredients” that are used exclusively to identify a specific chemical or biological entity in a test), subjecting them to FDA-assured quality control in manufacture. The FDA does not intend to regulate ASRs used in genetic tests differently from other restricted Class I medical devices that are exempt from premarket notification requirements.

Rationale/Source
The 1997 TEC Assessment concluded that the 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 MTC 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.

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

Archived Medical Policy

Archived medical policies are no longer subject to periodic review, are maintained for reference, and may be returned to active status if the need is identified.

Policy # 00202
Original Effective Date: 05/17/2006
Archived Date: 05/16/2012

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines (BCBSLAMPCG) are obtained from Current Procedural Terminology (CPT®), copyright 2012 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>Codes 83890 thru 83914 were deleted effective 1/1/2013. The appropriate molecular pathology (Tier 2) procedure code describing the analytical services performed should be used to report services. If molecular pathology procedure services are not described in any Tier 1 or Tier 2 code the unlisted molecular pathology procedure codes should be used.</td>
</tr>
<tr>
<td>HCPCS</td>
<td>S3840</td>
</tr>
<tr>
<td>ICD-9 Diagnosis</td>
<td>198.89, 226</td>
</tr>
<tr>
<td>ICD-9 Procedure</td>
<td>No Code</td>
</tr>
</tbody>
</table>

Policy History

Original Effective Date: 05/17/2006
05/03/2006 Medical Director review
06/21/2006 Medical Policy Committee approval
05/02/2007 Medical Director review
05/23/2007 Medical Policy Committee approval. Coverage eligibility unchanged.
05/07/2008 Medical Director review
05/21/2008 Medical Policy Committee approval. Coverage eligibility unchanged.
05/07/2009 Medical Director review
05/20/2009 Medical Policy Committee approval. Coverage eligibility unchanged
06/03/2010 Medical Policy Committee review
06/16/2010 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Genetic Testing for Germline Mutations of the RET Proto-Oncogene in Medullary Carcinoma of the Thyroid

Archived Medical Policy

Archived medical policies are no longer subject to periodic review, are maintained for reference, and may be returned to active status if the need is identified.

Policy # 00202
Original Effective Date: 05/17/2006
Archived Date: 05/16/2012

05/05/2011 Medical Policy Committee review
05/18/2011 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/03/2012 Medical Policy Committee review. Recommend archiving policy.
05/16/2012 Medical Policy Implementation Committee approval. Archived medical policy.
02/19/2013 Coding updated

Next Scheduled Review Date: Archived medical policy.

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

† Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.